**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 1 million IU/ml powder and solvent for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 1 million IU of interferon alfa-2b produced in *E.coli* by recombinant DNA technology.
After reconstitution, 1 ml contains 1 million IU of interferon alfa-2b.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

White to cream coloured powder.
Clear and colourless solvent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C:
*Adult patients:*
Viraferon is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section 4.4).

The best way to use Viraferon in this indication is in combination with ribavirin.

*Chidren and adolescents:*
Viraferon is intended for use, in a combination regimen with ribavirin, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials (see sections 4.4, 4.8 and 5.1).

### 4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

If adverse events develop during the course of treatment with Viraferon for any indication, modify the dosage or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dosage adjustment, or disease progresses, discontinue treatment with Viraferon. At the discretion of the physician, the patient may self-administer the dose for maintenance dosage regimens administered subcutaneously.

*Chronic Hepatitis B*: The recommended dosage is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/$mm^3$, granulocytes < 1,000/$mm^3$, thrombocytes < 100,000/$mm^3$). Treatment should be discontinued in case of severe leukopaenia (< 1,200/$mm^3$), severe neutropaenia (< 750/$mm^3$) or severe thrombocytopaenia (< 70,000/$mm^3$).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue Viraferon therapy.

*Chronic Hepatitis C*: Viraferon is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

*Children 3 years of age or older and adolescents*: Interferon alfa-2b 3 MIU/$m^2$ is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsule SPC for dose of ribavirin capsules and dosage modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC).

Relapse patients (adults):
Viraferon is given in combination with ribavirin.

Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for 6 months.

Naïve patients:
*Adults:* The efficacy of Viraferon is enhanced when given in combination with ribavirin. Viraferon should be given alone mainly in case of intolerance or contraindication to ribavirin.

Viraferon in combination with ribavirin:
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Viraferon alone:

The optimal duration of therapy with Viraferon alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with Viraferon alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

*Children and adolescents:* The efficacy and safety of Viraferon in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Virological response is defined as absence of detectable HCV-RNA at Week 12. Treatment should be discontinued in these patients.
Genotype 2/3: The recommended duration of treatment is 24 weeks.

Virological responses after 1 year of treatment and 6 months of follow-up were 36 % for genotype 1 and 81 % for genotype 2/3/4.

Viraferon may be administered using either glass or plastic disposable injection syringes.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.

Children and adolescents:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin: Also see ribavirin SPC if interferon alfa-2b is to be administered in combination with ribavirin in patients with chronic hepatitis C.

**4.4 Special warnings and precautions for use**

*For all patients:*

Psychiatric and central nervous system (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Viraferon therapy, and even after treatment discontinuation mainly during the 6-month follow-up periodand in the follow-up period. Among children and adolescents treated with Viraferon in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others), confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric

symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Viraferon be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of or history of severe psychiatric conditions:*
If a treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases, termination of Viraferon therapy. Any patient developing liver function abnormalities during treatment with Viraferon must be monitored closely and treatment discontinued if signs and symptoms progress.

Hypotension may occur during Viraferon therapy or up to two days post-therapy and may require supportive treatment.

Adequate hydration must be maintained in patients undergoing Viraferon therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Viraferon must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instance after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with Viraferon, must have a prompt and complete eye examination. Periodic visual examinations during Viraferon therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of Viraferon should be considered in patients who develop new or worsening ophthalmological disorders.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of Viraferon.

Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require Viraferon therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of Viraferon therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of Viraferon in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Discontinue treatment with Viraferon in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decompensation.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived albumin.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

There are no reports of virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes.

It is strongly recommended that every time that Viraferon is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

<u>Chronic Hepatitis C:</u>
Combination therapy with ribavirin: Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy: Infrequently, adult patients treated for chronic hepatitis C with Viraferon developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using Viraferon therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which Viraferon may alter thyroid status is unknown. Prior to initiation of Viraferon therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of Viraferon therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, Viraferon treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of Viraferon therapy has not reversed thyroid dysfunction occurring during treatment (also see Children and adolescents, Thyroid monitoring).

*Supplemental monitoring specific for children and adolescents*

Thyroid Monitoring**:** Approximately 12 % of children treated with interferon alfa-2b and ribavirin developed increase in TSH. Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of Viraferon therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Growth and Development: During a 1-year course of therapy there was a decrease in the rate of linear growth (mean percentile decrease of 9 %) and a decrease in the rate of weight gain (mean percentile decrease of 13 %). A general reversal of these trends was noted during the 6 months follow-up post treatment. However, based on interim data from a long-term follow-up study, 12 (14 %) of 84 children had a > 15 percentile decrease in rate of linear growth, of whom 5 (6 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In addition, preclicinal juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3). Therefore, the risk/benefit of the combined use of interferon alfa-2b and ribavirin should be assessed in young children prior to the initiation of therapy. Physicians are advised to monitor the growth of children taking ribavirin in combination with interferon alfa-2b. There are no data on long term effects on growth and development and on sexual maturation.

HCV/HIV Coinfection**:** Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Viraferon and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders**:** Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Viraferon and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests:
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with Viraferon.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during Viraferon therapy to greater than or equal to 2 times baseline, Viraferon therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, liver function tests: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin must be monitored at two-week intervals.

Effect on fertility: Interferon may impair fertility (see section 4.6 and section 5.3).

**4.5 Interaction with other medicinal products and other forms of interaction**

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with Viraferon.

Interactions between Viraferon and other medicinal products have not been fully evaluated. Caution must be exercised when administering Viraferon in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dosage adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

(Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C).

**4.6 Pregnancy and lactation**

Women of childbearing potential have to use effective contraception during treatment. Viraferon must be used with caution in fertile men. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

There are no adequate data from the use of interferon alfa-2b in pregnant women.Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Viraferon is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

Combination therapy with ribavirin: Ribavirin causes serious birth defects when administered during pregnancy. Ribavirin therapy is contraindicated in women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking Viraferon in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must

each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

### 4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with Viraferon, and therefore it is recommended that they avoid driving or operating machinery.

### 4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/$m^2$/week in hairy cell leukaemia up to 100 MIU/$m^2$/week in melanoma), the most commonly reported undesirable effects were fever, fatigue, headache and myalgia. Fever and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

In clinical trials conducted in the hepatitis C population, patients were treated with Viraferon alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of Viraferon three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10); rarely (≥1/10,000, <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1.** Adverse reactions reported during clinical trials or following the marketing use of Viraferon alone or in combination with ribavirin

| System Organ Class | Adverse Reactions |
|---|---|
| **Infections and infestations** | |
| Very common: | Pharyngitis*, infection viral* |
| Common: | Bronchitis, sinusitis, herpes simplex (resistance), rhinitis |
| Rarely: | Pneumonia[§] |
| **Blood and lymphatic system disorders** | |
| Very common: | Leukopaenia |
| Common: | Thrombocytopaenia, lymphadenopathy, lymphopenia |
| Very rarely: | Aplastic anaemia |
| Not known**:** | Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura |
| **Immune system disorders**[§] | |
| Very rarely: | Sarcoidosis, exacerbation of sarcoidosis |
| Not known: | Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis[§] |
| **Endocrine disorders** | |
| Common: | Hypothyroidism[§], hyperthyroidism[§] |
| Very rarely: | Diabetes, aggravated diabetes |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcaemia, dehydration, hyperuricemia, thirst |
| Very rarely: | Hyperglycaemia, hypertriglyceridaemia[§], increased appetite |
| **Psychiatric disorders**[§] | |

| | |
|---|---|
| Very common: | Depression, insomnia, anxiety, emotional lability*, agitation, nervousness |
| Common: | Confusion, sleep disorder, libido decreased |
| Rarely: | Suicide ideation |
| Very rarely: | Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations |
| Not known: | Mental status change[§] |
| **Nervous system disorders**[§] | |
| Very common: | Dizziness, headache, concentration impaired, mouth dry |
| Common: | Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion |
| Very rarely: | Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy, neuropathy, polyneuropathy |
| Not known: | Mononeuropathies, coma[§] |
| **Eye disorders** | |
| Very common: | Vision blurred |
| Common: | Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain |
| Rarely: | Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§] |
| **Ear and labyrinth** | |
| Common: | Vertigo, tinnitus |
| Very rarely: | Hearing loss, hearing disorder |
| **Cardiac disorders** | |
| Common: | Palpitation, tachycardia |
| Rarely: | Cardiomyopathy |
| Very rarely: | Myocardial infarction, cardiac ischaemia |
| Not known: | Arrhythmia |
| **Vascular disorders** | |
| Common: | Hypertension |
| Very rarely: | Peripheral ischaemia, hypotension[§] |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common: | Dyspnoea*, coughing* |
| Common: | Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive |
| Very rarely: | Pulmonary infiltrates[§], pneumonitis[§] |
| **Gastrointestinal disorders** | |
| Very common: | Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia |
| Common: | Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools |
| Very rarely: | Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding |
| Not known: | Periodontal disorder NOS, dental disorder NOS[§] |
| **Hepatobiliary disorders** | |
| Common: | Hepatomegaly |
| Very rarely: | Hepatotoxicity, (including fatality) |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, pruritus*, skin dry*, rash*, sweating increased |
| Common: | Psoriasis (new or aggravated)[§], rash maculopapular, rash |

| | |
|---|---|
| Very rarely: | erythematous, eczema, erythema, skin disorder<br>Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders**<br>Very common:<br>Common:<br>Very rarely: | <br>Myalgia, arthralgia, musculoskeletal pain<br>Arthritis<br>Rhabdomyolysis, myositis, leg cramps, back pain |
| **Renal and urinary disorders**<br>Common:<br>Very rarely: | <br>Micturition frequency<br>Renal failure, renal insufficiency, nephrotic syndrome |
| **Reproductive system and breast disorders**<br>Common: | <br>Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder |
| **General disorders and administration site conditions**<br>Very common:<br><br><br>Common:<br>Very rarely: | <br>Injection site inflammation, injection site reaction*, fatigue, rigors, fever§, flu-like symptoms§, asthenia, irritability, chest pain, malaise<br>Injection site pain<br>Injection site necrosis, face oedema |
| **Investigations**<br>Very common: | <br>Weight decrease |

*These events were only common with Viraferon alone
§See section 4.4

These undesirable effects have also been reported with Viraferon alone.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

For safety with respect to transmissible agents, see section 4.4.

**Paediatric population**

*Children and adolescents – Chronic Hepatitis C*
In clinical trials of 118 children or adolescents 3 to 16 years of age, 6 % discontinued therapy due to adverse events. In general, the adverse event profile in the limited paediatric population studied was similar to that observed in adults, although there is a paediatric specific concern regarding growth inhibition as decrease in height (mean percentile decrease of growth velocity of 9 %) and weight (mean percentile decrease of 13 %)

percentile were observed during treatment (see section 4.4). Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from paediatric clinical trials.
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 2** Adverse reactions very commonly and commonly reported in paediatric clinical trials
Very common (≥1/10) - Common (≥1/100, <1/10)

| System Organ Class | Adverse Reactions |
|---|---|
| **Infection and infestations** | |
| Very common: | Viral infection, pharyngitis |
| Common: | Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | |
| Common: | Neoplasm (unspecified) |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, neutropaenia |
| Common: | Thrombocytopaenia, lymphadenopathy |
| **Endocrine disorders** | |
| Very common: | Hypothyroidism[§], |
| Common: | Hyperthyroidism[§], virilism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypertriglyceridemia[§], hyperuricemia, increased appetite |
| **Psychiatric disorders[§]** | |
| Very common: | Depression, emotional lability, insomnia |
| Common: | Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy |
| **Nervous system disorders[§]** | |
| Very common: | Headache, dizziness |
| Common: | Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence |
| **Eye disorders** | |
| Common: | Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder |
| **Vascular disorders** | |
| Common: | Raynaud's disease, flushing, pallor |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing |
| **Gastrointestinal disorders** | |

| | |
|---|---|
| Very common:<br>Common: | Diarrhoea, vomiting, nausea, abdominal pain<br>Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder |
| **Hepatobiliary disorders**<br>Common: | Hepatic function abnormal |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common: | Alopecia, rash<br>Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased |
| **Musculoskeletal and connective tissue disorders**<br>Very common: | Arthralgia, myalgia, musculoskeletal pain |
| **Renal and urinary disorders**<br>Common: | Enuresis, micturition disorder, urinary incontinence |
| **Reproductive system and breast disorders**<br>Common: | Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder<br>Male: testicular pain |
| **General disorders and administration site conditions**<br>Very common:<br><br>Common: | Injection site inflammation, injection site reaction, fatigue, rigors, fever[§], influenza-like symptoms[§], malaise, irritability<br>Chest pain, asthenia, oedema, injection site pain |
| **Investigations**<br>Very common: | Growth rate decrease (height and/or weight decrease for age)[§] |
| **Injury and poisoning**<br>Common: | Skin laceration |

[§]See section 4.4

### 4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, cytokines and immunomodulators, interferons, interferon alfa-2b, ATC code: L03A B05

Viraferon is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of Viraferon is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $l0^8$ IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. Viraferon has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B:
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/$m^2$ 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C:
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

Adult patients: Viraferon alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of Viraferon used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/ml), a liver biopsy consistent with

a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Viraferon was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with Viraferon alone or in combination with ribavirin (from two studies) are shown in **Table 3**.

Co-administration of Viraferon with ribavirin increased the efficacy of Viraferon by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of Viraferon + ribavirin, compared with Viraferon alone, is maintained across all subgroups. The relative benefit of combination therapy with Viraferon + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received Viraferon in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

| **Table 3** Sustained virologic response rates with Viraferon + ribavirin (one year of treatment) by genotype and viral load | | | |
|---|---|---|---|
| **HCV Genotype** | **I**<br>**N=503**<br>**C95-132/I95-143** | **I/R**<br>**N=505**<br>**C95-132/I95-143** | **I/R**<br>**N=505**<br>**C/I98-580** |
| **All Genotypes** | **16 %** | **41 %** | **47 %** |
| **Genotype 1** | 9 % | 29 % | 33 % |
| Genotype 1<br>≤ 2 million copies/ml | 25 % | 33 % | 45 % |
| Genotype 1<br>> 2 million copies/ml | 3 % | 27 % | 29 % |
| **Genotype 2/3** | 31 % | 65 % | 79 % |

I Viraferon (3 MIU 3 times a week)
I/R Viraferon (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

*HCV/HIV Co-infected patients*
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received Viraferon plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or Viraferon (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or Viraferon (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

| **Table 4** | Sustained virological response based on genotype after Viraferon in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients | | | | | |
|---|---|---|---|---|---|---|
| | **Study 1**[1] | | | **Study 2**[2] | | |
| | pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg) | Viraferon (3 MIU TIW) + ribavirin (800 mg) | p value[a] | pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Viraferon (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients: A total of 345 interferon alpha relapse patients were treated in two clinical trials with Viraferon monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to Viraferon increased by as much as 10-fold the efficacy of Viraferon used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/ml by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non pegylated interferon alfa-2b or non pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Clinical trials in paediatric patients with chronic hepatitis C:
Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received Viraferon 3 MIU/$m^2$ 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. Sustained virological response rates in children and adolescents

were similar to those in adults. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

| **Table 5.** Virological response in previously untreated paediatric patients | |
|---|---|
| | **Viraferon 3 MIU/m$^2$** 3 times a week<br>+<br>**ribavirin 15 mg/kg/day** |
| Overall Response[1] (n=118) | 54 (46 %)* |
| Genotype 1 (n=92) | 33 (36 %)* |
| Genotype 2/3/4 (n=26) | 21 (81 %)* |

*Number (%) of patients
1. Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

## 5.2 Pharmacokinetic properties

The pharmacokinetics of Viraferon were studied in healthy volunteers following single 5 million IU/m$^2$ and 10 million IU doses administered subcutaneously, at 5 million IU/m$^2$ administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. $C_{max}$ occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/ml) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

*Children and adolescents*: Multiple-dose pharmacokinetic properties for Viraferon injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 6**. The pharmacokinetics of Viraferon and ribavirin (dose-normalized) are similar in adults and children or adolescents.

| **Table 6.** Mean (% CV) multiple-dose pharmacokinetic parameters for Viraferon and ribavirin capsules when administered to children or adolescents with chronic hepatitis C | | |
|---|---|---|
| **Parameter** | **Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17) | **Viraferon** 3 MIU/$m^2$ 3 times a week (n = 54) |
| $T_{max}$ (hr) | 1.9 (83) | 5.9 (36) |
| $C_{max}$ (ng/ml) | 3,275 (25) | 51 (48) |
| AUC* | 29,774 (26) | 622 (48) |
| Apparent clearance l/hr/kg | 0.27 (27) | Not done |

*$AUC_{12}$ (ng.hr/ml) for ribavirin; $AUC_{0-24}$ (IU.hr/ml) for Viraferon

Interferon neutralising factor assays were performed on serum samples of patients who received Viraferon in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

### 5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x $10^6$ IU/kg/day for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x $10^6$ IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour (see section 4.4 and Rebetol SPC if Viraferon is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Glycine,
Disodium phosphate anhydrous,

Sodium dihydrogen phosphate monohydrate,
Human albumin solution.

Solvent: water for injections

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

3 years

After reconstitution: An immediate use is recommended. However, the chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Within its shelf-life, for the purpose of transport and/or to facilitate ambulatory use the non-reconstituted product can be kept at or below 25°C for a period up to four weeks before use. If the product is not reconstituted during the four-week period, it cannot be put back in the refrigerator for a new storage period and must be discarded.

### 6.5 Nature and contents of container

24 mg of powder (corresponding to 1 MIU) in a vial (type I glass), with a stopper (butyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene)
and 1 ml water for injections in an ampoule (type I glass)
with 1 injection syringe, 2 injection needles and 1 cleansing swab.
Pack sizes of 1.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

Reconstitution of Viraferon, powder for solution for injection, for parenteral administration: Viraferon is supplied as a powder at strengths of 1 million IU/ml for single-dose use. Vials must be reconstituted with 1 ml of water for injections. The reconstituted solutions are isotonic for parenteral administration.

Proper precautions should be taken during reconstitution to prevent microbial contamination (refer to package leaflet).

Using a sterilised injection syringe and injection needle, inject 1 ml water for injections into the vial of Viraferon. Agitate gently to facilitate complete dissolution of the powder. The appropriate dose can then be withdrawn with a sterile injection syringe and injected.

As for all parenteral medicinal products, inspect the reconstituted solution visually for particulate matter and discoloration prior to administration. The reconstituted solution should be clear and colourless.

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to "How to self inject Viraferon").

Any unused product must be discarded after withdrawal of the dose.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBER

EU/1/99/128/001

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 9 March 2000
Date of last renewal : 23 May 2005

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 3 million IU/ml powder and solvent for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 3 million IU of interferon alfa-2b produced in *E.coli* by recombinant DNA technology.
After reconstitution, 1 ml contains 3 million IU of interferon alfa-2b.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

White to cream coloured powder.
Clear and colourless solvent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C:
*Adult patients:*
Viraferon is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section 4.4).

The best way to use Viraferon in this indication is in combination with ribavirin.

*Chidren and adolescents:*
Viraferon is intended for use, in a combination regimen with ribavirin, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials (see sections 4.4, 4.8 and 5.1).

### 4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

If adverse events develop during the course of treatment with Viraferon for any indication, modify the dosage or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dosage adjustment, or disease progresses, discontinue treatment with Viraferon. At the discretion of the physician, the patient may self-administer the dose for maintenance dosage regimens administered subcutaneously.

*Chronic Hepatitis B*: The recommended dosage is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/$mm^3$, granulocytes < 1,000/$mm^3$, thrombocytes < 100,000/$mm^3$). Treatment should be discontinued in case of severe leukopaenia (< 1,200/$mm^3$), severe neutropaenia (< 750/$mm^3$) or severe thrombocytopaenia (< 70,000/$mm^3$).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue Viraferon therapy.

*Chronic Hepatitis C*: Viraferon is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

*Children 3 years of age or older and adolescents*: Interferon alfa-2b 3 MIU/$m^2$ is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsule SPC for dose of ribavirin capsules and dosage modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC).

Relapse patients (adults):
Viraferon is given in combination with ribavirin.

Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for 6 months.

Naïve patients:
*Adults:* The efficacy of Viraferon is enhanced when given in combination with ribavirin. Viraferon should be given alone mainly in case of intolerance or contraindication to ribavirin.

Viraferon in combination with ribavirin:
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Viraferon alone:

The optimal duration of therapy with Viraferon alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with Viraferon alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

*Children and adolescents:* The efficacy and safety of Viraferon in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Virological response is defined as absence of detectable HCV-RNA at Week 12. Treatment should be discontinued in these patients.
Genotype 2/3: The recommended duration of treatment is 24 weeks.

Virological responses after 1 year of treatment and 6 months of follow-up were 36 % for genotype 1 and 81 % for genotype 2/3/4.

Viraferon may be administered using either glass or plastic disposable injection syringes.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.

Children and adolescents:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin: Also see ribavirin SPC if interferon alfa-2b is to be administered in combination with ribavirin in patients with chronic hepatitis C.

**4.4 Special warnings and precautions for use**

*For all patients:*

Psychiatric and central nervous system (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Viraferon therapy, and even after treatment discontinuation mainly during the 6-month follow-up periodand in the follow-up period. Among children and adolescents treated with Viraferon in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others), confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric

symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Viraferon be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of or history of severe psychiatric conditions:*
If a treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases, termination of Viraferon therapy. Any patient developing liver function abnormalities during treatment with Viraferon must be monitored closely and treatment discontinued if signs and symptoms progress.

Hypotension may occur during Viraferon therapy or up to two days post-therapy and may require supportive treatment.

Adequate hydration must be maintained in patients undergoing Viraferon therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Viraferon must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instance after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with Viraferon, must have a prompt and complete eye examination. Periodic visual examinations during Viraferon therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of Viraferon should be considered in patients who develop new or worsening ophthalmological disorders.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of Viraferon.

Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require Viraferon therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of Viraferon therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of Viraferon in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Discontinue treatment with Viraferon in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decompensation.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived albumin.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

There are no reports of virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes.

It is strongly recommended that every time that Viraferon is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

<u>Chronic Hepatitis C:</u>
Combination therapy with ribavirin: Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy: Infrequently, adult patients treated for chronic hepatitis C with Viraferon developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using Viraferon therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which Viraferon may alter thyroid status is unknown. Prior to initiation of Viraferon therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of Viraferon therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, Viraferon treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of Viraferon therapy has not reversed thyroid dysfunction occurring during treatment (also see Children and adolescents, Thyroid monitoring).

*Supplemental monitoring specific for children and adolescents*

Thyroid Monitoring**:** Approximately 12 % of children treated with interferon alfa-2b and ribavirin developed increase in TSH. Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of Viraferon therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Growth and Development: During a 1-year course of therapy there was a decrease in the rate of linear growth (mean percentile decrease of 9 %) and a decrease in the rate of weight gain (mean percentile decrease of 13 %). A general reversal of these trends was noted during the 6 months follow-up post treatment. However, based on interim data from a long-term follow-up study, 12 (14 %) of 84 children had a > 15 percentile decrease in rate of linear growth, of whom 5 (6 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In addition, preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3). Therefore, the risk/benefit of the combined use of interferon alfa-2b and ribavirin should be assessed in young children prior to the initiation of therapy. Physicians are advised to monitor the growth of children taking ribavirin in combination with interferon alfa-2b. There are no data on long term effects on growth and development and on sexual maturation.

HCV/HIV Coinfection: Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Viraferon and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders**:** Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Viraferon and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests:
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with Viraferon.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during Viraferon therapy to greater than or equal to 2 times baseline, Viraferon therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, liver function tests: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin must be monitored at two-week intervals.

Effect on fertility: Interferon may impair fertility (see section 4.6 and section 5.3).

## 4.5 Interaction with other medicinal products and other forms of interaction

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with Viraferon.

Interactions between Viraferon and other medicinal products have not been fully evaluated. Caution must be exercised when administering Viraferon in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dosage adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

(Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C).

## 4.6 Pregnancy and lactation

Women of childbearing potential have to use effective contraception during treatment. Viraferon must be used with caution in fertile men. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Viraferon is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

Combination therapy with ribavirin: Ribavirin causes serious birth defects when administered during pregnancy. Ribavirin therapy is contraindicated in women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking Viraferon in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must

each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

### 4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with Viraferon, and therefore it is recommended that they avoid driving or operating machinery.

### 4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/$m^2$/week in hairy cell leukaemia up to 100 MIU/$m^2$/week in melanoma), the most commonly reported undesirable effects were fever, fatigue, headache and myalgia. Fever and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

In clinical trials conducted in the hepatitis C population, patients were treated with Viraferon alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of Viraferon three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10); rarely (≥1/10,000, <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1.** Adverse reactions reported during clinical trials or following the marketing use of Viraferon alone or in combination with ribavirin

| System Organ Class | Adverse Reactions |
|---|---|
| **Infections and infestations** | |
| Very common: | Pharyngitis*, infection viral* |
| Common: | Bronchitis, sinusitis, herpes simplex (resistance), rhinitis |
| Rarely: | Pneumonia[§] |
| **Blood and lymphatic system disorders** | |
| Very common: | Leukopaenia |
| Common: | Thrombocytopaenia, lymphadenopathy, lymphopenia |
| Very rarely: | Aplastic anaemia |
| Not known**:** | Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura |
| **Immune system disorders**[§] | |
| Very rarely: | Sarcoidosis, exacerbation of sarcoidosis |
| Not known: | Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis[§] |
| **Endocrine disorders** | |
| Common: | Hypothyroidism[§], hyperthyroidism[§] |
| Very rarely: | Diabetes, aggravated diabetes |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcaemia, dehydration, hyperuricemia, thirst |
| Very rarely: | Hyperglycaemia, hypertriglyceridaemia[§], increased appetite |
| **Psychiatric disorders**[§] | |

| | |
|---|---|
| Very common: | Depression, insomnia, anxiety, emotional lability*, agitation, nervousness |
| Common: | Confusion, sleep disorder, libido decreased |
| Rarely: | Suicide ideation |
| Very rarely: | Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations |
| Not known: | Mental status change[§] |
| **Nervous system disorders**[§] | |
| Very common: | Dizziness, headache, concentration impaired, mouth dry |
| Common: | Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion |
| Very rarely: | Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy, neuropathy, polyneuropathy |
| Not known: | Mononeuropathies, coma[§] |
| **Eye disorders** | |
| Very common: | Vision blurred |
| Common: | Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain |
| Rarely: | Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§] |
| **Ear and labyrinth** | |
| Common: | Vertigo, tinnitus |
| Very rarely: | Hearing loss, hearing disorder |
| **Cardiac disorders** | |
| Common: | Palpitation, tachycardia |
| Rarely: | Cardiomyopathy |
| Very rarely: | Myocardial infarction, cardiac ischaemia |
| Not known: | Arrhythmia |
| **Vascular disorders** | |
| Common: | Hypertension |
| Very rarely: | Peripheral ischaemia, hypotension[§] |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common: | Dyspnoea*, coughing* |
| Common: | Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive |
| Very rarely: | Pulmonary infiltrates[§], pneumonitis[§] |
| **Gastrointestinal disorders** | |
| Very common: | Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia |
| Common: | Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools |
| Very rarely: | Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding |
| Not known: | Periodontal disorder NOS, dental disorder NOS[§] |
| **Hepatobiliary disorders** | |
| Common: | Hepatomegaly |
| Very rarely: | Hepatotoxicity, (including fatality) |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, pruritus*, skin dry*, rash*, sweating increased |
| Common: | Psoriasis (new or aggravated)[§], rash maculopapular, rash |

| | |
|---|---|
| Very rarely: | erythematous, eczema, erythema, skin disorder<br>Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders**<br>Very common:<br>Common:<br>Very rarely: | <br>Myalgia, arthralgia, musculoskeletal pain<br>Arthritis<br>Rhabdomyolysis, myositis, leg cramps, back pain |
| **Renal and urinary disorders**<br>Common:<br>Very rarely: | <br>Micturition frequency<br>Renal failure, renal insufficiency, nephrotic syndrome |
| **Reproductive system and breast disorders**<br>Common: | <br>Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder |
| **General disorders and administration site conditions**<br>Very common:<br><br><br>Common:<br>Very rarely: | <br>Injection site inflammation, injection site reaction*, fatigue, rigors, fever§, flu-like symptoms§, asthenia, irritability, chest pain, malaise<br>Injection site pain<br>Injection site necrosis, face oedema |
| **Investigations**<br>Very common: | <br>Weight decrease |

*These events were only common with Viraferon alone
§See section 4.4

These undesirable effects have also been reported with Viraferon alone.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

For safety with respect to transmissible agents, see section 4.4.

**Paediatric population**

*Children and adolescents – Chronic Hepatitis C*
In clinical trials of 118 children or adolescents 3 to 16 years of age, 6 % discontinued therapy due to adverse events. In general, the adverse event profile in the limited paediatric population studied was similar to that observed in adults, although there is a paediatric specific concern regarding growth inhibition as decrease in height (mean percentile decrease of growth velocity of 9 %) and weight (mean percentile decrease of 13 %)

percentile were observed during treatment (see section 4.4). Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from paediatric clinical trials.
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 2** Adverse reactions very commonly and commonly reported in paediatric clinical trials
Very common (≥1/10) - Common (≥1/100, <1/10)

| System Organ Class | Adverse Reactions |
|---|---|
| **Infection and infestations** | |
| Very common: | Viral infection, pharyngitis |
| Common: | Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | |
| Common: | Neoplasm (unspecified) |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, neutropaenia |
| Common: | Thrombocytopaenia, lymphadenopathy |
| **Endocrine disorders** | |
| Very common: | Hypothyroidism[§], |
| Common: | Hyperthyroidism[§], virilism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypertriglyceridemia[§], hyperuricemia, increased appetite |
| **Psychiatric disorders**[§] | |
| Very common: | Depression, emotional lability, insomnia |
| Common: | Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy |
| **Nervous system disorders**[§] | |
| Very common: | Headache, dizziness |
| Common: | Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence |
| **Eye disorders** | |
| Common: | Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder |
| **Vascular disorders** | |
| Common: | Raynaud's disease, flushing, pallor |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing |
| **Gastrointestinal disorders** | |

| | |
|---|---|
| Very common:<br>Common: | Diarrhoea, vomiting, nausea, abdominal pain<br>Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder |
| **Hepatobiliary disorders**<br>Common: | Hepatic function abnormal |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common: | Alopecia, rash<br>Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased |
| **Musculoskeletal and connective tissue disorders**<br>Very common: | Arthralgia, myalgia, musculoskeletal pain |
| **Renal and urinary disorders**<br>Common: | Enuresis, micturition disorder, urinary incontinence |
| **Reproductive system and breast disorders**<br>Common: | Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder<br>Male: testicular pain |
| **General disorders and administration site conditions**<br>Very common:<br><br>Common: | Injection site inflammation, injection site reaction, fatigue, rigors, fever[§], influenza-like symptoms[§], malaise, irritability<br>Chest pain, asthenia, oedema, injection site pain |
| **Investigations**<br>Very common: | Growth rate decrease (height and/or weight decrease for age)[§] |
| **Injury and poisoning**<br>Common: | Skin laceration |

[§]See section 4.4

### 4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, cytokines and immunomodulators, interferons, interferon alfa-2b, ATC code: L03A B05

Viraferon is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of Viraferon is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $l0^8$ IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. Viraferon has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B:
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/$m^2$ 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C:
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

Adult patients: Viraferon alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of Viraferon used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/ml), a liver biopsy consistent with

a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Viraferon was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with Viraferon alone or in combination with ribavirin (from two studies) are shown in **Table 3**.

Co-administration of Viraferon with ribavirin increased the efficacy of Viraferon by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of Viraferon + ribavirin, compared with Viraferon alone, is maintained across all subgroups. The relative benefit of combination therapy with Viraferon + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received Viraferon in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

| **Table 3** Sustained virologic response rates with Viraferon + ribavirin (one year of treatment) by genotype and viral load | | | |
|---|---|---|---|
| **HCV Genotype** | **I**<br>**N=503**<br>**C95-132/I95-143** | **I/R**<br>**N=505**<br>**C95-132/I95-143** | **I/R**<br>**N=505**<br>**C/I98-580** |
| **All Genotypes** | **16 %** | **41 %** | **47 %** |
| **Genotype 1** | 9 % | 29 % | 33 % |
| Genotype 1<br>≤ 2 million copies/ml | 25 % | 33 % | 45 % |
| Genotype 1<br>> 2 million copies/ml | 3 % | 27 % | 29 % |
| **Genotype 2/3** | 31 % | 65 % | 79 % |

I Viraferon (3 MIU 3 times a week)
I/R Viraferon (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

*HCV/HIV Co-infected patients*
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received Viraferon plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.**
Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or Viraferon (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or Viraferon (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

| **Table 4** | Sustained virological response based on genotype after Viraferon in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients | | | | | |
|---|---|---|---|---|---|---|
| | **Study 1**[1] | | | **Study 2**[2] | | |
| | pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg) | Viraferon (3 MIU TIW) + ribavirin (800 mg) | p value[a] | pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Viraferon (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients: A total of 345 interferon alpha relapse patients were treated in two clinical trials with Viraferon monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to Viraferon increased by as much as 10-fold the efficacy of Viraferon used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/ml by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non pegylated interferon alfa-2b or non pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Clinical trials in paediatric patients with chronic hepatitis C:
Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received Viraferon 3 MIU/$m^2$ 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. Sustained virological response rates in children and adolescents

were similar to those in adults. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

| **Table 5.** Virological response in previously untreated paediatric patients | |
|---|---|
| | **Viraferon 3 MIU/m$^2$** 3 times a week<br>+<br>**ribavirin 15 mg/kg/day** |
| Overall Response[1] (n=118) | 54 (46 %)* |
| Genotype 1 (n=92) | 33 (36 %)* |
| Genotype 2/3/4 (n=26) | 21 (81 %)* |

*Number (%) of patients
1. Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

## 5.2 Pharmacokinetic properties

The pharmacokinetics of Viraferon were studied in healthy volunteers following single 5 million IU/m$^2$ and 10 million IU doses administered subcutaneously, at 5 million IU/m$^2$ administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. $C_{max}$ occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/ml) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

*Children and adolescents*: Multiple-dose pharmacokinetic properties for Viraferon injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 6**. The pharmacokinetics of Viraferon and ribavirin (dose-normalized) are similar in adults and children or adolescents.

| **Table 6.** Mean (% CV) multiple-dose pharmacokinetic parameters for Viraferon and ribavirin capsules when administered to children or adolescents with chronic hepatitis C | | |
|---|---|---|
| **Parameter** | **Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17) | **Viraferon** 3 MIU/$m^2$ 3 times a week (n = 54) |
| $T_{max}$ (hr) | 1.9 (83) | 5.9 (36) |
| $C_{max}$ (ng/ml) | 3,275 (25) | 51 (48) |
| AUC* | 29,774 (26) | 622 (48) |
| Apparent clearance l/hr/kg | 0.27 (27) | Not done |

*$AUC_{12}$ (ng.hr/ml) for ribavirin; $AUC_{0-24}$ (IU.hr/ml) for Viraferon

Interferon neutralising factor assays were performed on serum samples of patients who received Viraferon in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

### 5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x $10^6$ IU/kg/day for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x $10^6$ IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour (see section 4.4 and Rebetol SPC if Viraferon is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Glycine,
Disodium phosphate anhydrous,

Sodium dihydrogen phosphate monohydrate,
Human albumin solution.

Solvent: water for injections

## 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

## 6.3 Shelf life

3 years

After reconstitution: An immediate use is recommended. However, the chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC.

## 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Within its shelf-life, for the purpose of transport and/or to facilitate ambulatory use the non-reconstituted product can be kept at or below 25°C for a period up to four weeks before use. If the product is not reconstituted during the four-week period, it cannot be put back in the refrigerator for a new storage period and must be discarded.

## 6.5 Nature and contents of container

24 mg of powder (corresponding to 3 MIU) in a vial (type I glass), with a stopper (butyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene)
and 1 ml of water for injections in an ampoule (type I glass)
with 1 injection syringe, 2 injection needles and 1 cleansing swab.
Pack sizes of 1

Or

24 mg of powder (corresponding to 3 MIU) in a vial (type I glass), with a stopper (butyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene)
and 1 ml of water for injections in an ampoule (type I glass)
Pack sizes of 6
Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

Reconstitution of Viraferon, powder for solution for injection, for parenteral administration: Viraferon is supplied as a powder at strengths of 3 million IU/ml for single-dose use. Vials must be reconstituted with 1 ml of water for injections. The reconstituted solutions are isotonic for parenteral administration.

Proper precautions should be taken during reconstitution to prevent microbial contamination (refer to package leaflet).

Using a sterilised injection syringe and injection needle, inject 1 ml water for injections into the vial of Viraferon. Agitate gently to facilitate complete dissolution of the powder. The appropriate dose can then be withdrawn with a sterile injection syringe and injected.

As for all parenteral medicinal products, inspect the reconstituted solution visually for particulate matter and discoloration prior to administration. The reconstituted solution should be clear and colourless.

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to "How to self inject Viraferon").

Any unused product must be discarded after withdrawal of the dose.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/99/128/002
EU/1/99/128/003

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 9 March 2000
Date of last renewal : 23 May 2005

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 5 million IU/ml powder and solvent for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 5 million IU of interferon alfa-2b produced in *E.coli* by recombinant DNA technology.
After reconstitution, 1 ml contains 5 million IU of interferon alfa-2b.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

White to cream coloured powder.
Clear and colourless solvent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C:
*Adult patients:*
Viraferon is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section 4.4).

The best way to use Viraferon in this indication is in combination with ribavirin.

*Chidren and adolescents:*
Viraferon is intended for use, in a combination regimen with ribavirin, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials (see sections 4.4, 4.8 and 5.1).

### 4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

If adverse events develop during the course of treatment with Viraferon for any indication, modify the dosage or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dosage adjustment, or disease progresses, discontinue treatment with Viraferon. At the discretion of the physician, the patient may self-administer the dose for maintenance dosage regimens administered subcutaneously.

*Chronic Hepatitis B*: The recommended dosage is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/$mm^3$, granulocytes < 1,000/$mm^3$, thrombocytes < 100,000/$mm^3$). Treatment should be discontinued in case of severe leukopaenia (< 1,200/$mm^3$), severe neutropaenia (< 750/$mm^3$) or severe thrombocytopaenia (< 70,000/$mm^3$).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue Viraferon therapy.

*Chronic Hepatitis C*: Viraferon is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

*Children 3 years of age or older and adolescents*: Interferon alfa-2b 3 MIU/$m^2$ is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsule SPC for dose of ribavirin capsules and dosage modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC).

Relapse patients (adults):
Viraferon is given in combination with ribavirin.

Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for 6 months.

Naïve patients:
*Adults:* The efficacy of Viraferon is enhanced when given in combination with ribavirin. Viraferon should be given alone mainly in case of intolerance or contraindication to ribavirin.

Viraferon in combination with ribavirin:
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Viraferon alone:

The optimal duration of therapy with Viraferon alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with Viraferon alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

*Children and adolescents:* The efficacy and safety of Viraferon in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Virological response is defined as absence of detectable HCV-RNA at Week 12. Treatment should be discontinued in these patients.
Genotype 2/3: The recommended duration of treatment is 24 weeks.

Virological responses after 1 year of treatment and 6 months of follow-up were 36 % for genotype 1 and 81 % for genotype 2/3/4.

Viraferon may be administered using either glass or plastic disposable injection syringes.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.

Children and adolescents:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin: Also see ribavirin SPC if interferon alfa-2b is to be administered in combination with ribavirin in patients with chronic hepatitis C.

**4.4 Special warnings and precautions for use**

*For all patients:*

Psychiatric and central nervous system (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Viraferon therapy, and even after treatment discontinuation mainly during the 6-month follow-up periodand in the follow-up period. Among children and adolescents treated with Viraferon in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others), confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric

symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Viraferon be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of or history of severe psychiatric conditions:*
If a treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases, termination of Viraferon therapy. Any patient developing liver function abnormalities during treatment with Viraferon must be monitored closely and treatment discontinued if signs and symptoms progress.

Hypotension may occur during Viraferon therapy or up to two days post-therapy and may require supportive treatment.

Adequate hydration must be maintained in patients undergoing Viraferon therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Viraferon must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instance after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with Viraferon, must have a prompt and complete eye examination. Periodic visual examinations during Viraferon therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of Viraferon should be considered in patients who develop new or worsening ophthalmological disorders.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of Viraferon.

Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require Viraferon therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of Viraferon therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of Viraferon in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Discontinue treatment with Viraferon in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decompensation.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived albumin.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

There are no reports of virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes.

It is strongly recommended that every time that Viraferon is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

<u>Chronic Hepatitis C:</u>
Combination therapy with ribavirin: Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy: Infrequently, adult patients treated for chronic hepatitis C with Viraferon developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using Viraferon therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which Viraferon may alter thyroid status is unknown. Prior to initiation of Viraferon therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of Viraferon therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, Viraferon treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of Viraferon therapy has not reversed thyroid dysfunction occurring during treatment (also see Children and adolescents, Thyroid monitoring).

*Supplemental monitoring specific for children and adolescents*

Thyroid Monitoring**:** Approximately 12 % of children treated with interferon alfa-2b and ribavirin developed increase in TSH. Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of Viraferon therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Growth and Development: During a 1-year course of therapy there was a decrease in the rate of linear growth (mean percentile decrease of 9 %) and a decrease in the rate of weight gain (mean percentile decrease of 13 %). A general reversal of these trends was noted during the 6 months follow-up post treatment. However, based on interim data from a long-term follow-up study, 12 (14 %) of 84 children had a > 15 percentile decrease in rate of linear growth, of whom 5 (6 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In addition, preclicinal juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3). Therefore, the risk/benefit of the combined use of interferon alfa-2b and ribavirin should be assessed in young children prior to the initiation of therapy. Physicians are advised to monitor the growth of children taking ribavirin in combination with interferon alfa-2b. There are no data on long term effects on growth and development and on sexual maturation.

HCV/HIV Coinfection**:** Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Viraferon and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders**:** Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Viraferon and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests:
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with Viraferon.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during Viraferon therapy to greater than or equal to 2 times baseline, Viraferon therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, liver function tests: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin must be monitored at two-week intervals.

Effect on fertility: Interferon may impair fertility (see section 4.6 and section 5.3).

## 4.5 Interaction with other medicinal products and other forms of interaction

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with Viraferon.

Interactions between Viraferon and other medicinal products have not been fully evaluated. Caution must be exercised when administering Viraferon in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dosage adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

(Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C).

## 4.6 Pregnancy and lactation

Women of childbearing potential have to use effective contraception during treatment. Viraferon must be used with caution in fertile men. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Viraferon is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

Combination therapy with ribavirin: Ribavirin causes serious birth defects when administered during pregnancy. Ribavirin therapy is contraindicated in women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking Viraferon in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must

each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

### 4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with Viraferon, and therefore it is recommended that they avoid driving or operating machinery.

### 4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/$m^2$/week in hairy cell leukaemia up to 100 MIU/$m^2$/week in melanoma), the most commonly reported undesirable effects were fever, fatigue, headache and myalgia. Fever and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

In clinical trials conducted in the hepatitis C population, patients were treated with Viraferon alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of Viraferon three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10); rarely (≥1/10,000, <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1.** Adverse reactions reported during clinical trials or following the marketing use of Viraferon alone or in combination with ribavirin

| System Organ Class | Adverse Reactions |
|---|---|
| **Infections and infestations** | |
| Very common: | Pharyngitis*, infection viral* |
| Common: | Bronchitis, sinusitis, herpes simplex (resistance), rhinitis |
| Rarely: | Pneumonia§ |
| **Blood and lymphatic system disorders** | |
| Very common: | Leukopaenia |
| Common: | Thrombocytopaenia, lymphadenopathy, lymphopenia |
| Very rarely: | Aplastic anaemia |
| Not known**:** | Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura |
| **Immune system disorders§** | |
| Very rarely: | Sarcoidosis, exacerbation of sarcoidosis |
| Not known: | Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis§ |
| **Endocrine disorders** | |
| Common: | Hypothyroidism§, hyperthyroidism§ |
| Very rarely: | Diabetes, aggravated diabetes |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcaemia, dehydration, hyperuricemia, thirst |
| Very rarely: | Hyperglycaemia, hypertriglyceridaemia§, increased appetite |
| **Psychiatric disorders§** | |

| | |
|---|---|
| Very common:<br><br>Common:<br>Rarely:<br>Very rarely:<br><br>Not known: | Depression, insomnia, anxiety, emotional lability*, agitation, nervousness<br>Confusion, sleep disorder, libido decreased<br>Suicide ideation<br>Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations<br>Mental status change[§] |
| **Nervous system disorders**[§]<br>Very common:<br>Common:<br><br>Very rarely:<br><br><br>Not known: | <br>Dizziness, headache, concentration impaired, mouth dry<br>Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion<br>Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy, neuropathy, polyneuropathy<br>Mononeuropathies, coma[§] |
| **Eye disorders**<br>Very common:<br>Common:<br><br>Rarely: | <br>Vision blurred<br>Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain<br>Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§] |
| **Ear and labyrinth**<br>Common:<br>Very rarely: | <br>Vertigo, tinnitus<br>Hearing loss, hearing disorder |
| **Cardiac disorders**<br>Common:<br>Rarely:<br>Very rarely:<br>Not known: | <br>Palpitation, tachycardia<br>Cardiomyopathy<br>Myocardial infarction, cardiac ischaemia<br>Arrhythmia |
| **Vascular disorders**<br>Common:<br>Very rarely: | <br>Hypertension<br>Peripheral ischaemia, hypotension[§] |
| **Respiratory, thoracic and mediastinal disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br><br>Dyspnoea*, coughing*<br>Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive<br>Pulmonary infiltrates[§], pneumonitis[§] |
| **Gastrointestinal disorders**<br>Very common:<br><br>Common:<br><br>Very rarely:<br><br>Not known: | <br>Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia<br>Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools<br>Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding<br>Periodontal disorder NOS, dental disorder NOS[§] |
| **Hepatobiliary disorders**<br>Common:<br>Very rarely: | <br>Hepatomegaly<br>Hepatotoxicity, (including fatality) |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common: | <br>Alopecia, pruritus*, skin dry*, rash*, sweating increased<br>Psoriasis (new or aggravated)[§], rash maculopapular, rash |

| | |
|---|---|
| Very rarely: | erythematous, eczema, erythema, skin disorder<br>Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders**<br>Very common:<br>Common:<br>Very rarely: | <br>Myalgia, arthralgia, musculoskeletal pain<br>Arthritis<br>Rhabdomyolysis, myositis, leg cramps, back pain |
| **Renal and urinary disorders**<br>Common:<br>Very rarely: | <br>Micturition frequency<br>Renal failure, renal insufficiency, nephrotic syndrome |
| **Reproductive system and breast disorders**<br>Common: | <br>Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder |
| **General disorders and administration site conditions**<br>Very common:<br><br><br>Common:<br>Very rarely: | <br>Injection site inflammation, injection site reaction*, fatigue, rigors, fever§, flu-like symptoms§, asthenia, irritability, chest pain, malaise<br>Injection site pain<br>Injection site necrosis, face oedema |
| **Investigations**<br>Very common: | <br>Weight decrease |

*These events were only common with Viraferon alone
§See section 4.4

These undesirable effects have also been reported with Viraferon alone.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

For safety with respect to transmissible agents, see section 4.4.

**Paediatric population**

*Children and adolescents – Chronic Hepatitis C*
In clinical trials of 118 children or adolescents 3 to 16 years of age, 6 % discontinued therapy due to adverse events. In general, the adverse event profile in the limited paediatric population studied was similar to that observed in adults, although there is a paediatric specific concern regarding growth inhibition as decrease in height (mean percentile decrease of growth velocity of 9 %) and weight (mean percentile decrease of 13 %)

percentile were observed during treatment (see section 4.4). Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from paediatric clinical trials.
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 2** Adverse reactions very commonly and commonly reported in paediatric clinical trials
Very common (≥1/10) - Common (≥1/100, <1/10)

| System Organ Class | Adverse Reactions |
|---|---|
| **Infection and infestations** | |
| Very common: | Viral infection, pharyngitis |
| Common: | Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | |
| Common: | Neoplasm (unspecified) |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, neutropaenia |
| Common: | Thrombocytopaenia, lymphadenopathy |
| **Endocrine disorders** | |
| Very common: | Hypothyroidism[§], |
| Common: | Hyperthyroidism[§], virilism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypertriglyceridemia[§], hyperuricemia, increased appetite |
| **Psychiatric disorders**[§] | |
| Very common: | Depression, emotional lability, insomnia |
| Common: | Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy |
| **Nervous system disorders**[§] | |
| Very common: | Headache, dizziness |
| Common: | Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence |
| **Eye disorders** | |
| Common: | Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder |
| **Vascular disorders** | |
| Common: | Raynaud's disease, flushing, pallor |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing |
| **Gastrointestinal disorders** | |

| | |
|---|---|
| Very common:<br>Common: | Diarrhoea, vomiting, nausea, abdominal pain<br>Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder |
| **Hepatobiliary disorders**<br>Common: | Hepatic function abnormal |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common: | Alopecia, rash<br>Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased |
| **Musculoskeletal and connective tissue disorders**<br>Very common: | Arthralgia, myalgia, musculoskeletal pain |
| **Renal and urinary disorders**<br>Common: | Enuresis, micturition disorder, urinary incontinence |
| **Reproductive system and breast disorders**<br>Common: | Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder<br>Male: testicular pain |
| **General disorders and administration site conditions**<br>Very common:<br><br>Common: | Injection site inflammation, injection site reaction, fatigue, rigors, fever[§], influenza-like symptoms[§], malaise, irritability<br>Chest pain, asthenia, oedema, injection site pain |
| **Investigations**<br>Very common: | Growth rate decrease (height and/or weight decrease for age)[§] |
| **Injury and poisoning**<br>Common: | Skin laceration |

[§]See section 4.4

### 4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, cytokines and immunomodulators, interferons, interferon alfa-2b, ATC code: L03A B05

Viraferon is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of Viraferon is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $l0^8$ IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. Viraferon has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B:
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/$m^2$ 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C:
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

Adult patients: Viraferon alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of Viraferon used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/ml), a liver biopsy consistent with

a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Viraferon was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with Viraferon alone or in combination with ribavirin (from two studies) are shown in **Table 3**.

Co-administration of Viraferon with ribavirin increased the efficacy of Viraferon by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of Viraferon + ribavirin, compared with Viraferon alone, is maintained across all subgroups. The relative benefit of combination therapy with Viraferon + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received Viraferon in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

| **Table 3** Sustained virologic response rates with Viraferon + ribavirin (one year of treatment) by genotype and viral load | | | |
|---|---|---|---|
| **HCV Genotype** | **I**<br>**N=503**<br>**C95-132/I95-143** | **I/R**<br>**N=505**<br>**C95-132/I95-143** | **I/R**<br>**N=505**<br>**C/I98-580** |
| **All Genotypes** | **16 %** | **41 %** | **47 %** |
| **Genotype 1** | 9 % | 29 % | 33 % |
| Genotype 1<br>≤ 2 million copies/ml | 25 % | 33 % | 45 % |
| Genotype 1<br>> 2 million copies/ml | 3 % | 27 % | 29 % |
| **Genotype 2/3** | 31 % | 65 % | 79 % |

I Viraferon (3 MIU 3 times a week)
I/R Viraferon (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

*HCV/HIV Co-infected patients*
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received Viraferon plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or Viraferon (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or Viraferon (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

| **Table 4** | Sustained virological response based on genotype after Viraferon in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients | | | | | |
|---|---|---|---|---|---|---|
| | **Study 1**[1] | | | **Study 2**[2] | | |
| | pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg) | Viraferon (3 MIU TIW) + ribavirin (800 mg) | p value[a] | pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Viraferon (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients: A total of 345 interferon alpha relapse patients were treated in two clinical trials with Viraferon monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to Viraferon increased by as much as 10-fold the efficacy of Viraferon used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/ml by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non pegylated interferon alfa-2b or non pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Clinical trials in paediatric patients with chronic hepatitis C:
Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received Viraferon 3 MIU/$m^2$ 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. Sustained virological response rates in children and adolescents

were similar to those in adults. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

| **Table 5.** Virological response in previously untreated paediatric patients | |
|---|---|
| | **Viraferon 3 MIU/m$^2$** 3 times a week<br>+<br>**ribavirin 15 mg/kg/day** |
| Overall Response[1] (n=118) | 54 (46 %)* |
| Genotype 1 (n=92) | 33 (36 %)* |
| Genotype 2/3/4 (n=26) | 21 (81 %)* |

*Number (%) of patients
1. Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

## 5.2 Pharmacokinetic properties

The pharmacokinetics of Viraferon were studied in healthy volunteers following single 5 million IU/m$^2$ and 10 million IU doses administered subcutaneously, at 5 million IU/m$^2$ administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. $C_{max}$ occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/ml) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

*Children and adolescents*: Multiple-dose pharmacokinetic properties for Viraferon injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 6**. The pharmacokinetics of Viraferon and ribavirin (dose-normalized) are similar in adults and children or adolescents.

| **Table 6.** Mean (% CV) multiple-dose pharmacokinetic parameters for Viraferon and ribavirin capsules when administered to children or adolescents with chronic hepatitis C | | |
|---|---|---|
| **Parameter** | **Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17) | **Viraferon** 3 MIU/$m^2$ 3 times a week (n = 54) |
| $T_{max}$ (hr) | 1.9 (83) | 5.9 (36) |
| $C_{max}$ (ng/ml) | 3,275 (25) | 51 (48) |
| AUC* | 29,774 (26) | 622 (48) |
| Apparent clearance l/hr/kg | 0.27 (27) | Not done |

*$AUC_{12}$ (ng.hr/ml) for ribavirin; $AUC_{0-24}$ (IU.hr/ml) for Viraferon

Interferon neutralising factor assays were performed on serum samples of patients who received Viraferon in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

### 5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x $10^6$ IU/kg/day for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x $10^6$ IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour (see section 4.4 and Rebetol SPC if Viraferon is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Glycine,
Disodium phosphate anhydrous,

Sodium dihydrogen phosphate monohydrate,
Human albumin solution.

Solvent: water for injections

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

3 years

After reconstitution: An immediate use is recommended. However, the chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Within its shelf-life, for the purpose of transport and/or to facilitate ambulatory use the non-reconstituted product can be kept at or below 25°C for a period up to four weeks before use. If the product is not reconstituted during the four-week period, it cannot be put back in the refrigerator for a new storage period and must be discarded.

### 6.5 Nature and contents of container

24 mg of powder (corresponding to 5 MIU) in a vial (type I glass), with a stopper (butyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene)
and 1 ml water for injections in an ampoule (type I glass)
with 1 injection syringe, 2 injection needles and 1 cleansing swab.
Pack sizes of 1

Or

24 mg of powder (corresponding to 5 MIU) in a vial (type I glass), with a stopper (butyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene)
and 1 ml water for injections in an ampoule (type I glass)
Pack sizes of 6
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

Reconstitution of Viraferon, powder for solution for injection, for parenteral administration: Viraferon is supplied as a powder at strengths of 5 million IU/ml for single-dose use. Vials must be reconstituted with 1 ml of water for injections. The reconstituted solutions are isotonic for parenteral administration.

Proper precautions should be taken during reconstitution to prevent microbial contamination (refer to package leaflet).

Using a sterilised injection syringe and injection needle, inject 1 ml water for injections into the vial of Viraferon. Agitate gently to facilitate complete dissolution of the powder. The appropriate dose can then be withdrawn with a sterile injection syringe and injected.

As for all parenteral medicinal products, inspect the reconstituted solution visually for particulate matter and discoloration prior to administration. The reconstituted solution should be clear and colourless.

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to "How to self inject Viraferon").

Any unused product must be discarded after withdrawal of the dose.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/99/128/004
EU/1/99/128/005

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 9 March 2000
Date of last renewal : 23 May 2005

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 10 million IU/ml powder and solvent for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 10 million IU of interferon alfa-2b produced in *E.coli* by recombinant DNA technology.
After reconstitution, 1 ml contains 10 million IU of interferon alfa-2b.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

White to cream coloured powder.
Clear and colourless solvent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C:
*Adult patients:*
Viraferon is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section 4.4).

The best way to use Viraferon in this indication is in combination with ribavirin.

*Chidren and adolescents:*
Viraferon is intended for use, in a combination regimen with ribavirin, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials (see sections 4.4, 4.8 and 5.1).

### 4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

If adverse events develop during the course of treatment with Viraferon for any indication, modify the dosage or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dosage adjustment, or disease progresses, discontinue treatment with Viraferon. At the discretion of the physician, the patient may self-administer the dose for maintenance dosage regimens administered subcutaneously.

*Chronic Hepatitis B*: The recommended dosage is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/$mm^3$, granulocytes < 1,000/$mm^3$, thrombocytes < 100,000/$mm^3$). Treatment should be discontinued in case of severe leukopaenia (< 1,200/$mm^3$), severe neutropaenia (< 750/$mm^3$) or severe thrombocytopaenia (< 70,000/$mm^3$).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue Viraferon therapy.

*Chronic Hepatitis C*: Viraferon is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

*Children 3 years of age or older and adolescents*: Interferon alfa-2b 3 MIU/$m^2$ is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsule SPC for dose of ribavirin capsules and dosage modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC).

Relapse patients (adults):
Viraferon is given in combination with ribavirin.

Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for 6 months.

Naïve patients:
*Adults:* The efficacy of Viraferon is enhanced when given in combination with ribavirin. Viraferon should be given alone mainly in case of intolerance or contraindication to ribavirin.

Viraferon in combination with ribavirin:
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Viraferon alone:

The optimal duration of therapy with Viraferon alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with Viraferon alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

*Children and adolescents:* The efficacy and safety of Viraferon in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Virological response is defined as absence of detectable HCV-RNA at Week 12. Treatment should be discontinued in these patients.
Genotype 2/3: The recommended duration of treatment is 24 weeks.

Virological responses after 1 year of treatment and 6 months of follow-up were 36 % for genotype 1 and 81 % for genotype 2/3/4.

Viraferon may be administered using either glass or plastic disposable injection syringes.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.

Children and adolescents:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin: Also see ribavirin SPC if interferon alfa-2b is to be administered in combination with ribavirin in patients with chronic hepatitis C.

**4.4 Special warnings and precautions for use**

*For all patients:*

Psychiatric and central nervous system (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Viraferon therapy, and even after treatment discontinuation mainly during the 6-month follow-up periodand in the follow-up period. Among children and adolescents treated with Viraferon in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others), confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric

symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Viraferon be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of or history of severe psychiatric conditions:*
If a treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases, termination of Viraferon therapy. Any patient developing liver function abnormalities during treatment with Viraferon must be monitored closely and treatment discontinued if signs and symptoms progress.

Hypotension may occur during Viraferon therapy or up to two days post-therapy and may require supportive treatment.

Adequate hydration must be maintained in patients undergoing Viraferon therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Viraferon must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instance after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with Viraferon, must have a prompt and complete eye examination. Periodic visual examinations during Viraferon therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of Viraferon should be considered in patients who develop new or worsening ophthalmological disorders.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of Viraferon.

Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require Viraferon therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of Viraferon therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of Viraferon in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Discontinue treatment with Viraferon in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decompensation.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived albumin.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

There are no reports of virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes.

It is strongly recommended that every time that Viraferon is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

<u>Chronic Hepatitis C:</u>
Combination therapy with ribavirin: Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy: Infrequently, adult patients treated for chronic hepatitis C with Viraferon developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using Viraferon therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which Viraferon may alter thyroid status is unknown. Prior to initiation of Viraferon therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of Viraferon therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, Viraferon treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of Viraferon therapy has not reversed thyroid dysfunction occurring during treatment (also see Children and adolescents, Thyroid monitoring).

*Supplemental monitoring specific for children and adolescents*
Thyroid Monitoring: Approximately 12 % of children treated with interferon alfa-2b and ribavirin developed increase in TSH. Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of Viraferon therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Growth and Development: During a 1-year course of therapy there was a decrease in the rate of linear growth (mean percentile decrease of 9 %) and a decrease in the rate of weight gain (mean percentile decrease of 13 %). A general reversal of these trends was noted during the 6 months follow-up post treatment. However, based on interim data from a long-term follow-up study, 12 (14 %) of 84 children had a > 15 percentile decrease in rate of linear growth, of whom 5 (6 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In addition, preclicinal juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3). Therefore, the risk/benefit of the combined use of interferon alfa-2b and ribavirin should be assessed in young children prior to the initiation of therapy. Physicians are advised to monitor the growth of children taking ribavirin in combination with interferon alfa-2b. There are no data on long term effects on growth and development and on sexual maturation.

HCV/HIV Coinfection**:** Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Viraferon and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders**:** Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Viraferon and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests:
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with Viraferon.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during Viraferon therapy to greater than or equal to 2 times baseline, Viraferon therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, liver function tests: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin must be monitored at two-week intervals.

Effect on fertility: Interferon may impair fertility (see section 4.6 and section 5.3).

**4.5 Interaction with other medicinal products and other forms of interaction**

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with Viraferon.

Interactions between Viraferon and other medicinal products have not been fully evaluated. Caution must be exercised when administering Viraferon in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dosage adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

(Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C).

**4.6 Pregnancy and lactation**

Women of childbearing potential have to use effective contraception during treatment. Viraferon must be used with caution in fertile men. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Viraferon is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

Combination therapy with ribavirin: Ribavirin causes serious birth defects when administered during pregnancy. Ribavirin therapy is contraindicated in women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking Viraferon in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must

each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

### 4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with Viraferon, and therefore it is recommended that they avoid driving or operating machinery.

### 4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/$m^2$/week in hairy cell leukaemia up to 100 MIU/$m^2$/week in melanoma), the most commonly reported undesirable effects were fever, fatigue, headache and myalgia. Fever and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

In clinical trials conducted in the hepatitis C population, patients were treated with Viraferon alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of Viraferon three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10); rarely (≥1/10,000, <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1.** Adverse reactions reported during clinical trials or following the marketing use of Viraferon alone or in combination with ribavirin

| System Organ Class | Adverse Reactions |
|---|---|
| **Infections and infestations** | |
| Very common: | Pharyngitis*, infection viral* |
| Common: | Bronchitis, sinusitis, herpes simplex (resistance), rhinitis |
| Rarely: | Pneumonia[§] |
| **Blood and lymphatic system disorders** | |
| Very common: | Leukopaenia |
| Common: | Thrombocytopaenia, lymphadenopathy, lymphopenia |
| Very rarely: | Aplastic anaemia |
| Not known**:** | Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura |
| **Immune system disorders**[§] | |
| Very rarely: | Sarcoidosis, exacerbation of sarcoidosis |
| Not known: | Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis[§] |
| **Endocrine disorders** | |
| Common: | Hypothyroidism[§], hyperthyroidism[§] |
| Very rarely: | Diabetes, aggravated diabetes |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcaemia, dehydration, hyperuricemia, thirst |
| Very rarely: | Hyperglycaemia, hypertriglyceridaemia[§], increased appetite |
| **Psychiatric disorders**[§] | |

| | |
|---|---|
| Very common: | Depression, insomnia, anxiety, emotional lability*, agitation, nervousness |
| Common: | Confusion, sleep disorder, libido decreased |
| Rarely: | Suicide ideation |
| Very rarely: | Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations |
| Not known: | Mental status change[§] |
| **Nervous system disorders**[§] | |
| Very common: | Dizziness, headache, concentration impaired, mouth dry |
| Common: | Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion |
| Very rarely: | Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy, neuropathy, polyneuropathy |
| Not known: | Mononeuropathies, coma[§] |
| **Eye disorders** | |
| Very common: | Vision blurred |
| Common: | Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain |
| Rarely: | Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§] |
| **Ear and labyrinth** | |
| Common: | Vertigo, tinnitus |
| Very rarely: | Hearing loss, hearing disorder |
| **Cardiac disorders** | |
| Common: | Palpitation, tachycardia |
| Rarely: | Cardiomyopathy |
| Very rarely: | Myocardial infarction, cardiac ischaemia |
| Not known: | Arrhythmia |
| **Vascular disorders** | |
| Common: | Hypertension |
| Very rarely: | Peripheral ischaemia, hypotension[§] |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common: | Dyspnoea*, coughing* |
| Common: | Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive |
| Very rarely: | Pulmonary infiltrates[§], pneumonitis[§] |
| **Gastrointestinal disorders** | |
| Very common: | Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia |
| Common: | Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools |
| Very rarely: | Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding |
| Not known: | Periodontal disorder NOS, dental disorder NOS[§] |
| **Hepatobiliary disorders** | |
| Common: | Hepatomegaly |
| Very rarely: | Hepatotoxicity, (including fatality) |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, pruritus*, skin dry*, rash*, sweating increased |
| Common: | Psoriasis (new or aggravated)[§], rash maculopapular, rash |

| | |
|---|---|
| Very rarely: | erythematous, eczema, erythema, skin disorder<br>Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders**<br>Very common:<br>Common:<br>Very rarely: | <br>Myalgia, arthralgia, musculoskeletal pain<br>Arthritis<br>Rhabdomyolysis, myositis, leg cramps, back pain |
| **Renal and urinary disorders**<br>Common:<br>Very rarely: | <br>Micturition frequency<br>Renal failure, renal insufficiency, nephrotic syndrome |
| **Reproductive system and breast disorders**<br>Common: | <br>Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder |
| **General disorders and administration site conditions**<br>Very common:<br><br><br>Common:<br>Very rarely: | <br>Injection site inflammation, injection site reaction*, fatigue, rigors, fever§, flu-like symptoms§, asthenia, irritability, chest pain, malaise<br>Injection site pain<br>Injection site necrosis, face oedema |
| **Investigations**<br>Very common: | <br>Weight decrease |

*These events were only common with Viraferon alone
§See section 4.4

These undesirable effects have also been reported with Viraferon alone.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

For safety with respect to transmissible agents, see section 4.4.

**Paediatric population**

*Children and adolescents – Chronic Hepatitis C*
In clinical trials of 118 children or adolescents 3 to 16 years of age, 6 % discontinued therapy due to adverse events. In general, the adverse event profile in the limited paediatric population studied was similar to that observed in adults, although there is a paediatric specific concern regarding growth inhibition as decrease in height (mean percentile decrease of growth velocity of 9 %) and weight (mean percentile decrease of 13 %)

percentile were observed during treatment (see section 4.4). Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from paediatric clinical trials.
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 2** Adverse reactions very commonly and commonly reported in paediatric clinical trials
Very common (≥1/10) - Common (≥1/100, <1/10)

| System Organ Class | Adverse Reactions |
|---|---|
| **Infection and infestations** | |
| Very common: | Viral infection, pharyngitis |
| Common: | Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | |
| Common: | Neoplasm (unspecified) |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, neutropaenia |
| Common: | Thrombocytopaenia, lymphadenopathy |
| **Endocrine disorders** | |
| Very common: | Hypothyroidism[§], |
| Common: | Hyperthyroidism[§], virilism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypertriglyceridemia[§], hyperuricemia, increased appetite |
| **Psychiatric disorders[§]** | |
| Very common: | Depression, emotional lability, insomnia |
| Common: | Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy |
| **Nervous system disorders[§]** | |
| Very common: | Headache, dizziness |
| Common: | Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence |
| **Eye disorders** | |
| Common: | Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder |
| **Vascular disorders** | |
| Common: | Raynaud's disease, flushing, pallor |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing |
| **Gastrointestinal disorders** | |

| | |
|---|---|
| Very common:<br>Common: | Diarrhoea, vomiting, nausea, abdominal pain<br>Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder |
| **Hepatobiliary disorders**<br>Common: | Hepatic function abnormal |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common: | Alopecia, rash<br>Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased |
| **Musculoskeletal and connective tissue disorders**<br>Very common: | Arthralgia, myalgia, musculoskeletal pain |
| **Renal and urinary disorders**<br>Common: | Enuresis, micturition disorder, urinary incontinence |
| **Reproductive system and breast disorders**<br>Common: | Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder<br>Male: testicular pain |
| **General disorders and administration site conditions**<br>Very common:<br><br>Common: | Injection site inflammation, injection site reaction, fatigue, rigors, fever[§], influenza-like symptoms[§], malaise, irritability<br>Chest pain, asthenia, oedema, injection site pain |
| **Investigations**<br>Very common: | Growth rate decrease (height and/or weight decrease for age)[§] |
| **Injury and poisoning**<br>Common: | Skin laceration |

[§]See section 4.4

### 4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, cytokines and immunomodulators, interferons, interferon alfa-2b, ATC code: L03A B05

Viraferon is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of Viraferon is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $l0^8$ IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. Viraferon has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B:
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/$m^2$ 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C:
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

Adult patients: Viraferon alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of Viraferon used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/ml), a liver biopsy consistent with

a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Viraferon was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with Viraferon alone or in combination with ribavirin (from two studies) are shown in **Table 3.**

Co-administration of Viraferon with ribavirin increased the efficacy of Viraferon by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of Viraferon + ribavirin, compared with Viraferon alone, is maintained across all subgroups. The relative benefit of combination therapy with Viraferon + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received Viraferon in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

| **Table 3** Sustained virologic response rates with Viraferon + ribavirin (one year of treatment) by genotype and viral load | | | |
|---|---|---|---|
| **HCV Genotype** | **I**<br>**N=503**<br>**C95-132/I95-143** | **I/R**<br>**N=505**<br>**C95-132/I95-143** | **I/R**<br>**N=505**<br>**C/I98-580** |
| **All Genotypes** | **16 %** | **41 %** | **47 %** |
| **Genotype 1** | 9 % | 29 % | 33 % |
| Genotype 1<br>≤ 2 million copies/ml | 25 % | 33 % | 45 % |
| Genotype 1<br>> 2 million copies/ml | 3 % | 27 % | 29 % |
| **Genotype 2/3** | 31 % | 65 % | 79 % |

I Viraferon (3 MIU 3 times a week)
I/R Viraferon (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

*HCV/HIV Co-infected patients*
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received Viraferon plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or Viraferon (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or Viraferon (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

| **Table 4** | Sustained virological response based on genotype after Viraferon in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients | | | | | |
|---|---|---|---|---|---|---|
| | **Study 1**[1] | | | **Study 2**[2] | | |
| | pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg) | Viraferon (3 MIU TIW) + ribavirin (800 mg) | p value[a] | pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Viraferon (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients: A total of 345 interferon alpha relapse patients were treated in two clinical trials with Viraferon monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to Viraferon increased by as much as 10-fold the efficacy of Viraferon used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/ml by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non pegylated interferon alfa-2b or non pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Clinical trials in paediatric patients with chronic hepatitis C:
Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received Viraferon 3 MIU/$m^2$ 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. Sustained virological response rates in children and adolescents

were similar to those in adults. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

| **Table 5.** Virological response in previously untreated paediatric patients | |
|---|---|
| | **Viraferon 3 MIU/m$^2$** 3 times a week<br>+<br>**ribavirin 15 mg/kg/day** |
| Overall Response[1] (n=118) | 54 (46 %)* |
| Genotype 1 (n=92) | 33 (36 %)* |
| Genotype 2/3/4 (n=26) | 21 (81 %)* |

*Number (%) of patients
1. Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

## 5.2 Pharmacokinetic properties

The pharmacokinetics of Viraferon were studied in healthy volunteers following single 5 million IU/m$^2$ and 10 million IU doses administered subcutaneously, at 5 million IU/m$^2$ administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. $C_{max}$ occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/ml) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

*Children and adolescents*: Multiple-dose pharmacokinetic properties for Viraferon injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 6**. The pharmacokinetics of Viraferon and ribavirin (dose-normalized) are similar in adults and children or adolescents.

| **Table 6.** Mean (% CV) multiple-dose pharmacokinetic parameters for Viraferon and ribavirin capsules when administered to children or adolescents with chronic hepatitis C | | |
|---|---|---|
| **Parameter** | **Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17) | **Viraferon** 3 MIU/$m^2$ 3 times a week (n = 54) |
| $T_{max}$ (hr) | 1.9 (83) | 5.9 (36) |
| $C_{max}$ (ng/ml) | 3,275 (25) | 51 (48) |
| AUC* | 29,774 (26) | 622 (48) |
| Apparent clearance l/hr/kg | 0.27 (27) | Not done |

*$AUC_{12}$ (ng.hr/ml) for ribavirin; $AUC_{0-24}$ (IU.hr/ml) for Viraferon

Interferon neutralising factor assays were performed on serum samples of patients who received Viraferon in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

### 5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x $10^6$ IU/kg/day for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x $10^6$ IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour (see section 4.4 and Rebetol SPC if Viraferon is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Glycine,
Disodium phosphate anhydrous,

Sodium dihydrogen phosphate monohydrate,
Human albumin solution.

Solvent: water for injections

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

3 years

After reconstitution: An immediate use is recommended. However, the chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Within its shelf-life, for the purpose of transport and/or to facilitate ambulatory use the non-reconstituted product can be kept at or below 25°C for a period up to four weeks before use. If the product is not reconstituted during the four-week period, it cannot be put back in the refrigerator for a new storage period and must be discarded.

### 6.5 Nature and contents of container

24 mg of powder (corresponding to 10 MIU) in a vial (type I glass), with a stopper (butyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene)
and 1 ml water for injections in an ampoule (type I glass)
with 1 injection syringe, 2 injection needles and 1 cleansing swab.
Pack sizes of 1 and 10

Or

24 mg of powder (corresponding to 10 MIU) in a vial (type I glass), with a stopper (butyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene)
and 1 ml water for injections in an ampoule (type I glass).
Pack sizes of 6
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

Reconstitution of Viraferon, powder for solution for injection, for parenteral administration: Viraferon is supplied as a powder at strengths of 10 million IU/ml for single-dose use. Vials must be reconstituted with 1 ml of water for injections. The reconstituted solutions are isotonic for parenteral administration.

Proper precautions should be taken during reconstitution to prevent microbial contamination (refer to package leaflet).

Using a sterilised injection syringe and injection needle, inject 1 ml water for injections into the vial of Viraferon. Agitate gently to facilitate complete dissolution of the powder. The appropriate dose can then be withdrawn with a sterile injection syringe and injected.

As for all parenteral medicinal products, inspect the reconstituted solution visually for particulate matter and discoloration prior to administration. The reconstituted solution should be clear and colourless.

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to "How to self inject Viraferon").

Any unused product must be discarded after withdrawal of the dose.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/99/128/006
EU/1/99/128/007
EU/1/99/128/008

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 9 March 2000
Date of last renewal : 23 May 2005

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 3 million IU/0.5 ml solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of Viraferon solution for injection, single dose vial, contains 3 million IU of recombinant interferon alfa-2b produced in *E.coli* by recombinant DNA technology, in 0.5 ml of solution.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection
Solution is clear and colourless.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C:
*Adult patients:*
Viraferon is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section 4.4).

The best way to use Viraferon in this indication is in combination with ribavirin.

*Chidren and adolescents:*
Viraferon is intended for use, in a combination regimen with ribavirin, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials (see sections 4.4, 4.8 and 5.1).

### 4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

If adverse events develop during the course of treatment with Viraferon for any indication, modify the dosage or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dosage adjustment, or disease progresses, discontinue treatment with Viraferon.

At the discretion of the physician, the patient may self-administer the dose for maintenance dosage regimens administered subcutaneously.

*Chronic Hepatitis B*: The recommended dosage is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/$mm^3$, granulocytes < 1,000/$mm^3$, thrombocytes < 100,000/$mm^3$). Treatment should be discontinued in case of severe leukopaenia (< 1,200/$mm^3$), severe neutropaenia (< 750/$mm^3$) or severe thrombocytopaenia (< 70,000/$mm^3$).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue Viraferon therapy.

*Chronic Hepatitis C*: Viraferon is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

*Children 3 years of age or older and adolescents*: Interferon alfa-2b 3 MIU/$m^2$ is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsule SPC for dose of ribavirin capsules and dosage modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC).

Relapse patients (adults):
Viraferon is given in combination with ribavirin.

Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for 6 months.

Naïve patients:
*Adults:* The efficacy of Viraferon is enhanced when given in combination with ribavirin. Viraferon should be given alone mainly in case of intolerance or contraindication to ribavirin.

Viraferon in combination with ribavirin:
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Viraferon alone:
The optimal duration of therapy with Viraferon alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with Viraferon alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

*Children and adolescents:* The efficacy and safety of Viraferon in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Virological response is defined as absence of detectable HCV-RNA at Week 12. Treatment should be discontinued in these patients.
Genotype 2/3: The recommended duration of treatment is 24 weeks.

Virological responses after 1 year of treatment and 6 months of follow-up were 36 % for genotype 1 and 81 % for genotype 2/3/4.

Viraferon may be administered using either glass or plastic disposable injection syringes.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.

Children and adolescents:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin: Also see ribavirin SPC if interferon alfa-2b is to be administered in combination with ribavirin in patients with chronic hepatitis C.

**4.4 Special warnings and precautions for use**

*For all patients:*

Psychiatric and central nervous system (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Viraferon therapy, and even after treatment discontinuation mainly during the 6-month follow-up periodand in the follow-up period. Among children and adolescents treated with Viraferon in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others), confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Viraferon be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of or history of severe psychiatric conditions:*
If a treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases, termination of Viraferon therapy. Any patient developing liver function abnormalities during treatment with Viraferon must be monitored closely and treatment discontinued if signs and symptoms progress.

Hypotension may occur during Viraferon therapy or up to two days post-therapy and may require supportive treatment.

Adequate hydration must be maintained in patients undergoing Viraferon therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Viraferon must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instance after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with Viraferon, must have a prompt and complete eye examination. Periodic visual examinations during Viraferon therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of Viraferon should be considered in patients who develop new or worsening ophthalmological disorders.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of Viraferon.

Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require Viraferon therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of Viraferon therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of Viraferon in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Discontinue treatment with Viraferon in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decompensation.

Chronic Hepatitis C:
Combination therapy with ribavirin: Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy: Infrequently, adult patients treated for chronic hepatitis C with Viraferon developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using Viraferon therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which Viraferon may alter thyroid status is unknown. Prior to initiation of Viraferon therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of Viraferon therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, Viraferon treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of Viraferon therapy has not reversed thyroid dysfunction occurring during treatment (also see Children and adolescents, Thyroid monitoring).

*Supplemental monitoring specific for children and adolescents*

Thyroid Monitoring**:** Approximately 12 % of children treated with interferon alfa-2b and ribavirin developed increase in TSH. Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of Viraferon therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Growth and Development: During a 1-year course of therapy there was a decrease in the rate of linear growth (mean percentile decrease of 9 %) and a decrease in the rate of weight gain (mean percentile decrease of 13 %). A general reversal of these trends was noted during the 6 months follow-up post treatment. However, based on interim data from a long-term follow-up study, 12 (14 %) of 84 children had a > 15 percentile decrease in rate of linear growth, of whom 5 (6 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In addition, preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3). Therefore, the risk/benefit of the combined use of interferon alfa-2b and ribavirin should be assessed in young children prior to the initiation of therapy. Physicians are advised to monitor the growth of children taking ribavirin in combination with interferon alfa-2b. There are no data on long term effects on growth and development and on sexual maturation.

HCV/HIV Coinfection**:** Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Viraferon and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders**:** Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Viraferon and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests:
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with Viraferon.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during Viraferon therapy to greater than or equal to 2 times baseline, Viraferon therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, liver function tests: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin must be monitored at two-week intervals.

Effect on fertility: Interferon may impair fertility (see section 4.6 and section 5.3).

### 4.5 Interaction with other medicinal products and other forms of interaction

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with Viraferon.

Interactions between Viraferon and other medicinal products have not been fully evaluated. Caution must be exercised when administering Viraferon in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dosage adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

(Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C).

## 4.6 Pregnancy and lactation

Women of childbearing potential have to use effective contraception during treatment. Viraferon must be used with caution in fertile men. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Viraferon is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

Combination therapy with ribavirin: Ribavirin causes serious birth defects when administered during pregnancy. Ribavirin therapy is contraindicated in women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking Viraferon in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

## 4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with Viraferon, and therefore it is recommended that they avoid driving or operating machinery.

## 4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/$m^2$/week in hairy cell leukaemia up to 100 MIU/$m^2$/week in melanoma), the most commonly reported undesirable effects were fever, fatigue, headache and myalgia. Fever and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

In clinical trials conducted in the hepatitis C population, patients were treated with Viraferon alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of Viraferon three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10); rarely (≥1/10,000, <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1.** Adverse reactions reported during clinical trials or following the marketing use of Viraferon alone or in combination with ribavirin

| System Organ Class | Adverse Reactions |
|---|---|
| **Infections and infestations** | |
| Very common: | Pharyngitis*, infection viral* |
| Common: | Bronchitis, sinusitis, herpes simplex (resistance), rhinitis |
| Rarely: | Pneumonia§ |
| **Blood and lymphatic system disorders** | |
| Very common: | Leukopaenia |
| Common: | Thrombocytopaenia, lymphadenopathy, lymphopenia |
| Very rarely: | Aplastic anaemia |
| Not known**:** | Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura |
| **Immune system disorders**§ | |
| Very rarely: | Sarcoidosis, exacerbation of sarcoidosis |
| Not known: | Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis§ |
| **Endocrine disorders** | |
| Common: | Hypothyroidism§, hyperthyroidism§ |
| Very rarely: | Diabetes, aggravated diabetes |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcaemia, dehydration, hyperuricemia, thirst |
| Very rarely: | Hyperglycaemia, hypertriglyceridaemia§, increased appetite |
| **Psychiatric disorders**§ | |
| Very common: | Depression, insomnia, anxiety, emotional lability*, agitation, nervousness |
| Common: | Confusion, sleep disorder, libido decreased |
| Rarely: | Suicide ideation |
| Very rarely: | Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations |
| Not known: | Mental status change§ |
| **Nervous system disorders**§ | |
| Very common: | Dizziness, headache, concentration impaired, mouth dry |
| Common: | Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion |
| Very rarely: | Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy, neuropathy, polyneuropathy |
| Not known: | Mononeuropathies, coma§ |
| **Eye disorders** | |
| Very common: | Vision blurred |
| Common: | Conjunctivitis, vision abnormal, lacrimal gland disorder, eye |

| | |
|---|---|
| Rarely: | pain<br>Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§] |
| **Ear and labyrinth**<br>Common:<br>Very rarely: | <br>Vertigo, tinnitus<br>Hearing loss, hearing disorder |
| **Cardiac disorders**<br>Common:<br>Rarely:<br>Very rarely:<br>Not known: | <br>Palpitation, tachycardia<br>Cardiomyopathy<br>Myocardial infarction, cardiac ischaemia<br>Arrhythmia |
| **Vascular disorders**<br>Common:<br>Very rarely: | <br>Hypertension<br>Peripheral ischaemia, hypotension[§] |
| **Respiratory, thoracic and mediastinal disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br>Dyspnoea*, coughing*<br>Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive<br>Pulmonary infiltrates[§], pneumonitis[§] |
| **Gastrointestinal disorders**<br>Very common:<br><br>Common:<br><br>Very rarely:<br><br>Not known: | <br>Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia<br>Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools<br>Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding<br>Periodontal disorder NOS, dental disorder NOS[§] |
| **Hepatobiliary disorders**<br>Common:<br>Very rarely: | <br>Hepatomegaly<br>Hepatotoxicity, (including fatality) |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br>Alopecia, pruritus*, skin dry*, rash*, sweating increased<br>Psoriasis (new or aggravated)[§], rash maculopapular, rash erythematous, eczema, erythema, skin disorder<br>Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders**<br>Very common:<br>Common:<br>Very rarely: | <br>Myalgia, arthralgia, musculoskeletal pain<br>Arthritis<br>Rhabdomyolysis, myositis, leg cramps, back pain |
| **Renal and urinary disorders**<br>Common:<br>Very rarely: | <br>Micturition frequency<br>Renal failure, renal insufficiency, nephrotic syndrome |
| **Reproductive system and breast disorders**<br>Common: | <br>Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder |
| **General disorders and administration site conditions**<br>Very common: | <br>Injection site inflammation, injection site reaction*, fatigue, |

| | |
|---|---|
| | rigors, fever[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise |
| Common: | Injection site pain |
| Very rarely: | Injection site necrosis, face oedema |
| **Investigations** | |
| Very common: | Weight decrease |

*These events were only common with Viraferon alone
[§]See section 4.4

These undesirable effects have also been reported with Viraferon alone.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts, decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

**Paediatric population**

*Children and adolescents – Chronic Hepatitis C*
In clinical trials of 118 children or adolescents 3 to 16 years of age, 6 % discontinued therapy due to adverse events. In general, the adverse event profile in the limited paediatric population studied was similar to that observed in adults, although there is a paediatric specific concern regarding growth inhibition as decrease in height (mean percentile decrease of growth velocity of 9 %) and weight (mean percentile decrease of 13 %) percentile were observed during treatment (see section 4.4). Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from paediatric clinical trials.
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 2** Adverse reactions very commonly and commonly reported in paediatric clinical trials
Very common (≥1/10) - Common (≥1/100, <1/10)

| **System Organ Class** | **Adverse Reactions** |
|---|---|
| **Infection and infestations** | |
| Very common: | Viral infection, pharyngitis |
| Common: | Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, |

| | |
|---|---|
| | vaginitis, gastroenteritis |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)**<br>Common: | <br><br><br>Neoplasm (unspecified) |
| **Blood and lymphatic system disorders**<br>Very common:<br>Common: | <br><br>Anaemia, neutropaenia<br>Thrombocytopaenia, lymphadenopathy |
| **Endocrine disorders**<br>Very common:<br>Common: | <br>Hypothyroidism[§],<br>Hyperthyroidism[§], virilism |
| **Metabolism and nutrition disorders**<br>Very common:<br>Common: | <br><br>Anorexia<br>Hypertriglyceridemia[§], hyperuricemia, increased appetite |
| **Psychiatric disorders**[§]<br>Very common:<br>Common: | <br>Depression, emotional lability, insomnia<br>Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy |
| **Nervous system disorders**[§]<br>Very common:<br>Common: | <br>Headache, dizziness<br>Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence |
| **Eye disorders**<br>Common: | <br>Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder |
| **Vascular disorders**<br>Common: | <br>Raynaud's disease, flushing, pallor |
| **Respiratory, thoracic and mediastinal disorders**<br>Common: | <br><br>Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing |
| **Gastrointestinal disorders**<br>Very common:<br>Common: | <br>Diarrhoea, vomiting, nausea, abdominal pain<br>Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder |
| **Hepatobiliary disorders**<br>Common: | <br>Hepatic function abnormal |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common: | <br><br>Alopecia, rash<br>Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased |
| **Musculoskeletal and connective tissue disorders**<br>Very common: | <br><br>Arthralgia, myalgia, musculoskeletal pain |
| **Renal and urinary disorders**<br>Common: | <br>Enuresis, micturition disorder, urinary incontinence |
| **Reproductive system and breast disorders** | |

| | |
|---|---|
| Common: | Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder<br>Male: testicular pain |
| **General disorders and administration site conditions**<br>Very common:<br><br>Common: | <br><br>Injection site inflammation, injection site reaction, fatigue, rigors, fever[§], influenza-like symptoms[§], malaise, irritability<br>Chest pain, asthenia, oedema, injection site pain |
| **Investigations**<br>Very common: | <br>Growth rate decrease (height and/or weight decrease for age)[§] |
| **Injury and poisoning**<br>Common: | <br>Skin laceration |

[§]See section 4.4

### 4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, cytokines and immunomodulators, interferons, interferon alfa-2b, ATC code: L03A B05

Viraferon is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of Viraferon is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $l0^8$ IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. Viraferon has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B:
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/$m^2$ 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C:
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

Adult patients: Viraferon alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of Viraferon used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/ml), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Viraferon was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with Viraferon alone or in combination with ribavirin (from two studies) are shown in **Table 3**.

Co-administration of Viraferon with ribavirin increased the efficacy of Viraferon by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of Viraferon + ribavirin, compared with Viraferon alone, is maintained across all subgroups. The relative benefit of combination therapy with Viraferon + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received Viraferon in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained

response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

**Table 3** Sustained virologic response rates with Viraferon + ribavirin (one year of treatment) by genotype and viral load

| **HCV Genotype** | **I N=503 C95-132/I95-143** | **I/R N=505 C95-132/I95-143** | **I/R N=505 C/I98-580** |
|---|---|---|---|
| **All Genotypes** | **16 %** | **41 %** | **47 %** |
| **Genotype 1** | 9 % | 29 % | 33 % |
| Genotype 1 ≤ 2 million copies/ml | 25 % | 33 % | 45 % |
| Genotype 1 > 2 million copies/ml | 3 % | 27 % | 29 % |
| **Genotype 2/3** | 31 % | 65 % | 79 % |

I Viraferon (3 MIU 3 times a week)
I/R Viraferon (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

*HCV/HIV Co-infected patients*
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received Viraferon plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or Viraferon (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or Viraferon (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

**Table 4** Sustained virological response based on genotype after Viraferon in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients

| | **Study 1**[1] | | | **Study 2**[2] | | |
|---|---|---|---|---|---|---|
| | pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg) | Viraferon (3 MIU TIW) + ribavirin (800 mg) | p value[a] | pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Viraferon (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |

| | | | | | | |
|---|---|---|---|---|---|---|
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients: A total of 345 interferon alpha relapse patients were treated in two clinical trials with Viraferon monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to Viraferon increased by as much as 10-fold the efficacy of Viraferon used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/ml by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non pegylated interferon alfa-2b or non pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Clinical trials in paediatric patients with chronic hepatitis C:
Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received Viraferon 3 MIU/$m^2$ 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. Sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

**Table 5.** Virological response in previously untreated paediatric patients

| | **Viraferon 3 MIU/$m^2$** 3 times a week + **ribavirin 15 mg/kg/day** |
|---|---|
| Overall Response[1] (n=118) | 54 (46 %)* |

| | |
|---|---|
| Genotype 1 (n=92) | 33 (36 %)* |
| Genotype 2/3/4 (n=26) | 21 (81 %)* |

*Number (%) of patients
1. Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

## 5.2 Pharmacokinetic properties

The pharmacokinetics of Viraferon were studied in healthy volunteers following single 5 million IU/$m^2$ and 10 million IU doses administered subcutaneously, at 5 million IU/$m^2$ administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. $C_{max}$ occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/ml) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

*Children and adolescents*: Multiple-dose pharmacokinetic properties for Viraferon injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 6**. The pharmacokinetics of Viraferon and ribavirin (dose-normalized) are similar in adults and children or adolescents.

**Table 6.** Mean (% CV) multiple-dose pharmacokinetic parameters for Viraferon and ribavirin capsules when administered to children or adolescents with chronic hepatitis C

| **Parameter** | **Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17) | **Viraferon** 3 MIU/$m^2$ 3 times a week (n = 54) |
|---|---|---|
| $T_{max}$ (hr) | 1.9 (83) | 5.9 (36) |
| $C_{max}$ (ng/ml) | 3,275 (25) | 51 (48) |
| AUC* | 29,774 (26) | 622 (48) |
| Apparent clearance l/hr/kg | 0.27 (27) | Not done |

*$AUC_{12}$ (ng.hr/ml) for ribavirin; $AUC_{0-24}$ (IU.hr/ml) for Viraferon

Interferon neutralising factor assays were performed on serum samples of patients who received Viraferon in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

## 5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x $10^6$ IU/kg/day

for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x $10^6$ IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour (see section 4.4 and Rebetol SPC if Viraferon is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Disodium phosphate anhydrous,
Sodium dihydrogen phosphate monohydrate,
Edetate disodium,
Sodium chloride,
M-cresol,
Polysorbate 80,
Water for injections.

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

18 months

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Within its shelf-life, for the purpose of transport, the solution can be kept at or below 25ºC for a period up to seven days before use. Viraferon can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it cannot be put back in the refrigerator for a new storage period and must be discarded.

### 6.5 Nature and contents of container

0.5 ml of solution (corresponding to 3 MIU) in a vial (type I glass), with a stopper (halobutyl rubber) in an flip-off seal (aluminium) with a bonnet (polypropylene).
Pack sizes of 1

Or

0.5 ml of solution (corresponding to 3 MIU) in a vial (type I glass), with a stopper (halobutyl rubber) in an flip-off seal (aluminium) with a bonnet (polypropylene).
with 1 injection syringe, 1 injection needle and 1 cleansing swab.
Packs sizes of 1, 6 or 12.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

Viraferon solution for injection, may be injected directly after withdrawal of the appropriate doses from the vial with a sterile injection syringe.

As with all parenteral medicinal products, prior to administration inspect Viraferon, solution for injection, visually for particulate matter and discolouration. The solution should be clear and colourless.

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to "How to self inject Viraferon").

Any unused product must be discarded after withdrawal of the dose.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/99/128/009
EU/1/99/128/010
EU/1/99/128/011
EU/1/99/128/012

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 9 March 2000
Date of last renewal : 23 May 2005

## 10. DATE OF REVISION OF THE TEXT

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 5 million IU/0.5 ml solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of Viraferon solution for injection, single dose vial, contains 5 million IU of recombinant interferon alfa-2b produced in *E.coli* by recombinant DNA technology, in 0.5 ml of solution.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection
Solution is clear and colourless.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C:
*Adult patients:*
Viraferon is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section 4.4).

The best way to use Viraferon in this indication is in combination with ribavirin.

*Chidren and adolescents:*
Viraferon is intended for use, in a combination regimen with ribavirin, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials (see sections 4.4, 4.8 and 5.1).

### 4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

If adverse events develop during the course of treatment with Viraferon for any indication, modify the dosage or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dosage adjustment, or disease progresses, discontinue treatment with Viraferon.

At the discretion of the physician, the patient may self-administer the dose for maintenance dosage regimens administered subcutaneously.

*Chronic Hepatitis B*: The recommended dosage is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/$mm^3$, granulocytes < 1,000/$mm^3$, thrombocytes < 100,000/$mm^3$). Treatment should be discontinued in case of severe leukopaenia (< 1,200/$mm^3$), severe neutropaenia (< 750/$mm^3$) or severe thrombocytopaenia (< 70,000/$mm^3$).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue Viraferon therapy.

*Chronic Hepatitis C*: Viraferon is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

*Children 3 years of age or older and adolescents*: Interferon alfa-2b 3 MIU/$m^2$ is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsule SPC for dose of ribavirin capsules and dosage modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC).

Relapse patients (adults):
Viraferon is given in combination with ribavirin.

Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for 6 months.

Naïve patients:
*Adults:* The efficacy of Viraferon is enhanced when given in combination with ribavirin. Viraferon should be given alone mainly in case of intolerance or contraindication to ribavirin.

Viraferon in combination with ribavirin:
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Viraferon alone:
The optimal duration of therapy with Viraferon alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with Viraferon alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

*Children and adolescents:* The efficacy and safety of Viraferon in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Virological response is defined as absence of detectable HCV-RNA at Week 12. Treatment should be discontinued in these patients.
Genotype 2/3: The recommended duration of treatment is 24 weeks.

Virological responses after 1 year of treatment and 6 months of follow-up were 36 % for genotype 1 and 81 % for genotype 2/3/4.

Viraferon may be administered using either glass or plastic disposable injection syringes.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
  Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.

Children and adolescents:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin: Also see ribavirin SPC if interferon alfa-2b is to be administered in combination with ribavirin in patients with chronic hepatitis C.

**4.4 Special warnings and precautions for use**

*For all patients:*

Psychiatric and central nervous system (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Viraferon therapy, and even after treatment discontinuation mainly during the 6-month follow-up periodand in the follow-up period. Among children and adolescents treated with Viraferon in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others), confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Viraferon be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of or history of severe psychiatric conditions:*
If a treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases, termination of Viraferon therapy. Any patient developing liver function abnormalities during treatment with Viraferon must be monitored closely and treatment discontinued if signs and symptoms progress.

Hypotension may occur during Viraferon therapy or up to two days post-therapy and may require supportive treatment.

Adequate hydration must be maintained in patients undergoing Viraferon therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Viraferon must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instance after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with Viraferon, must have a prompt and complete eye examination. Periodic visual examinations during Viraferon therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of Viraferon should be considered in patients who develop new or worsening ophthalmological disorders.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of Viraferon.

Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require Viraferon therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of Viraferon therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of Viraferon in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Discontinue treatment with Viraferon in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decompensation.

Chronic Hepatitis C:
Combination therapy with ribavirin: Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy: Infrequently, adult patients treated for chronic hepatitis C with Viraferon developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using Viraferon therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which Viraferon may alter thyroid status is unknown. Prior to initiation of Viraferon therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of Viraferon therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, Viraferon treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of Viraferon therapy has not reversed thyroid dysfunction occurring during treatment (also see Children and adolescents, Thyroid monitoring).

*Supplemental monitoring specific for children and adolescents*

Thyroid Monitoring**:** Approximately 12 % of children treated with interferon alfa-2b and ribavirin developed increase in TSH. Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of Viraferon therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Growth and Development: During a 1-year course of therapy there was a decrease in the rate of linear growth (mean percentile decrease of 9 %) and a decrease in the rate of weight gain (mean percentile decrease of 13 %). A general reversal of these trends was noted during the 6 months follow-up post treatment. However, based on interim data from a long-term follow-up study, 12 (14 %) of 84 children had a > 15 percentile decrease in rate of linear growth, of whom 5 (6 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In addition, preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3). Therefore, the risk/benefit of the combined use of interferon alfa-2b and ribavirin should be assessed in young children prior to the initiation of therapy. Physicians are advised to monitor the growth of children taking ribavirin in combination with interferon alfa-2b. There are no data on long term effects on growth and development and on sexual maturation.

HCV/HIV Coinfection**:** Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Viraferon and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders**:** Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Viraferon and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests:
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with Viraferon.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during Viraferon therapy to greater than or equal to 2 times baseline, Viraferon therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, liver function tests: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin must be monitored at two-week intervals.

Effect on fertility: Interferon may impair fertility (see section 4.6 and section 5.3).

### 4.5 Interaction with other medicinal products and other forms of interaction

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with Viraferon.

Interactions between Viraferon and other medicinal products have not been fully evaluated. Caution must be exercised when administering Viraferon in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dosage adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

(Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C).

## 4.6 Pregnancy and lactation

Women of childbearing potential have to use effective contraception during treatment. Viraferon must be used with caution in fertile men. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Viraferon is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

Combination therapy with ribavirin: Ribavirin causes serious birth defects when administered during pregnancy. Ribavirin therapy is contraindicated in women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking Viraferon in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

## 4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with Viraferon, and therefore it is recommended that they avoid driving or operating machinery.

## 4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/$m^2$/week in hairy cell leukaemia up to 100 MIU/$m^2$/week in melanoma), the most commonly reported undesirable effects were fever, fatigue, headache and myalgia. Fever and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

In clinical trials conducted in the hepatitis C population, patients were treated with Viraferon alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of Viraferon three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10); rarely (≥1/10,000, <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1.** Adverse reactions reported during clinical trials or following the marketing use of Viraferon alone or in combination with ribavirin

| System Organ Class | Adverse Reactions |
|---|---|
| **Infections and infestations** | |
| Very common: | Pharyngitis*, infection viral* |
| Common: | Bronchitis, sinusitis, herpes simplex (resistance), rhinitis |
| Rarely: | Pneumonia§ |
| **Blood and lymphatic system disorders** | |
| Very common: | Leukopaenia |
| Common: | Thrombocytopaenia, lymphadenopathy, lymphopenia |
| Very rarely: | Aplastic anaemia |
| Not known**:** | Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura |
| **Immune system disorders**§ | |
| Very rarely: | Sarcoidosis, exacerbation of sarcoidosis |
| Not known: | Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis§ |
| **Endocrine disorders** | |
| Common: | Hypothyroidism§, hyperthyroidism§ |
| Very rarely: | Diabetes, aggravated diabetes |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcaemia, dehydration, hyperuricemia, thirst |
| Very rarely: | Hyperglycaemia, hypertriglyceridaemia§, increased appetite |
| **Psychiatric disorders**§ | |
| Very common: | Depression, insomnia, anxiety, emotional lability*, agitation, nervousness |
| Common: | Confusion, sleep disorder, libido decreased |
| Rarely: | Suicide ideation |
| Very rarely: | Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations |
| Not known: | Mental status change§ |
| **Nervous system disorders**§ | |
| Very common: | Dizziness, headache, concentration impaired, mouth dry |
| Common: | Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion |
| Very rarely: | Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy, neuropathy, polyneuropathy |
| Not known: | Mononeuropathies, coma§ |
| **Eye disorders** | |
| Very common: | Vision blurred |
| Common: | Conjunctivitis, vision abnormal, lacrimal gland disorder, eye |

| | |
|---|---|
| Rarely: | pain<br>Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§] |
| **Ear and labyrinth**<br>Common:<br>Very rarely: | <br>Vertigo, tinnitus<br>Hearing loss, hearing disorder |
| **Cardiac disorders**<br>Common:<br>Rarely:<br>Very rarely:<br>Not known: | <br>Palpitation, tachycardia<br>Cardiomyopathy<br>Myocardial infarction, cardiac ischaemia<br>Arrhythmia |
| **Vascular disorders**<br>Common:<br>Very rarely: | <br>Hypertension<br>Peripheral ischaemia, hypotension[§] |
| **Respiratory, thoracic and mediastinal disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br><br>Dyspnoea*, coughing*<br>Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive<br>Pulmonary infiltrates[§], pneumonitis[§] |
| **Gastrointestinal disorders**<br>Very common:<br><br>Common:<br><br>Very rarely:<br><br>Not known: | <br>Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia<br>Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools<br>Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding<br>Periodontal disorder NOS, dental disorder NOS[§] |
| **Hepatobiliary disorders**<br>Common:<br>Very rarely: | <br>Hepatomegaly<br>Hepatotoxicity, (including fatality) |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br>Alopecia, pruritus*, skin dry*, rash*, sweating increased<br>Psoriasis (new or aggravated)[§], rash maculopapular, rash erythematous, eczema, erythema, skin disorder<br>Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders**<br>Very common:<br>Common:<br>Very rarely: | <br><br>Myalgia, arthralgia, musculoskeletal pain<br>Arthritis<br>Rhabdomyolysis, myositis, leg cramps, back pain |
| **Renal and urinary disorders**<br>Common:<br>Very rarely: | <br>Micturition frequency<br>Renal failure, renal insufficiency, nephrotic syndrome |
| **Reproductive system and breast disorders**<br>Common: | <br><br>Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder |
| **General disorders and administration site conditions**<br>Very common: | <br><br>Injection site inflammation, injection site reaction*, fatigue, |

| | |
|---|---|
| | rigors, fever[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise |
| Common: | Injection site pain |
| Very rarely: | Injection site necrosis, face oedema |
| **Investigations** | |
| Very common: | Weight decrease |

*These events were only common with Viraferon alone
[§]See section 4.4

These undesirable effects have also been reported with Viraferon alone.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts, decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

**Paediatric population**

*Children and adolescents – Chronic Hepatitis C*
In clinical trials of 118 children or adolescents 3 to 16 years of age, 6 % discontinued therapy due to adverse events. In general, the adverse event profile in the limited paediatric population studied was similar to that observed in adults, although there is a paediatric specific concern regarding growth inhibition as decrease in height (mean percentile decrease of growth velocity of 9 %) and weight (mean percentile decrease of 13 %) percentile were observed during treatment (see section 4.4). Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from paediatric clinical trials.
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 2** Adverse reactions very commonly and commonly reported in paediatric clinical trials
Very common (≥1/10) - Common (≥1/100, <1/10)

| **System Organ Class** | **Adverse Reactions** |
|---|---|
| **Infection and infestations** | |
| Very common: | Viral infection, pharyngitis |
| Common: | Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, |

| | |
|---|---|
| | vaginitis, gastroenteritis |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)**<br>Common: | Neoplasm (unspecified) |
| **Blood and lymphatic system disorders**<br>Very common:<br>Common: | Anaemia, neutropaenia<br>Thrombocytopaenia, lymphadenopathy |
| **Endocrine disorders**<br>Very common:<br>Common: | Hypothyroidism[§],<br>Hyperthyroidism[§], virilism |
| **Metabolism and nutrition disorders**<br>Very common:<br>Common: | Anorexia<br>Hypertriglyceridemia[§], hyperuricemia, increased appetite |
| **Psychiatric disorders**[§]<br>Very common:<br>Common: | Depression, emotional lability, insomnia<br>Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy |
| **Nervous system disorders**[§]<br>Very common:<br>Common: | Headache, dizziness<br>Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence |
| **Eye disorders**<br>Common: | Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder |
| **Vascular disorders**<br>Common: | Raynaud's disease, flushing, pallor |
| **Respiratory, thoracic and mediastinal disorders**<br>Common: | Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing |
| **Gastrointestinal disorders**<br>Very common:<br>Common: | Diarrhoea, vomiting, nausea, abdominal pain<br>Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder |
| **Hepatobiliary disorders**<br>Common: | Hepatic function abnormal |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common: | Alopecia, rash<br>Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased |
| **Musculoskeletal and connective tissue disorders**<br>Very common: | Arthralgia, myalgia, musculoskeletal pain |
| **Renal and urinary disorders**<br>Common: | Enuresis, micturition disorder, urinary incontinence |
| **Reproductive system and breast disorders** | |

| | |
|---|---|
| Common: | Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder<br>Male: testicular pain |
| **General disorders and administration site conditions**<br>Very common:<br><br>Common: | <br><br>Injection site inflammation, injection site reaction, fatigue, rigors, fever[§], influenza-like symptoms[§], malaise, irritability<br>Chest pain, asthenia, oedema, injection site pain |
| **Investigations**<br>Very common: | <br>Growth rate decrease (height and/or weight decrease for age)[§] |
| **Injury and poisoning**<br>Common: | <br>Skin laceration |

[§]See section 4.4

### 4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, cytokines and immunomodulators, interferons, interferon alfa-2b, ATC code: L03A B05

Viraferon is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of Viraferon is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $l0^8$ IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. Viraferon has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B:
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/$m^2$ 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C:
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

Adult patients: Viraferon alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of Viraferon used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/ml), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Viraferon was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with Viraferon alone or in combination with ribavirin (from two studies) are shown in **Table 3**.

Co-administration of Viraferon with ribavirin increased the efficacy of Viraferon by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of Viraferon + ribavirin, compared with Viraferon alone, is maintained across all subgroups. The relative benefit of combination therapy with Viraferon + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received Viraferon in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained

response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

**Table 3** Sustained virologic response rates with Viraferon + ribavirin (one year of treatment) by genotype and viral load

| **HCV Genotype** | **I N=503 C95-132/I95-143** | **I/R N=505 C95-132/I95-143** | **I/R N=505 C/I98-580** |
|---|---|---|---|
| **All Genotypes** | **16 %** | **41 %** | **47 %** |
| **Genotype 1** | 9 % | 29 % | 33 % |
| Genotype 1 ≤ 2 million copies/ml | 25 % | 33 % | 45 % |
| Genotype 1 > 2 million copies/ml | 3 % | 27 % | 29 % |
| **Genotype 2/3** | 31 % | 65 % | 79 % |

I Viraferon (3 MIU 3 times a week)
I/R Viraferon (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

*HCV/HIV Co-infected patients*
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received Viraferon plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or Viraferon (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or Viraferon (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

**Table 4** Sustained virological response based on genotype after Viraferon in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients

| | **Study 1**[1] | | | **Study 2**[2] | | |
|---|---|---|---|---|---|---|
| | pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg) | Viraferon (3 MIU TIW) + ribavirin (800 mg) | p value[a] | pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Viraferon (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |

| | | | | | | |
|---|---|---|---|---|---|---|
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients: A total of 345 interferon alpha relapse patients were treated in two clinical trials with Viraferon monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to Viraferon increased by as much as 10-fold the efficacy of Viraferon used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/ml by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non pegylated interferon alfa-2b or non pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Clinical trials in paediatric patients with chronic hepatitis C:
Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received Viraferon 3 MIU/$m^2$ 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. Sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

**Table 5.** Virological response in previously untreated paediatric patients

| | **Viraferon 3 MIU/$m^2$** 3 times a week<br>+<br>**ribavirin 15 mg/kg/day** |
|---|---|
| Overall Response[1] (n=118) | 54 (46 %)* |

| | |
|---|---|
| Genotype 1 (n=92) | 33 (36 %)* |
| Genotype 2/3/4 (n=26) | 21 (81 %)* |

*Number (%) of patients
1. Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

## 5.2 Pharmacokinetic properties

The pharmacokinetics of Viraferon were studied in healthy volunteers following single 5 million IU/$m^2$ and 10 million IU doses administered subcutaneously, at 5 million IU/$m^2$ administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. $C_{max}$ occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/ml) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

*Children and adolescents*: Multiple-dose pharmacokinetic properties for Viraferon injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 6**. The pharmacokinetics of Viraferon and ribavirin (dose-normalized) are similar in adults and children or adolescents.

**Table 6.** Mean (% CV) multiple-dose pharmacokinetic parameters for Viraferon and ribavirin capsules when administered to children or adolescents with chronic hepatitis C

| **Parameter** | **Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17) | **Viraferon** 3 MIU/$m^2$ 3 times a week (n = 54) |
|---|---|---|
| $T_{max}$ (hr) | 1.9 (83) | 5.9 (36) |
| $C_{max}$ (ng/ml) | 3,275 (25) | 51 (48) |
| AUC* | 29,774 (26) | 622 (48) |
| Apparent clearance l/hr/kg | 0.27 (27) | Not done |

*$AUC_{12}$ (ng.hr/ml) for ribavirin; $AUC_{0-24}$ (IU.hr/ml) for Viraferon

Interferon neutralising factor assays were performed on serum samples of patients who received Viraferon in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

## 5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x $10^6$ IU/kg/day

for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x $10^6$ IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour (see section 4.4 and Rebetol SPC if Viraferon is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Disodium phosphate anhydrous,
Sodium dihydrogen phosphate monohydrate,
Edetate disodium,
Eodium chloride,
M-cresol,
Polysorbate 80,
Water for injections.

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

18 months

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Within its shelf-life, for the purpose of transport, the solution can be kept at or below 25ºC for a period up to seven days before use. Viraferon can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it cannot be put back in the refrigerator for a new storage period and must be discarded.

### 6.5 Nature and contents of container

0.5 ml of solution (corresponding to 5 MIU) in a vial (type I glass), with a stopper (halobutyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene)
Pack sizes of 1

Or

0.5 ml of solution (corresponding to 5 MIU) in a vial (type I glass), with a stopper (halobutyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene)
with 1 injection syringe, 1 injection needle and 1 cleansing swab.
Packs sizes of 1, 6 or 12.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

Viraferon solution for injection, may be injected directly after withdrawal of the appropriate doses from the vial with a sterile injection syringe.

As with all parenteral medicinal products, prior to administration inspect Viraferon, solution for injection, visually for particulate matter and discolouration. The solution should be clear and colourless.

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to "How to self inject Viraferon").

Any unused product must be discarded after withdrawal of the dose.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/99/128/013
EU/1/99/128/014
EU/1/99/128/015
EU/1/99/128/016

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 9 March 2000
Date of last renewal : 23 May 2005

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 10 million IU/ml solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of Viraferon solution for injection, single dose vial, contains 10 million IU of recombinant interferon alfa-2b produced in *E.coli* by recombinant DNA technology, in 1 ml of solution.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection
Solution is clear and colourless.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C:
*Adult patients:*
Viraferon is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section 4.4).

The best way to use Viraferon in this indication is in combination with ribavirin.

*Chidren and adolescents:*
Viraferon is intended for use, in a combination regimen with ribavirin, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials (see sections 4.4, 4.8 and 5.1).

### 4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

If adverse events develop during the course of treatment with Viraferon for any indication, modify the dosage or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dosage adjustment, or disease progresses, discontinue treatment with Viraferon.

At the discretion of the physician, the patient may self-administer the dose for maintenance dosage regimens administered subcutaneously.

*Chronic Hepatitis B*: The recommended dosage is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/$mm^3$, granulocytes < 1,000/$mm^3$, thrombocytes < 100,000/$mm^3$). Treatment should be discontinued in case of severe leukopaenia (< 1,200/$mm^3$), severe neutropaenia (< 750/$mm^3$) or severe thrombocytopaenia (< 70,000/$mm^3$).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue Viraferon therapy.

*Chronic Hepatitis C*: Viraferon is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

*Children 3 years of age or older and adolescents*: Interferon alfa-2b 3 MIU/$m^2$ is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsule SPC for dose of ribavirin capsules and dosage modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC).

Relapse patients (adults):
Viraferon is given in combination with ribavirin.

Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for 6 months.

Naïve patients:
*Adults:* The efficacy of Viraferon is enhanced when given in combination with ribavirin. Viraferon should be given alone mainly in case of intolerance or contraindication to ribavirin.

Viraferon in combination with ribavirin:
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Viraferon alone:
The optimal duration of therapy with Viraferon alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with Viraferon alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

*Children and adolescents:* The efficacy and safety of Viraferon in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Virological response is defined as absence of detectable HCV-RNA at Week 12. Treatment should be discontinued in these patients.
Genotype 2/3: The recommended duration of treatment is 24 weeks.

Virological responses after 1 year of treatment and 6 months of follow-up were 36 % for genotype 1 and 81 % for genotype 2/3/4.

Viraferon may be administered using either glass or plastic disposable injection syringes.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.

Children and adolescents:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin: Also see ribavirin SPC if interferon alfa-2b is to be administered in combination with ribavirin in patients with chronic hepatitis C.

**4.4 Special warnings and precautions for use**

*For all patients:*

Psychiatric and central nervous system (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Viraferon therapy, and even after treatment discontinuation mainly during the 6-month follow-up periodand in the follow-up period. Among children and adolescents treated with Viraferon in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others), confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Viraferon be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of or history of severe psychiatric conditions:*
If a treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases, termination of Viraferon therapy. Any patient developing liver function abnormalities during treatment with Viraferon must be monitored closely and treatment discontinued if signs and symptoms progress.

Hypotension may occur during Viraferon therapy or up to two days post-therapy and may require supportive treatment.

Adequate hydration must be maintained in patients undergoing Viraferon therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Viraferon must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instance after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with Viraferon, must have a prompt and complete eye examination. Periodic visual examinations during Viraferon therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of Viraferon should be considered in patients who develop new or worsening ophthalmological disorders.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of Viraferon.

Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require Viraferon therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of Viraferon therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of Viraferon in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Discontinue treatment with Viraferon in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decompensation.

Chronic Hepatitis C:
Combination therapy with ribavirin: Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy: Infrequently, adult patients treated for chronic hepatitis C with Viraferon developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using Viraferon therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which Viraferon may alter thyroid status is unknown. Prior to initiation of Viraferon therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of Viraferon therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, Viraferon treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of Viraferon therapy has not reversed thyroid dysfunction occurring during treatment (also see Children and adolescents, Thyroid monitoring).

*Supplemental monitoring specific for children and adolescents*

Thyroid Monitoring**:** Approximately 12 % of children treated with interferon alfa-2b and ribavirin developed increase in TSH. Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of Viraferon therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Growth and Development: During a 1-year course of therapy there was a decrease in the rate of linear growth (mean percentile decrease of 9 %) and a decrease in the rate of weight gain (mean percentile decrease of 13 %). A general reversal of these trends was noted during the 6 months follow-up post treatment. However, based on interim data from a long-term follow-up study, 12 (14 %) of 84 children had a > 15 percentile decrease in rate of linear growth, of whom 5 (6 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In addition, preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3). Therefore, the risk/benefit of the combined use of interferon alfa-2b and ribavirin should be assessed in young children prior to the initiation of therapy. Physicians are advised to monitor the growth of children taking ribavirin in combination with interferon alfa-2b. There are no data on long term effects on growth and development and on sexual maturation.

HCV/HIV Coinfection**:** Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Viraferon and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders**:** Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Viraferon and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests:
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with Viraferon.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during Viraferon therapy to greater than or equal to 2 times baseline, Viraferon therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, liver function tests: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin must be monitored at two-week intervals.

Effect on fertility: Interferon may impair fertility (see section 4.6 and section 5.3).

## 4.5 Interaction with other medicinal products and other forms of interaction

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with Viraferon.

Interactions between Viraferon and other medicinal products have not been fully evaluated. Caution must be exercised when administering Viraferon in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dosage adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

(Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C).

## 4.6 Pregnancy and lactation

Women of childbearing potential have to use effective contraception during treatment. Viraferon must be used with caution in fertile men. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Viraferon is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

Combination therapy with ribavirin: Ribavirin causes serious birth defects when administered during pregnancy. Ribavirin therapy is contraindicated in women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking Viraferon in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

## 4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with Viraferon, and therefore it is recommended that they avoid driving or operating machinery.

## 4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/$m^2$/week in hairy cell leukaemia up to 100 MIU/$m^2$/week in melanoma), the most commonly reported undesirable effects were fever, fatigue, headache and myalgia. Fever and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

In clinical trials conducted in the hepatitis C population, patients were treated with Viraferon alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of Viraferon three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10); rarely (≥1/10,000, <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1.** Adverse reactions reported during clinical trials or following the marketing use of Viraferon alone or in combination with ribavirin

| System Organ Class | Adverse Reactions |
|---|---|
| **Infections and infestations** | |
| Very common: | Pharyngitis*, infection viral* |
| Common: | Bronchitis, sinusitis, herpes simplex (resistance), rhinitis |
| Rarely: | Pneumonia[§] |
| **Blood and lymphatic system disorders** | |
| Very common: | Leukopaenia |
| Common: | Thrombocytopaenia, lymphadenopathy, lymphopenia |
| Very rarely: | Aplastic anaemia |
| Not known**:** | Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura |
| **Immune system disorders**[§] | |
| Very rarely: | Sarcoidosis, exacerbation of sarcoidosis |
| Not known: | Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis[§] |
| **Endocrine disorders** | |
| Common: | Hypothyroidism[§], hyperthyroidism[§] |
| Very rarely: | Diabetes, aggravated diabetes |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcaemia, dehydration, hyperuricemia, thirst |
| Very rarely: | Hyperglycaemia, hypertriglyceridaemia[§], increased appetite |
| **Psychiatric disorders**[§] | |
| Very common: | Depression, insomnia, anxiety, emotional lability*, agitation, nervousness |
| Common: | Confusion, sleep disorder, libido decreased |
| Rarely: | Suicide ideation |
| Very rarely: | Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations |
| Not known: | Mental status change[§] |
| **Nervous system disorders**[§] | |
| Very common: | Dizziness, headache, concentration impaired, mouth dry |
| Common: | Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion |
| Very rarely: | Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy, neuropathy, polyneuropathy |
| Not known: | Mononeuropathies, coma[§] |
| **Eye disorders** | |
| Very common: | Vision blurred |

| | |
|---|---|
| Common:<br><br>Rarely: | Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain<br>Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§] |
| **Ear and labyrinth**<br>Common:<br>Very rarely: | <br>Vertigo, tinnitus<br>Hearing loss, hearing disorder |
| **Cardiac disorders**<br>Common:<br>Rarely:<br>Very rarely:<br>Not known: | <br>Palpitation, tachycardia<br>Cardiomyopathy<br>Myocardial infarction, cardiac ischaemia<br>Arrhythmia |
| **Vascular disorders**<br>Common:<br>Very rarely: | <br>Hypertension<br>Peripheral ischaemia, hypotension[§] |
| **Respiratory, thoracic and mediastinal disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br><br>Dyspnoea*, coughing*<br>Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive<br>Pulmonary infiltrates[§], pneumonitis[§] |
| **Gastrointestinal disorders**<br>Very common:<br><br>Common:<br><br>Very rarely:<br><br>Not known: | <br>Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia<br>Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools<br>Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding<br>Periodontal disorder NOS, dental disorder NOS[§] |
| **Hepatobiliary disorders**<br>Common:<br>Very rarely: | <br>Hepatomegaly<br>Hepatotoxicity, (including fatality) |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br>Alopecia, pruritus*, skin dry*, rash*, sweating increased<br>Psoriasis (new or aggravated)[§], rash maculopapular, rash erythematous, eczema, erythema, skin disorder<br>Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders**<br>Very common:<br>Common:<br>Very rarely: | <br><br>Myalgia, arthralgia, musculoskeletal pain<br>Arthritis<br>Rhabdomyolysis, myositis, leg cramps, back pain |
| **Renal and urinary disorders**<br>Common:<br>Very rarely: | <br>Micturition frequency<br>Renal failure, renal insufficiency, nephrotic syndrome |
| **Reproductive system and breast disorders**<br>Common: | <br><br>Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder |
| **General disorders and administration site conditions** | |

| | |
|---|---|
| Very common:<br><br><br>Common:<br>Very rarely: | Injection site inflammation, injection site reaction*, fatigue, rigors, fever[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise<br>Injection site pain<br>Injection site necrosis, face oedema |
| **Investigations**<br>Very common: | <br>Weight decrease |

*These events were only common with Viraferon alone
[§]See section 4.4

These undesirable effects have also been reported with Viraferon alone.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

**Paediatric population**

*Children and adolescents – Chronic Hepatitis C*
In clinical trials of 118 children or adolescents 3 to 16 years of age, 6 % discontinued therapy due to adverse events. In general, the adverse event profile in the limited paediatric population studied was similar to that observed in adults, although there is a paediatric specific concern regarding growth inhibition as decrease in height (mean percentile decrease of growth velocity of 9 %) and weight (mean percentile decrease of 13 %) percentile were observed during treatment (see section 4.4). Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from paediatric clinical trials.
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 2** Adverse reactions very commonly and commonly reported in paediatric clinical trials
Very common (≥1/10) - Common (≥1/100, <1/10)

| System Organ Class | Adverse Reactions |
|---|---|
| **Infection and infestations** | |
| Very common: | Viral infection, pharyngitis |
| Common: | Fungal infection, bacterial infection, pulmonary infection, otitis |

| | |
|---|---|
| | media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)**<br>Common: | Neoplasm (unspecified) |
| **Blood and lymphatic system disorders**<br>Very common:<br>Common: | Anaemia, neutropaenia<br>Thrombocytopaenia, lymphadenopathy |
| **Endocrine disorders**<br>Very common:<br>Common: | Hypothyroidism[§],<br>Hyperthyroidism[§], virilism |
| **Metabolism and nutrition disorders**<br>Very common:<br>Common: | Anorexia<br>Hypertriglyceridemia[§], hyperuricemia, increased appetite |
| **Psychiatric disorders**[§]<br>Very common:<br>Common: | Depression, emotional lability, insomnia<br>Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy |
| **Nervous system disorders**[§]<br>Very common:<br>Common: | Headache, dizziness<br>Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence |
| **Eye disorders**<br>Common: | Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder |
| **Vascular disorders**<br>Common: | Raynaud's disease, flushing, pallor |
| **Respiratory, thoracic and mediastinal disorders**<br>Common: | Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing |
| **Gastrointestinal disorders**<br>Very common:<br>Common: | Diarrhoea, vomiting, nausea, abdominal pain<br>Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder |
| **Hepatobiliary disorders**<br>Common: | Hepatic function abnormal |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common: | Alopecia, rash<br>Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased |
| **Musculoskeletal and connective tissue disorders**<br>Very common: | Arthralgia, myalgia, musculoskeletal pain |
| **Renal and urinary disorders**<br>Common: | Enuresis, micturition disorder, urinary incontinence |
| **Reproductive system and** | |

| | |
|---|---|
| **breast disorders**<br>Common: | <br>Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder<br>Male: testicular pain |
| **General disorders and administration site conditions**<br>Very common:<br><br>Common: | <br><br>Injection site inflammation, injection site reaction, fatigue, rigors, fever[§], influenza-like symptoms[§], malaise, irritability<br>Chest pain, asthenia, oedema, injection site pain |
| **Investigations**<br>Very common: | <br>Growth rate decrease (height and/or weight decrease for age)[§] |
| **Injury and poisoning**<br>Common: | <br>Skin laceration |

[§]See section 4.4

### 4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, cytokines and immunomodulators, interferons, interferon alfa-2b, ATC code: L03A B05

Viraferon is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of Viraferon is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $10^8$ IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. Viraferon has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B:
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/$m^2$ 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C:
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

Adult patients: Viraferon alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of Viraferon used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/ml), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Viraferon was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with Viraferon alone or in combination with ribavirin (from two studies) are shown in **Table 3**.

Co-administration of Viraferon with ribavirin increased the efficacy of Viraferon by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of Viraferon + ribavirin, compared with Viraferon alone, is maintained across all subgroups. The relative benefit of combination therapy with Viraferon + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received Viraferon in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained

response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

**Table 3** Sustained virologic response rates with Viraferon + ribavirin (one year of treatment) by genotype and viral load

| HCV Genotype | I<br>N=503<br>C95-132/I95-143 | I/R<br>N=505<br>C95-132/I95-143 | I/R<br>N=505<br>C/I98-580 |
|---|---|---|---|
| **All Genotypes** | **16 %** | **41 %** | **47 %** |
| **Genotype 1** | 9 % | 29 % | 33 % |
| Genotype 1<br>≤ 2 million copies/ml | 25 % | 33 % | 45 % |
| Genotype 1<br>> 2 million copies/ml | 3 % | 27 % | 29 % |
| **Genotype 2/3** | 31 % | 65 % | 79 % |

I Viraferon (3 MIU 3 times a week)
I/R Viraferon (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

*HCV/HIV Co-infected patients*
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received Viraferon plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.**
Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or Viraferon (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or Viraferon (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

**Table 4** Sustained virological response based on genotype after Viraferon in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients

| | **Study 1**[1] | | | **Study 2**[2] | | |
|---|---|---|---|---|---|---|
| | pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg) | Viraferon (3 MIU TIW) + ribavirin (800 mg) | p value[a] | pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Viraferon (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |

| | | | | | | |
|---|---|---|---|---|---|---|
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients: A total of 345 interferon alpha relapse patients were treated in two clinical trials with Viraferon monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to Viraferon increased by as much as 10-fold the efficacy of Viraferon used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/ml by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non pegylated interferon alfa-2b or non pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Clinical trials in paediatric patients with chronic hepatitis C:
Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received Viraferon 3 MIU/$m^2$ 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. Sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

**Table 5.** Virological response in previously untreated paediatric patients

| | **Viraferon 3 MIU/$m^2$** 3 times a week + **ribavirin 15 mg/kg/day** |
|---|---|
| Overall Response[1] (n=118) | 54 (46 %)* |

| | |
|---|---|
| Genotype 1 (n=92) | 33 (36 %)* |
| Genotype 2/3/4 (n=26) | 21 (81 %)* |

*Number (%) of patients
1. Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

## 5.2 Pharmacokinetic properties

The pharmacokinetics of Viraferon were studied in healthy volunteers following single 5 million IU/$m^2$ and 10 million IU doses administered subcutaneously, at 5 million IU/$m^2$ administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. $C_{max}$ occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/ml) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

*Children and adolescents*: Multiple-dose pharmacokinetic properties for Viraferon injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 6**. The pharmacokinetics of Viraferon and ribavirin (dose-normalized) are similar in adults and children or adolescents.

**Table 6.** Mean (% CV) multiple-dose pharmacokinetic parameters for Viraferon and ribavirin capsules when administered to children or adolescents with chronic hepatitis C

| **Parameter** | **Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17) | **Viraferon** 3 MIU/$m^2$ 3 times a week (n = 54) |
|---|---|---|
| $T_{max}$ (hr) | 1.9 (83) | 5.9 (36) |
| $C_{max}$ (ng/ml) | 3,275 (25) | 51 (48) |
| AUC* | 29,774 (26) | 622 (48) |
| Apparent clearance l/hr/kg | 0.27 (27) | Not done |

*$AUC_{12}$ (ng.hr/ml) for ribavirin; $AUC_{0-24}$ (IU.hr/ml) for Viraferon

Interferon neutralising factor assays were performed on serum samples of patients who received Viraferon in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

## 5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x $10^6$ IU/kg/day

for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x $10^6$ IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour (see section 4.4 and Rebetol SPC if Viraferon is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Disodium phosphate anhydrous,
Sodium dihydrogen phosphate monohydrate,
Edetate disodium,
Sodium chloride,
M-cresol,
Polysorbate 80,
Water for injections.

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

18 months

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Within its shelf-life, for the purpose of transport, the solution can be kept at or below 25ºC for a period up to seven days before use. Viraferon can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it cannot be put back in the refrigerator for a new storage period and must be discarded.

### 6.5 Nature and contents of container

1 ml of solution (corresponding to 10 MIU) in a vial (type I glass), with a stopper (halobutyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene)
Pack sizes of 1

Or

1 ml of solution (corresponding to 10 MIU) in a vial (type I glass), with a stopper (halobutyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene)
with 1 injection syringe, 1 injection needle and 1 cleansing swab.
Packs sizes of 1, 6 or 12
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

Viraferon solution for injection, may be injected directly after withdrawal of the appropriate doses from the vial with a sterile injection syringe.

As with all parenteral medicinal products, prior to administration inspect Viraferon, solution for injection, visually for particulate matter and discolouration. The solution should be clear and colourless.

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to "How to self inject Viraferon").

Any unused product must be discarded after withdrawal of the dose.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/99/128/017
EU/1/99/128/018
EU/1/99/128/019
EU/1/99/128/020

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 9 March 2000
Date of last renewal : 23 May 2005

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 18 million IU/3 ml solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of Viraferon solution for injection, multiple dose vial, contains 18 million IU of recombinant interferon alfa-2b produced in E.coli by recombinant DNA technology, in 3 ml of solution.

One ml of solution contains 6 million IU of interferon alfa-2b.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection
Solution is clear and colourless.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C:
*Adult patients:*
Viraferon is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section 4.4).

The best way to use Viraferon in this indication is in combination with ribavirin.

*Chidren and adolescents:*
Viraferon is intended for use, in a combination regimen with ribavirin, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials (see sections 4.4, 4.8 and 5.1).

### 4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

If adverse events develop during the course of treatment with Viraferon for any indication, modify the dosage or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance

develops following adequate dosage adjustment, or disease progresses, discontinue treatment with Viraferon. At the discretion of the physician, the patient may self-administer the dose for maintenance dosage regimens administered subcutaneously.

*Chronic Hepatitis B*: The recommended dosage is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/$mm^3$, granulocytes < 1,000/$mm^3$, thrombocytes < 100,000/$mm^3$). Treatment should be discontinued in case of severe leukopaenia (< 1,200/$mm^3$), severe neutropaenia (< 750/$mm^3$) or severe thrombocytopaenia (< 70,000/$mm^3$).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue Viraferon therapy.

*Chronic Hepatitis C*: Viraferon is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

*Children 3 years of age or older and adolescents*: Interferon alfa-2b 3 MIU/$m^2$ is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsule SPC for dose of ribavirin capsules and dosage modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC).

Relapse patients (adults):
Viraferon is given in combination with ribavirin.

Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for 6 months.

Naïve patients:
*Adults:* The efficacy of Viraferon is enhanced when given in combination with ribavirin. Viraferon should be given alone mainly in case of intolerance or contraindication to ribavirin.

Viraferon in combination with ribavirin:
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Viraferon alone:
The optimal duration of therapy with Viraferon alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with Viraferon alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

*Children and adolescents:* The efficacy and safety of Viraferon in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Virological response is defined as absence of detectable HCV-RNA at Week 12. Treatment should be discontinued in these patients.
Genotype 2/3: The recommended duration of treatment is 24 weeks.

Virological responses after 1 year of treatment and 6 months of follow-up were 36 % for genotype 1 and 81 % for genotype 2/3/4.

Viraferon may be administered using either glass or plastic disposable injection syringes.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.

Children and adolescents:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin: Also see ribavirin SPC if interferon alfa-2b is to be administered in combination with ribavirin in patients with chronic hepatitis C.

**4.4 Special warnings and precautions for use**

*For all patients:*

Psychiatric and central nervous system (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Viraferon therapy, and even after treatment discontinuation mainly during the 6-month follow-up periodand in the follow-up period. Among children and adolescents treated with Viraferon in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others), confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Viraferon be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of or history of severe psychiatric conditions:*
If a treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases, termination of Viraferon therapy. Any patient developing liver function abnormalities during treatment with Viraferon must be monitored closely and treatment discontinued if signs and symptoms progress.

Hypotension may occur during Viraferon therapy or up to two days post-therapy and may require supportive treatment.

Adequate hydration must be maintained in patients undergoing Viraferon therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Viraferon must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instance after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with Viraferon, must have a prompt and complete eye examination. Periodic visual examinations during Viraferon therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of Viraferon should be considered in patients who develop new or worsening ophthalmological disorders.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of Viraferon.

Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require Viraferon therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of Viraferon therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of Viraferon in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Discontinue treatment with Viraferon in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decompensation.

Chronic Hepatitis C:
Combination therapy with ribavirin: Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy: Infrequently, adult patients treated for chronic hepatitis C with Viraferon developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using Viraferon therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which Viraferon may alter thyroid status is unknown. Prior to initiation of Viraferon therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of Viraferon therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, Viraferon treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of Viraferon therapy has not reversed thyroid dysfunction occurring during treatment (also see Children and adolescents, Thyroid monitoring).

*Supplemental monitoring specific for children and adolescents*

Thyroid Monitoring**:** Approximately 12 % of children treated with interferon alfa-2b and ribavirin developed increase in TSH. Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of Viraferon therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Growth and Development: During a 1-year course of therapy there was a decrease in the rate of linear growth (mean percentile decrease of 9 %) and a decrease in the rate of weight gain (mean percentile decrease of 13 %). A general reversal of these trends was noted during the 6 months follow-up post treatment. However, based on interim data from a long-term follow-up study, 12 (14 %) of 84 children had a > 15 percentile decrease in rate of linear growth, of whom 5 (6 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In addition, preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3). Therefore, the risk/benefit of the combined use of interferon alfa-2b and ribavirin should be assessed in young children prior to the initiation of therapy. Physicians are advised to monitor the growth of children taking ribavirin in combination with interferon alfa-2b. There are no data on long term effects on growth and development and on sexual maturation.

HCV/HIV Coinfection**:** Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Viraferon and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders**:** Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Viraferon and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests:
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with Viraferon.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during Viraferon therapy to greater than or equal to 2 times baseline, Viraferon therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, liver function tests: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin must be monitored at two-week intervals.

Effect on fertility: Interferon may impair fertility (see section 4.6 and section 5.3).

### 4.5 Interaction with other medicinal products and other forms of interaction

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with Viraferon.

Interactions between Viraferon and other medicinal products have not been fully evaluated. Caution must be exercised when administering Viraferon in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dosage adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

(Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C).

## 4.6 Pregnancy and lactation

Women of childbearing potential have to use effective contraception during treatment. Viraferon must be used with caution in fertile men. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Viraferon is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

Combination therapy with ribavirin: Ribavirin causes serious birth defects when administered during pregnancy. Ribavirin therapy is contraindicated in women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking Viraferon in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

## 4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with Viraferon, and therefore it is recommended that they avoid driving or operating machinery.

## 4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/$m^2$/week in hairy cell leukaemia up to 100 MIU/$m^2$/week in melanoma), the most commonly reported undesirable effects were fever, fatigue, headache and myalgia. Fever and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

In clinical trials conducted in the hepatitis C population, patients were treated with Viraferon alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of Viraferon three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10); rarely (≥1/10,000, <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1.** Adverse reactions reported during clinical trials or following the marketing use of Viraferon alone or in combination with ribavirin

| System Organ Class | Adverse Reactions |
|---|---|
| **Infections and infestations** | |
| Very common: | Pharyngitis*, infection viral* |
| Common: | Bronchitis, sinusitis, herpes simplex (resistance), rhinitis |
| Rarely: | Pneumonia[§] |
| **Blood and lymphatic system disorders** | |
| Very common: | Leukopaenia |
| Common: | Thrombocytopaenia, lymphadenopathy, lymphopenia |
| Very rarely: | Aplastic anaemia |
| Not known**:** | Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura |
| **Immune system disorders**[§] | |
| Very rarely: | Sarcoidosis, exacerbation of sarcoidosis |
| Not known: | Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis[§] |
| **Endocrine disorders** | |
| Common: | Hypothyroidism[§], hyperthyroidism[§] |
| Very rarely: | Diabetes, aggravated diabetes |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcaemia, dehydration, hyperuricemia, thirst |
| Very rarely: | Hyperglycaemia, hypertriglyceridaemia[§], increased appetite |
| **Psychiatric disorders**[§] | |
| Very common: | Depression, insomnia, anxiety, emotional lability*, agitation, nervousness |
| Common: | Confusion, sleep disorder, libido decreased |
| Rarely: | Suicide ideation |
| Very rarely: | Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations |
| Not known: | Mental status change[§] |
| **Nervous system disorders**[§] | |
| Very common: | Dizziness, headache, concentration impaired, mouth dry |
| Common: | Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion |
| Very rarely: | Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy, neuropathy, polyneuropathy |
| Not known: | Mononeuropathies, coma[§] |
| **Eye disorders** | |
| Very common: | Vision blurred |

| | |
|---|---|
| Common:<br><br>Rarely: | Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain<br>Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§] |
| **Ear and labyrinth**<br>Common:<br>Very rarely: | <br>Vertigo, tinnitus<br>Hearing loss, hearing disorder |
| **Cardiac disorders**<br>Common:<br>Rarely:<br>Very rarely:<br>Not known: | <br>Palpitation, tachycardia<br>Cardiomyopathy<br>Myocardial infarction, cardiac ischaemia<br>Arrhythmia |
| **Vascular disorders**<br>Common:<br>Very rarely: | <br>Hypertension<br>Peripheral ischaemia, hypotension[§] |
| **Respiratory, thoracic and mediastinal disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br><br>Dyspnoea*, coughing*<br>Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive<br>Pulmonary infiltrates[§], pneumonitis[§] |
| **Gastrointestinal disorders**<br>Very common:<br><br>Common:<br><br>Very rarely:<br><br>Not known: | <br>Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia<br>Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools<br>Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding<br>Periodontal disorder NOS, dental disorder NOS[§] |
| **Hepatobiliary disorders**<br>Common:<br>Very rarely: | <br>Hepatomegaly<br>Hepatotoxicity, (including fatality) |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br>Alopecia, pruritus*, skin dry*, rash*, sweating increased<br>Psoriasis (new or aggravated)[§], rash maculopapular, rash erythematous, eczema, erythema, skin disorder<br>Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders**<br>Very common:<br>Common:<br>Very rarely: | <br><br>Myalgia, arthralgia, musculoskeletal pain<br>Arthritis<br>Rhabdomyolysis, myositis, leg cramps, back pain |
| **Renal and urinary disorders**<br>Common:<br>Very rarely: | <br>Micturition frequency<br>Renal failure, renal insufficiency, nephrotic syndrome |
| **Reproductive system and breast disorders**<br>Common: | <br><br>Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder |
| **General disorders and administration site conditions** | |

| | |
|---|---|
| Very common:<br><br><br>Common:<br>Very rarely: | Injection site inflammation, injection site reaction*, fatigue, rigors, fever[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise<br>Injection site pain<br>Injection site necrosis, face oedema |
| **Investigations**<br>Very common: | <br>Weight decrease |

*These events were only common with Viraferon alone
[§]See section 4.4

These undesirable effects have also been reported with Viraferon alone.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

**Paediatric population**

*Children and adolescents – Chronic Hepatitis C*
In clinical trials of 118 children or adolescents 3 to 16 years of age, 6 % discontinued therapy due to adverse events. In general, the adverse event profile in the limited paediatric population studied was similar to that observed in adults, although there is a paediatric specific concern regarding growth inhibition as decrease in height (mean percentile decrease of growth velocity of 9 %) and weight (mean percentile decrease of 13 %) percentile were observed during treatment (see section 4.4). Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from paediatric clinical trials.
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 2** Adverse reactions very commonly and commonly reported in paediatric clinical trials
Very common (≥1/10) - Common (≥1/100, <1/10)

| System Organ Class | Adverse Reactions |
|---|---|
| **Infection and infestations** | |
| Very common: | Viral infection, pharyngitis |
| Common: | Fungal infection, bacterial infection, pulmonary infection, otitis |

| | |
|---|---|
| | media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)**<br>Common: | Neoplasm (unspecified) |
| **Blood and lymphatic system disorders**<br>Very common:<br>Common: | Anaemia, neutropaenia<br>Thrombocytopaenia, lymphadenopathy |
| **Endocrine disorders**<br>Very common:<br>Common: | Hypothyroidism[§],<br>Hyperthyroidism[§], virilism |
| **Metabolism and nutrition disorders**<br>Very common:<br>Common: | Anorexia<br>Hypertriglyceridemia[§], hyperuricemia, increased appetite |
| **Psychiatric disorders**[§]<br>Very common:<br>Common: | Depression, emotional lability, insomnia<br>Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy |
| **Nervous system disorders**[§]<br>Very common:<br>Common: | Headache, dizziness<br>Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence |
| **Eye disorders**<br>Common: | Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder |
| **Vascular disorders**<br>Common: | Raynaud's disease, flushing, pallor |
| **Respiratory, thoracic and mediastinal disorders**<br>Common: | Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing |
| **Gastrointestinal disorders**<br>Very common:<br>Common: | Diarrhoea, vomiting, nausea, abdominal pain<br>Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder |
| **Hepatobiliary disorders**<br>Common: | Hepatic function abnormal |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common: | Alopecia, rash<br>Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased |
| **Musculoskeletal and connective tissue disorders**<br>Very common: | Arthralgia, myalgia, musculoskeletal pain |
| **Renal and urinary disorders**<br>Common: | Enuresis, micturition disorder, urinary incontinence |
| **Reproductive system and** | |

| | |
|---|---|
| **breast disorders**<br>Common: | <br>Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder<br>Male: testicular pain |
| **General disorders and administration site conditions**<br>Very common:<br><br>Common: | <br><br>Injection site inflammation, injection site reaction, fatigue, rigors, fever[§], influenza-like symptoms[§], malaise, irritability<br>Chest pain, asthenia, oedema, injection site pain |
| **Investigations**<br>Very common: | <br>Growth rate decrease (height and/or weight decrease for age)[§] |
| **Injury and poisoning**<br>Common: | <br>Skin laceration |

[§]See section 4.4

### 4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, cytokines and immunomodulators, interferons, interferon alfa-2b, ATC code: L03A B05

Viraferon is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of Viraferon is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $10^8$ IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. Viraferon has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B:
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/$m^2$ 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C:
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

Adult patients: Viraferon alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of Viraferon used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/ml), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Viraferon was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with Viraferon alone or in combination with ribavirin (from two studies) are shown in **Table 3**.

Co-administration of Viraferon with ribavirin increased the efficacy of Viraferon by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of Viraferon + ribavirin, compared with Viraferon alone, is maintained across all subgroups. The relative benefit of combination therapy with Viraferon + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received Viraferon in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained

response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

**Table 3** Sustained virologic response rates with Viraferon + ribavirin (one year of treatment) by genotype and viral load

| **HCV Genotype** | **I N=503 C95-132/I95-143** | **I/R N=505 C95-132/I95-143** | **I/R N=505 C/I98-580** |
|---|---|---|---|
| **All Genotypes** | **16 %** | **41 %** | **47 %** |
| **Genotype 1** | 9 % | 29 % | 33 % |
| Genotype 1 ≤ 2 million copies/ml | 25 % | 33 % | 45 % |
| Genotype 1 > 2 million copies/ml | 3 % | 27 % | 29 % |
| **Genotype 2/3** | 31 % | 65 % | 79 % |

I Viraferon (3 MIU 3 times a week)
I/R Viraferon (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

*HCV/HIV Co-infected patients*
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received Viraferon plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or Viraferon (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or Viraferon (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

**Table 4** Sustained virological response based on genotype after Viraferon in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients

| | **Study 1**[1] | | | **Study 2**[2] | | |
|---|---|---|---|---|---|---|
| | pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg) | Viraferon (3 MIU TIW) + ribavirin (800 mg) | p value[a] | pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Viraferon (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |

| | | | | | | |
|---|---|---|---|---|---|---|
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients: A total of 345 interferon alpha relapse patients were treated in two clinical trials with Viraferon monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to Viraferon increased by as much as 10-fold the efficacy of Viraferon used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/ml by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non pegylated interferon alfa-2b or non pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Clinical trials in paediatric patients with chronic hepatitis C:
Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received Viraferon 3 MIU/$m^2$ 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. Sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

**Table 5.** Virological response in previously untreated paediatric patients

| | **Viraferon 3 MIU/$m^2$** 3 times a week<br>+<br>**ribavirin 15 mg/kg/day** |
|---|---|
| Overall Response[1] (n=118) | 54 (46 %)* |

| | |
|---|---|
| Genotype 1 (n=92) | 33 (36 %)* |
| Genotype 2/3/4 (n=26) | 21 (81 %)* |

*Number (%) of patients
1. Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

## 5.2 Pharmacokinetic properties

The pharmacokinetics of Viraferon were studied in healthy volunteers following single 5 million IU/$m^2$ and 10 million IU doses administered subcutaneously, at 5 million IU/$m^2$ administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. $C_{max}$ occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/ml) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

*Children and adolescents*: Multiple-dose pharmacokinetic properties for Viraferon injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 6**. The pharmacokinetics of Viraferon and ribavirin (dose-normalized) are similar in adults and children or adolescents.

**Table 6.** Mean (% CV) multiple-dose pharmacokinetic parameters for Viraferon and ribavirin capsules when administered to children or adolescents with chronic hepatitis C

| **Parameter** | **Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17) | **Viraferon** 3 MIU/$m^2$ 3 times a week (n = 54) |
|---|---|---|
| $T_{max}$ (hr) | 1.9 (83) | 5.9 (36) |
| $C_{max}$ (ng/ml) | 3,275 (25) | 51 (48) |
| AUC* | 29,774 (26) | 622 (48) |
| Apparent clearance l/hr/kg | 0.27 (27) | Not done |

*$AUC_{12}$ (ng.hr/ml) for ribavirin; $AUC_{0-24}$ (IU.hr/ml) for Viraferon

Interferon neutralising factor assays were performed on serum samples of patients who received Viraferon in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

## 5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x $10^6$ IU/kg/day

for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x $10^6$ IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour (see section 4.4 and Rebetol SPC if Viraferon is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Disodium phosphate anhydrous,
Sodium dihydrogen phosphate monohydrate,
Edetate disodium,
Sodium chloride,
M-cresol,
Polysorbate 80,
Water for injections.

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

2 years

After first opening the container: Chemical and physical in-use stability has been demonstrated for 28 days at 2ºC – 8ºC.
From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 2ºC – 8ºC. Other in-use storage times and conditions are the responsibility of the user.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Within its shelf-life, for the purpose of transport, the solution can be kept at or below 25ºC for a period up to seven days before use. Viraferon can be put back in the refrigerator at any time during this seven-day period.

If the product is not used during the seven-day period, it cannot be put back in the refrigerator for a new storage period and must be discarded.

### 6.5 Nature and contents of container

3 ml of solution (corresponding to 18 MIU) in a vial (type I glass), with a stopper (halobutyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene).
Pack sizes of 1, 2 or 12

Or

3 ml of solution (corresponding to 18 MIU) in a vial (type I glass), with a stopper (halobutyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene)
with 6 injection syringes, 6 injection needles and 12 cleansing swabs.
Pack sizes of 1
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

Viraferon solution for injection, may be injected directly after withdrawal of the appropriate doses from the vial with a sterile injection syringe.

As with all parenteral medicinal products, prior to administration inspect Viraferon, solution for injection, visually for particulate matter and discolouration. The solution should be clear and colourless.

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to "How to self inject Viraferon").

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/99/128/021
EU/1/99/128/022
EU/1/99/128/023
EU/1/99/128/024

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 9 March 2000
Date of last renewal : 23 May 2005

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 25 million IU/2.5 ml solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of Viraferon solution for injection, multiple dose vial, contains 25 million IU of recombinant interferon alfa-2b produced in E.coli by recombinant DNA technology, in 2.5 ml of solution.

One ml of solution contains 10 million IU of interferon alfa-2b.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection
Solution is clear and colourless.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C:
*Adult patients:*
Viraferon is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section 4.4).

The best way to use Viraferon in this indication is in combination with ribavirin.

*Chidren and adolescents:*
Viraferon is intended for use, in a combination regimen with ribavirin, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials (see sections 4.4, 4.8 and 5.1).

### 4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

If adverse events develop during the course of treatment with Viraferon for any indication, modify the dosage or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance

develops following adequate dosage adjustment, or disease progresses, discontinue treatment with Viraferon. At the discretion of the physician, the patient may self-administer the dose for maintenance dosage regimens administered subcutaneously.

*Chronic Hepatitis B*: The recommended dosage is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/$mm^3$, granulocytes < 1,000/$mm^3$, thrombocytes < 100,000/$mm^3$). Treatment should be discontinued in case of severe leukopaenia (< 1,200/$mm^3$), severe neutropaenia (< 750/$mm^3$) or severe thrombocytopaenia (< 70,000/$mm^3$).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue Viraferon therapy.

*Chronic Hepatitis C*: Viraferon is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

*Children 3 years of age or older and adolescents*: Interferon alfa-2b 3 MIU/$m^2$ is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsule SPC for dose of ribavirin capsules and dosage modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC).

Relapse patients (adults):
Viraferon is given in combination with ribavirin.

Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for 6 months.

Naïve patients:
*Adults:* The efficacy of Viraferon is enhanced when given in combination with ribavirin. Viraferon should be given alone mainly in case of intolerance or contraindication to ribavirin.

Viraferon in combination with ribavirin:
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Viraferon alone:
The optimal duration of therapy with Viraferon alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with Viraferon alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

*Children and adolescents:* The efficacy and safety of Viraferon in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Virological response is defined as absence of detectable HCV-RNA at Week 12. Treatment should be discontinued in these patients.
Genotype 2/3: The recommended duration of treatment is 24 weeks.

Virological responses after 1 year of treatment and 6 months of follow-up were 36 % for genotype 1 and 81 % for genotype 2/3/4.

Viraferon may be administered using either glass or plastic disposable injection syringes.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.

Children and adolescents:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin: Also see ribavirin SPC if interferon alfa-2b is to be administered in combination with ribavirin in patients with chronic hepatitis C.

**4.4 Special warnings and precautions for use**

*For all patients:*

Psychiatric and central nervous system (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Viraferon therapy, and even after treatment discontinuation mainly during the 6-month follow-up periodand in the follow-up period. Among children and adolescents treated with Viraferon in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others), confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Viraferon be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of or history of severe psychiatric conditions:*
If a treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases, termination of Viraferon therapy. Any patient developing liver function abnormalities during treatment with Viraferon must be monitored closely and treatment discontinued if signs and symptoms progress.

Hypotension may occur during Viraferon therapy or up to two days post-therapy and may require supportive treatment.

Adequate hydration must be maintained in patients undergoing Viraferon therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Viraferon must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instance after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with Viraferon, must have a prompt and complete eye examination. Periodic visual examinations during Viraferon therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of Viraferon should be considered in patients who develop new or worsening ophthalmological disorders.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of Viraferon.

Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require Viraferon therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of Viraferon therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of Viraferon in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Discontinue treatment with Viraferon in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decompensation.

Chronic Hepatitis C:
Combination therapy with ribavirin: Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy: Infrequently, adult patients treated for chronic hepatitis C with Viraferon developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using Viraferon therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which Viraferon may alter thyroid status is unknown. Prior to initiation of Viraferon therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of Viraferon therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, Viraferon treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of Viraferon therapy has not reversed thyroid dysfunction occurring during treatment (also see Children and adolescents, Thyroid monitoring).

*Supplemental monitoring specific for children and adolescents*

Thyroid Monitoring**:** Approximately 12 % of children treated with interferon alfa-2b and ribavirin developed increase in TSH. Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of Viraferon therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Growth and Development: During a 1-year course of therapy there was a decrease in the rate of linear growth (mean percentile decrease of 9 %) and a decrease in the rate of weight gain (mean percentile decrease of 13 %). A general reversal of these trends was noted during the 6 months follow-up post treatment. However, based on interim data from a long-term follow-up study, 12 (14 %) of 84 children had a > 15 percentile decrease in rate of linear growth, of whom 5 (6 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In addition, preclinal juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3). Therefore, the risk/benefit of the combined use of interferon alfa-2b and ribavirin should be assessed in young children prior to the initiation of therapy. Physicians are advised to monitor the growth of children taking ribavirin in combination with interferon alfa-2b. There are no data on long term effects on growth and development and on sexual maturation.

HCV/HIV Coinfection**:** Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Viraferon and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders**:** Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Viraferon and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests:
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with Viraferon.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during Viraferon therapy to greater than or equal to 2 times baseline, Viraferon therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, liver function tests: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin must be monitored at two-week intervals.

Effect on fertility: Interferon may impair fertility (see section 4.6 and section 5.3).

## 4.5 Interaction with other medicinal products and other forms of interaction

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with Viraferon.

Interactions between Viraferon and other medicinal products have not been fully evaluated. Caution must be exercised when administering Viraferon in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dosage adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

(Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C).

## 4.6 Pregnancy and lactation

Women of childbearing potential have to use effective contraception during treatment. Viraferon must be used with caution in fertile men. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Viraferon is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

Combination therapy with ribavirin: Ribavirin causes serious birth defects when administered during pregnancy. Ribavirin therapy is contraindicated in women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking Viraferon in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

## 4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with Viraferon, and therefore it is recommended that they avoid driving or operating machinery.

## 4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/$m^2$/week in hairy cell leukaemia up to 100 MIU/$m^2$/week in melanoma), the most commonly reported undesirable effects were fever, fatigue, headache and myalgia. Fever and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

In clinical trials conducted in the hepatitis C population, patients were treated with Viraferon alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of Viraferon three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10); rarely (≥1/10,000, <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1.** Adverse reactions reported during clinical trials or following the marketing use of Viraferon alone or in combination with ribavirin

| System Organ Class | Adverse Reactions |
|---|---|
| **Infections and infestations** | |
| Very common: | Pharyngitis*, infection viral* |
| Common: | Bronchitis, sinusitis, herpes simplex (resistance), rhinitis |
| Rarely: | Pneumonia§ |
| **Blood and lymphatic system disorders** | |
| Very common: | Leukopaenia |
| Common: | Thrombocytopaenia, lymphadenopathy, lymphopenia |
| Very rarely: | Aplastic anaemia |
| Not known**:** | Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura |
| **Immune system disorders**§ | |
| Very rarely: | Sarcoidosis, exacerbation of sarcoidosis |
| Not known: | Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis§ |
| **Endocrine disorders** | |
| Common: | Hypothyroidism§, hyperthyroidism§ |
| Very rarely: | Diabetes, aggravated diabetes |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcaemia, dehydration, hyperuricemia, thirst |
| Very rarely: | Hyperglycaemia, hypertriglyceridaemia§, increased appetite |
| **Psychiatric disorders**§ | |
| Very common: | Depression, insomnia, anxiety, emotional lability*, agitation, nervousness |
| Common: | Confusion, sleep disorder, libido decreased |
| Rarely: | Suicide ideation |
| Very rarely: | Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations |
| Not known: | Mental status change§ |
| **Nervous system disorders**§ | |
| Very common: | Dizziness, headache, concentration impaired, mouth dry |
| Common: | Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion |
| Very rarely: | Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy, neuropathy, polyneuropathy |
| Not known: | Mononeuropathies, coma§ |
| **Eye disorders** | |
| Very common: | Vision blurred |
| Common: | Conjunctivitis, vision abnormal, lacrimal gland disorder, eye |

| | |
|---|---|
| Rarely: | pain<br>Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§] |
| **Ear and labyrinth**<br>Common:<br>Very rarely: | <br>Vertigo, tinnitus<br>Hearing loss, hearing disorder |
| **Cardiac disorders**<br>Common:<br>Rarely:<br>Very rarely:<br>Not known: | <br>Palpitation, tachycardia<br>Cardiomyopathy<br>Myocardial infarction, cardiac ischaemia<br>Arrhythmia |
| **Vascular disorders**<br>Common:<br>Very rarely: | <br>Hypertension<br>Peripheral ischaemia, hypotension[§] |
| **Respiratory, thoracic and mediastinal disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br><br>Dyspnoea*, coughing*<br>Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive<br>Pulmonary infiltrates[§], pneumonitis[§] |
| **Gastrointestinal disorders**<br>Very common:<br><br>Common:<br><br>Very rarely:<br><br>Not known: | <br>Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia<br>Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools<br>Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding<br>Periodontal disorder NOS, dental disorder NOS[§] |
| **Hepatobiliary disorders**<br>Common:<br>Very rarely: | <br>Hepatomegaly<br>Hepatotoxicity, (including fatality) |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br>Alopecia, pruritus*, skin dry*, rash*, sweating increased<br>Psoriasis (new or aggravated)[§], rash maculopapular, rash erythematous, eczema, erythema, skin disorder<br>Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders**<br>Very common:<br>Common:<br>Very rarely: | <br><br>Myalgia, arthralgia, musculoskeletal pain<br>Arthritis<br>Rhabdomyolysis, myositis, leg cramps, back pain |
| **Renal and urinary disorders**<br>Common:<br>Very rarely: | <br>Micturition frequency<br>Renal failure, renal insufficiency, nephrotic syndrome |
| **Reproductive system and breast disorders**<br>Common: | <br><br>Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder |
| **General disorders and administration site conditions**<br>Very common: | <br><br>Injection site inflammation, injection site reaction*, fatigue, |

| | |
|---|---|
| | rigors, fever[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise |
| Common: | Injection site pain |
| Very rarely: | Injection site necrosis, face oedema |
| **Investigations** | |
| Very common: | Weight decrease |

*These events were only common with Viraferon alone
[§]See section 4.4

These undesirable effects have also been reported with Viraferon alone.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

**Paediatric population**

*Children and adolescents – Chronic Hepatitis C*
In clinical trials of 118 children or adolescents 3 to 16 years of age, 6 % discontinued therapy due to adverse events. In general, the adverse event profile in the limited paediatric population studied was similar to that observed in adults, although there is a paediatric specific concern regarding growth inhibition as decrease in height (mean percentile decrease of growth velocity of 9 %) and weight (mean percentile decrease of 13 %) percentile were observed during treatment (see section 4.4). Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from paediatric clinical trials.
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 2** Adverse reactions very commonly and commonly reported in paediatric clinical trials
Very common (≥1/10) - Common (≥1/100, <1/10)

| **System Organ Class** | **Adverse Reactions** |
|---|---|
| **Infection and infestations** | |
| Very common: | Viral infection, pharyngitis |
| Common: | Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, |

| | |
|---|---|
| | vaginitis, gastroenteritis |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)**<br>Common: | Neoplasm (unspecified) |
| **Blood and lymphatic system disorders**<br>Very common:<br>Common: | Anaemia, neutropaenia<br>Thrombocytopaenia, lymphadenopathy |
| **Endocrine disorders**<br>Very common:<br>Common: | Hypothyroidism[§],<br>Hyperthyroidism[§], virilism |
| **Metabolism and nutrition disorders**<br>Very common:<br>Common: | Anorexia<br>Hypertriglyceridemia[§], hyperuricemia, increased appetite |
| **Psychiatric disorders**[§]<br>Very common:<br>Common: | Depression, emotional lability, insomnia<br>Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy |
| **Nervous system disorders**[§]<br>Very common:<br>Common: | Headache, dizziness<br>Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence |
| **Eye disorders**<br>Common: | Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder |
| **Vascular disorders**<br>Common: | Raynaud's disease, flushing, pallor |
| **Respiratory, thoracic and mediastinal disorders**<br>Common: | Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing |
| **Gastrointestinal disorders**<br>Very common:<br>Common: | Diarrhoea, vomiting, nausea, abdominal pain<br>Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder |
| **Hepatobiliary disorders**<br>Common: | Hepatic function abnormal |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common: | Alopecia, rash<br>Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased |
| **Musculoskeletal and connective tissue disorders**<br>Very common: | Arthralgia, myalgia, musculoskeletal pain |
| **Renal and urinary disorders**<br>Common: | Enuresis, micturition disorder, urinary incontinence |
| **Reproductive system and breast disorders** | |

| | |
|---|---|
| Common: | Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder<br>Male: testicular pain |
| **General disorders and administration site conditions**<br>Very common:<br><br>Common: | <br><br>Injection site inflammation, injection site reaction, fatigue, rigors, fever[§], influenza-like symptoms[§], malaise, irritability<br>Chest pain, asthenia, oedema, injection site pain |
| **Investigations**<br>Very common: | <br>Growth rate decrease (height and/or weight decrease for age)[§] |
| **Injury and poisoning**<br>Common: | <br>Skin laceration |

[§]See section 4.4

### 4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, cytokines and immunomodulators, interferons, interferon alfa-2b, ATC code: L03A B05

Viraferon is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of Viraferon is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $l0^8$ IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. Viraferon has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B:
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/$m^2$ 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C:
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

Adult patients: Viraferon alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of Viraferon used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/ml), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Viraferon was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with Viraferon alone or in combination with ribavirin (from two studies) are shown in **Table 3.**

Co-administration of Viraferon with ribavirin increased the efficacy of Viraferon by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of Viraferon + ribavirin, compared with Viraferon alone, is maintained across all subgroups. The relative benefit of combination therapy with Viraferon + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received Viraferon in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained

response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

**Table 3** Sustained virologic response rates with Viraferon + ribavirin (one year of treatment) by genotype and viral load

| HCV Genotype | I N=503 C95-132/I95-143 | I/R N=505 C95-132/I95-143 | I/R N=505 C/I98-580 |
|---|---|---|---|
| **All Genotypes** | **16 %** | **41 %** | **47 %** |
| **Genotype 1** | 9 % | 29 % | 33 % |
| Genotype 1 ≤ 2 million copies/ml | 25 % | 33 % | 45 % |
| Genotype 1 > 2 million copies/ml | 3 % | 27 % | 29 % |
| **Genotype 2/3** | 31 % | 65 % | 79 % |

I Viraferon (3 MIU 3 times a week)
I/R Viraferon (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

*HCV/HIV Co-infected patients*
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received Viraferon plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or Viraferon (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or Viraferon (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

**Table 4** Sustained virological response based on genotype after Viraferon in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients

| | **Study 1**[1] | | | **Study 2**[2] | | |
|---|---|---|---|---|---|---|
| | pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg) | Viraferon (3 MIU TIW) + ribavirin (800 mg) | p value[a] | pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Viraferon (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |

| | | | | | | |
|---|---|---|---|---|---|---|
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients: A total of 345 interferon alpha relapse patients were treated in two clinical trials with Viraferon monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to Viraferon increased by as much as 10-fold the efficacy of Viraferon used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/ml by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non pegylated interferon alfa-2b or non pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Clinical trials in paediatric patients with chronic hepatitis C:
Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received Viraferon 3 MIU/$m^2$ 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. Sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

**Table 5.** Virological response in previously untreated paediatric patients

| | **Viraferon 3 MIU/$m^2$** 3 times a week<br>+<br>**ribavirin 15 mg/kg/day** |
|---|---|
| Overall Response[1] (n=118) | 54 (46 %)* |

| | |
|---|---|
| Genotype 1 (n=92) | 33 (36 %)* |
| Genotype 2/3/4 (n=26) | 21 (81 %)* |

*Number (%) of patients
1. Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

## 5.2 Pharmacokinetic properties

The pharmacokinetics of Viraferon were studied in healthy volunteers following single 5 million IU/$m^2$ and 10 million IU doses administered subcutaneously, at 5 million IU/$m^2$ administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. $C_{max}$ occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/ml) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

*Children and adolescents*: Multiple-dose pharmacokinetic properties for Viraferon injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 6**. The pharmacokinetics of Viraferon and ribavirin (dose-normalized) are similar in adults and children or adolescents.

**Table 6.** Mean (% CV) multiple-dose pharmacokinetic parameters for Viraferon and ribavirin capsules when administered to children or adolescents with chronic hepatitis C

| **Parameter** | **Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17) | **Viraferon** 3 MIU/$m^2$ 3 times a week (n = 54) |
|---|---|---|
| $T_{max}$ (hr) | 1.9 (83) | 5.9 (36) |
| $C_{max}$ (ng/ml) | 3,275 (25) | 51 (48) |
| AUC* | 29,774 (26) | 622 (48) |
| Apparent clearance l/hr/kg | 0.27 (27) | Not done |

*$AUC_{12}$ (ng.hr/ml) for ribavirin; $AUC_{0-24}$ (IU.hr/ml) for Viraferon

Interferon neutralising factor assays were performed on serum samples of patients who received Viraferon in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

## 5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x $10^6$ IU/kg/day

for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x $10^6$ IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour ((see section 4.4 and Rebetol SPC if Viraferon is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Disodium phosphate anhydrous,
Sodium dihydrogen phosphate monohydrate,
Edetate disodium,
Sodium chloride,
M-cresol,
Polysorbate 80,
Water for injections.

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

2 years

After first opening the container: Chemical and physical in-use stability has been demonstrated for 28 days at 2ºC – 8ºC.
From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 2ºC – 8ºC. Other in-use storage times and conditions are the responsibility of the user.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Within its shelf-life, for the purpose of transport, the solution can be kept at or below 25ºC for a period up to seven days before use. Viraferon can be put back in the refrigerator at any time during this seven-day period.

If the product is not used during the seven-day period, it cannot be put back in the refrigerator for a new storage period and must be discarded.

### 6.5 Nature and contents of container

2.5 ml of solution (corresponding to 25 MIU) in a vial (type I glass), with a stopper (halobutyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene).
Pack sizes of 1, 2 or 12

Or

2.5 ml of solution (corresponding to 25 MIU) in a vial (type I glass), with a stopper (halobutyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene)
with 6 injection syringes, 6 injection needles and 12 cleansing swabs.
Pack sizes of 1
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

Viraferon solution for injection, may be injected directly after withdrawal of the appropriate doses from the vial with a sterile injection syringe.

As with all parenteral medicinal products, prior to administration inspect Viraferon, solution for injection, visually for particulate matter and discolouration. The solution should be clear and colourless.

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to "How to self inject Viraferon").

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/99/128/025
EU/1/99/128/026
EU/1/99/128/027
EU/1/99/128/028

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 9 March 2000
Date of last renewal : 23 May 2005

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 18 million IU solution for injection, multidose pen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One cartridge contains 18 million IU of recombinant interferon alfa-2b produced in *E.coli* by recombinant DNA technology, in 1.2 ml.

One ml contains 15 million IU of interferon alfa-2b.

The pen is designed to deliver its contents of 18 million IU in doses ranging from 1.5 to 6 million IU. The pen will deliver a maximum of 12 doses of 1.5 million IU over a period not to exceed 4 weeks.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection
Solution is clear and colourless.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C:
*Adult patients:*
Viraferon is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section 4.4).

The best way to use Viraferon in this indication is in combination with ribavirin.

*Chidren and adolescents:*
Viraferon is intended for use, in a combination regimen with ribavirin, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials (see sections 4.4, 4.8 and 5.1).

### 4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Multidose presentations must be for individual patient use only.

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

If adverse events develop during the course of treatment with Viraferon for any indication, modify the dosage or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dosage adjustment, or disease progresses, discontinue treatment with Viraferon. At the discretion of the physician, the patient may self-administer the dose for maintenance dosage regimens administered subcutaneously.

*Chronic Hepatitis B*: The recommended dosage is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/$mm^3$, granulocytes < 1,000/$mm^3$, thrombocytes < 100,000/$mm^3$). Treatment should be discontinued in case of severe leukopaenia (< 1,200/$mm^3$), severe neutropaenia (< 750/$mm^3$) or severe thrombocytopaenia (< 70,000/$mm^3$).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue Viraferon therapy.

*Chronic Hepatitis C:* Viraferon is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

*Children 3 years of age or older and adolescents*: Interferon alfa-2b 3 MIU/$m^2$ is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsule SPC for dose of ribavirin capsules and dosage modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC).

Relapse patients (adults):
Viraferon is given in combination with ribavirin.

Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for 6 months.

Naïve patients:
*Adults:* The efficacy of Viraferon is enhanced when given in combination with ribavirin. Viraferon should be given alone mainly in case of intolerance or contraindication to ribavirin.

Viraferon in combination with ribavirin:
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Viraferon alone:
The optimal duration of therapy with Viraferon alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with Viraferon alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

*Children and adolescents:* The efficacy and safety of Viraferon in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Virological response is defined as absence of detectable HCV-RNA at Week 12. Treatment should be discontinued in these patients.
Genotype 2/3: The recommended duration of treatment is 24 weeks.

Virological responses after 1 year of treatment and 6 months of follow-up were 36 % for genotype 1 and 81 % for genotype 2/3/4.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.

Children and adolescents:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin: Also see ribavirin SPC if interferon alfa-2b is to be administered in combination with ribavirin in patients with chronic hepatitis C.

**4.4 Special warnings and precautions for use**

*For all patients:*

Psychiatric and central nervous system (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Viraferon therapy, and even after treatment discontinuation mainly during the 6-month follow-up periodand in the follow-up period. Among children and adolescents treated with Viraferon in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others), confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric

symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Viraferon be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of or history of severe psychiatric conditions:*
If a treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases, termination of Viraferon therapy. Any patient developing liver function abnormalities during treatment with Viraferon must be monitored closely and treatment discontinued if signs and symptoms progress.

Hypotension may occur during Viraferon therapy or up to two days post-therapy and may require supportive treatment.

Adequate hydration must be maintained in patients undergoing Viraferon therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Viraferon must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instance after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with Viraferon, must have a prompt and complete eye examination. Periodic visual examinations during Viraferon therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of Viraferon should be considered in patients who develop new or worsening ophthalmological disorders.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of Viraferon.

Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require Viraferon therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of Viraferon therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of Viraferon in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Discontinue treatment with Viraferon in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decompensation.

Chronic Hepatitis C:
Combination therapy with ribavirin: Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy: Infrequently, adult patients treated for chronic hepatitis C with Viraferon developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using Viraferon therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which Viraferon may alter thyroid status is unknown. Prior to initiation of Viraferon therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of Viraferon therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, Viraferon treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of

Viraferon therapy has not reversed thyroid dysfunction occurring during treatment (also see Children and adolescents, Thyroid monitoring).

*Supplemental monitoring specific for children and adolescents*
Thyroid Monitoring**:** Approximately 12 % of children treated with interferon alfa-2b and ribavirin developed increase in TSH. Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of Viraferon therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Growth and Development: During a 1-year course of therapy there was a decrease in the rate of linear growth (mean percentile decrease of 9 %) and a decrease in the rate of weight gain (mean percentile decrease of 13 %). A general reversal of these trends was noted during the 6 months follow-up post treatment. However, based on interim data from a long-term follow-up study, 12 (14 %) of 84 children had a > 15 percentile decrease in rate of linear growth, of whom 5 (6 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In addition, preclicinal juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3). Therefore, the risk/benefit of the combined use of interferon alfa-2b and ribavirin should be assessed in young children prior to the initiation of therapy. Physicians are advised to monitor the growth of children taking ribavirin in combination with interferon alfa-2b. There are no data on long term effects on growth and development and on sexual maturation.

HCV/HIV Coinfection**:** Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Viraferon and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders**:** Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Viraferon and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests:
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with Viraferon.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during Viraferon therapy to greater than or equal to 2 times baseline, Viraferon therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, liver function tests: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin must be monitored at two-week intervals.

Effect on fertility: Interferon may impair fertility (see section 4.6 and section 5.3).

## 4.5 Interaction with other medicinal products and other forms of interaction

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with Viraferon.

Interactions between Viraferon and other medicinal products have not been fully evaluated. Caution must be exercised when administering Viraferon in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dosage adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

(Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C).

## 4.6 Pregnancy and lactation

Women of childbearing potential have to use effective contraception during treatment. Viraferon must be used with caution in fertile men. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Viraferon is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

Combination therapy with ribavirin: Ribavirin causes serious birth defects when administered during pregnancy. Ribavirin therapy is contraindicated in women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking Viraferon in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

## 4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with Viraferon, and therefore it is recommended that they avoid driving or operating machinery.

## 4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/$m^2$/week in hairy cell leukaemia up to 100 MIU/$m^2$/week in melanoma), the most commonly reported undesirable effects were fever, fatigue, headache and myalgia. Fever and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

In clinical trials conducted in the hepatitis C population, patients were treated with Viraferon alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of Viraferon three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10); rarely (≥1/10,000, <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1.** Adverse reactions reported during clinical trials or following the marketing use of Viraferon alone or in combination with ribavirin

| System Organ Class | Adverse Reactions |
|---|---|
| **Infections and infestations** | |
| Very common: | Pharyngitis*, infection viral* |
| Common: | Bronchitis, sinusitis, herpes simplex (resistance), rhinitis |
| Rarely: | Pneumonia[§] |
| **Blood and lymphatic system disorders** | |
| Very common: | Leukopaenia |
| Common: | Thrombocytopaenia, lymphadenopathy, lymphopenia |
| Very rarely: | Aplastic anaemia |
| Not known**:** | Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura |
| **Immune system disorders**[§] | |
| Very rarely: | Sarcoidosis, exacerbation of sarcoidosis |
| Not known: | Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis[§] |
| **Endocrine disorders** | |
| Common: | Hypothyroidism[§], hyperthyroidism[§] |
| Very rarely: | Diabetes, aggravated diabetes |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcaemia, dehydration, hyperuricemia, thirst |
| Very rarely: | Hyperglycaemia, hypertriglyceridaemia[§], increased appetite |
| **Psychiatric disorders**[§] | |
| Very common: | Depression, insomnia, anxiety, emotional lability*, agitation, nervousness |
| Common: | Confusion, sleep disorder, libido decreased |
| Rarely: | Suicide ideation |
| Very rarely: | Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations |
| Not known: | Mental status change[§] |
| **Nervous system disorders**[§] | |
| Very common: | Dizziness, headache, concentration impaired, mouth dry |
| Common: | Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion |
| Very rarely: | Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy, neuropathy, polyneuropathy |
| Not known: | Mononeuropathies, coma[§] |
| **Eye disorders** | |
| Very common: | Vision blurred |

| | |
|---|---|
| Common:<br><br>Rarely: | Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain<br>Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§] |
| **Ear and labyrinth**<br>Common:<br>Very rarely: | <br>Vertigo, tinnitus<br>Hearing loss, hearing disorder |
| **Cardiac disorders**<br>Common:<br>Rarely:<br>Very rarely:<br>Not known: | <br>Palpitation, tachycardia<br>Cardiomyopathy<br>Myocardial infarction, cardiac ischaemia<br>Arrhythmia |
| **Vascular disorders**<br>Common:<br>Very rarely: | <br>Hypertension<br>Peripheral ischaemia, hypotension[§] |
| **Respiratory, thoracic and mediastinal disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br><br>Dyspnoea*, coughing*<br>Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive<br>Pulmonary infiltrates[§], pneumonitis[§] |
| **Gastrointestinal disorders**<br>Very common:<br><br>Common:<br><br>Very rarely:<br><br>Not known: | <br>Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia<br>Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools<br>Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding<br>Periodontal disorder NOS, dental disorder NOS[§] |
| **Hepatobiliary disorders**<br>Common:<br>Very rarely: | <br>Hepatomegaly<br>Hepatotoxicity, (including fatality) |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br>Alopecia, pruritus*, skin dry*, rash*, sweating increased<br>Psoriasis (new or aggravated)[§], rash maculopapular, rash erythematous, eczema, erythema, skin disorder<br>Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders**<br>Very common:<br>Common:<br>Very rarely: | <br><br>Myalgia, arthralgia, musculoskeletal pain<br>Arthritis<br>Rhabdomyolysis, myositis, leg cramps, back pain |
| **Renal and urinary disorders**<br>Common:<br>Very rarely: | <br>Micturition frequency<br>Renal failure, renal insufficiency, nephrotic syndrome |
| **Reproductive system and breast disorders**<br>Common: | <br><br>Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder |
| **General disorders and administration site conditions** | |

| | |
|---|---|
| Very common:<br><br><br>Common:<br>Very rarely: | Injection site inflammation, injection site reaction*, fatigue, rigors, fever[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise<br>Injection site pain<br>Injection site necrosis, face oedema |
| **Investigations**<br>Very common: | <br>Weight decrease |

*These events were only common with Viraferon alone
[§]See section 4.4

These undesirable effects have also been reported with Viraferon alone.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

**Paediatric population**

*Children and adolescents – Chronic Hepatitis C*
In clinical trials of 118 children or adolescents 3 to 16 years of age, 6 % discontinued therapy due to adverse events. In general, the adverse event profile in the limited paediatric population studied was similar to that observed in adults, although there is a paediatric specific concern regarding growth inhibition as decrease in height (mean percentile decrease of growth velocity of 9 %) and weight (mean percentile decrease of 13 %) percentile were observed during treatment (see section 4.4). Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from paediatric clinical trials.
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 2** Adverse reactions very commonly and commonly reported in paediatric clinical trials
Very common (≥1/10) - Common (≥1/100, <1/10)

| System Organ Class | Adverse Reactions |
|---|---|
| **Infection and infestations** | |
| Very common: | Viral infection, pharyngitis |
| Common: | Fungal infection, bacterial infection, pulmonary infection, otitis |

| | |
|---|---|
| | media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)**<br>Common: | Neoplasm (unspecified) |
| **Blood and lymphatic system disorders**<br>Very common:<br>Common: | Anaemia, neutropaenia<br>Thrombocytopaenia, lymphadenopathy |
| **Endocrine disorders**<br>Very common:<br>Common: | Hypothyroidism[§],<br>Hyperthyroidism[§], virilism |
| **Metabolism and nutrition disorders**<br>Very common:<br>Common: | Anorexia<br>Hypertriglyceridemia[§], hyperuricemia, increased appetite |
| **Psychiatric disorders**[§]<br>Very common:<br>Common: | Depression, emotional lability, insomnia<br>Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy |
| **Nervous system disorders**[§]<br>Very common:<br>Common: | Headache, dizziness<br>Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence |
| **Eye disorders**<br>Common: | Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder |
| **Vascular disorders**<br>Common: | Raynaud's disease, flushing, pallor |
| **Respiratory, thoracic and mediastinal disorders**<br>Common: | Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing |
| **Gastrointestinal disorders**<br>Very common:<br>Common: | Diarrhoea, vomiting, nausea, abdominal pain<br>Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder |
| **Hepatobiliary disorders**<br>Common: | Hepatic function abnormal |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common: | Alopecia, rash<br>Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased |
| **Musculoskeletal and connective tissue disorders**<br>Very common: | Arthralgia, myalgia, musculoskeletal pain |
| **Renal and urinary disorders**<br>Common: | Enuresis, micturition disorder, urinary incontinence |
| **Reproductive system and** | |

| | |
|---|---|
| **breast disorders**<br>Common: | <br>Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder<br>Male: testicular pain |
| **General disorders and administration site conditions**<br>Very common:<br><br>Common: | <br><br>Injection site inflammation, injection site reaction, fatigue, rigors, fever[§], influenza-like symptoms[§], malaise, irritability<br>Chest pain, asthenia, oedema, injection site pain |
| **Investigations**<br>Very common: | <br>Growth rate decrease (height and/or weight decrease for age)[§] |
| **Injury and poisoning**<br>Common: | <br>Skin laceration |

[§]See section 4.4

### 4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, cytokines and immunomodulators, interferons, interferon alfa-2b, ATC code: L03A B05

Viraferon is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of Viraferon is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $10^8$ IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. Viraferon has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B:
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/$m^2$ 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C:
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

Adult patients: Viraferon alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of Viraferon used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/ml), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Viraferon was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with Viraferon alone or in combination with ribavirin (from two studies) are shown in **Table 3**.

Co-administration of Viraferon with ribavirin increased the efficacy of Viraferon by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of Viraferon + ribavirin, compared with Viraferon alone, is maintained across all subgroups. The relative benefit of combination therapy with Viraferon + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received Viraferon in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained

response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

**Table 3** Sustained virologic response rates with Viraferon + ribavirin (one year of treatment) by genotype and viral load

| HCV Genotype | I N=503 C95-132/I95-143 | I/R N=505 C95-132/I95-143 | I/R N=505 C/I98-580 |
|---|---|---|---|
| **All Genotypes** | **16 %** | **41 %** | **47 %** |
| **Genotype 1** | 9 % | 29 % | 33 % |
| Genotype 1 ≤ 2 million copies/ml | 25 % | 33 % | 45 % |
| Genotype 1 > 2 million copies/ml | 3 % | 27 % | 29 % |
| **Genotype 2/3** | 31 % | 65 % | 79 % |

I Viraferon (3 MIU 3 times a week)
I/R Viraferon (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

*HCV/HIV Co-infected patients*
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received Viraferon plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.**
Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or Viraferon (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or Viraferon (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

**Table 4** Sustained virological response based on genotype after Viraferon in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients

| | **Study 1**[1] | | | **Study 2**[2] | | |
|---|---|---|---|---|---|---|
| | pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg) | Viraferon (3 MIU TIW) + ribavirin (800 mg) | p value[a] | pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Viraferon (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |

| | | | | | | |
|---|---|---|---|---|---|---|
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients: A total of 345 interferon alpha relapse patients were treated in two clinical trials with Viraferon monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to Viraferon increased by as much as 10-fold the efficacy of Viraferon used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/ml by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non pegylated interferon alfa-2b or non pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Clinical trials in paediatric patients with chronic hepatitis C:
Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received Viraferon 3 MIU/$m^2$ 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. Sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

**Table 5.** Virological response in previously untreated paediatric patients

| | **Viraferon 3 MIU/$m^2$** 3 times a week<br>+<br>**ribavirin 15 mg/kg/day** |
|---|---|
| Overall Response[1] (n=118) | 54 (46 %)* |

| | |
|---|---|
| Genotype 1 (n=92) | 33 (36 %)* |
| Genotype 2/3/4 (n=26) | 21 (81 %)* |

*Number (%) of patients
1. Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

## 5.2 Pharmacokinetic properties

The pharmacokinetics of Viraferon were studied in healthy volunteers following single 5 million IU/$m^2$ and 10 million IU doses administered subcutaneously, at 5 million IU/$m^2$ administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. $C_{max}$ occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/ml) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

*Children and adolescents*: Multiple-dose pharmacokinetic properties for Viraferon injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 6**. The pharmacokinetics of Viraferon and ribavirin (dose-normalized) are similar in adults and children or adolescents.

**Table 6.** Mean (% CV) multiple-dose pharmacokinetic parameters for Viraferon and ribavirin capsules when administered to children or adolescents with chronic hepatitis C

| **Parameter** | **Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17) | **Viraferon** 3 MIU/$m^2$ 3 times a week (n = 54) |
|---|---|---|
| $T_{max}$ (hr) | 1.9 (83) | 5.9 (36) |
| $C_{max}$ (ng/ml) | 3,275 (25) | 51 (48) |
| AUC* | 29,774 (26) | 622 (48) |
| Apparent clearance l/hr/kg | 0.27 (27) | Not done |

*$AUC_{12}$ (ng.hr/ml) for ribavirin; $AUC_{0-24}$ (IU.hr/ml) for Viraferon

Interferon neutralising factor assays were performed on serum samples of patients who received Viraferon in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

## 5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x $10^6$ IU/kg/day

for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x $10^6$ IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour (see section 4.4 and Rebetol SPC if Viraferon is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Disodium phosphate anhydrous,
Sodium dihydrogen phosphate monohydrate,
Edetate disodium,
Sodium chloride,
M-cresol,
Polysorbate 80,
Water for injections q.s.

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

15 months

Chemical and physical in-use stability has been demonstrated for 27 days at 2ºC – 8ºC.
From a microbiological point of view, once opened, the product may be stored for a maximum of 27 days at 2ºC – 8ºC. Other in-use storage times and conditions are the responsibility of the user.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.

### 6.5 Nature and contents of container

1.2 ml of solution (corresponding to 18 MIU) in a pen made of a cartridge (type I glass) sealed at one end with an cap (aluminium) containing a liner (bromobutyl rubber) and at the other end by a plunger (bromobutyl rubber)
with 12 injection needles and12 cleansing swabs
Pack sizes of 1, 2 or 8
Not all pack sizes may be marketed.

The pen is designed to deliver its contents of 18 million IU in doses ranging from 1.5 to 6 million IU. The pen will deliver a maximum of 12 doses of 1.5 million IU over a period not to exceed 4 weeks.

### 6.6 Special precautions for disposal

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

Viraferon, solution for injection, multidose pen is injected subcutaneously after attaching an injection needle and dialing the prescribed dose.

Remove the pen from the refrigerator approximately 30 minutes before administration to allow the injectable solution to reach room temperature (not more than 25°C).

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to "How to self inject Viraferon").

Each pen is intended for a maximum four-week use period and must then be discarded. A new injection needle must be used for each dose. After each use, the injection needle must be discarded safely and the pen must be returned immediately to the refrigerator. A maximum of 48 hours (two days) of exposure to 25°C is permitted over the four-week use period to cover accidental delays in returning the pen to the refrigerator. Sufficient needles and swabs are provided to use the Viraferon pen for administering the smallest measurable doses. Instruct the patient that any extra needles and swabs that remain after the final dose has been taken from the pen, must be discarded appropriately and safely.

As with all parenteral medicinal products, prior to administration inspect Viraferon, solution for injection, visually for particulate matter and discolouration. The solution should be clear and colourless.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/99/128/029
EU/1/99/128/030
EU/1/99/128/031

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 9 March 2000
Date of last renewal : 23 May 2005

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 30 million IU solution for injection, multidose pen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One cartridge contains 30 million IU of recombinant interferon alfa-2b produced in *E.coli* by recombinant DNA technology, in 1.2 ml.

One ml contains 25 million IU of interferon alfa-2b.

The pen is designed to deliver its contents of 30 million IU in doses ranging from 2.5 to 10 million IU. The pen will deliver a maximum of 12 doses of 2.5 million IU over a period not to exceed 4 weeks.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection
Solution is clear and colourless.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C:
*Adult patients:*
Viraferon is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section 4.4).

The best way to use Viraferon in this indication is in combination with ribavirin.

*Chidren and adolescents:*
Viraferon is intended for use, in a combination regimen with ribavirin, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials (see sections 4.4, 4.8 and 5.1).

### 4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Multidose presentations must be for individual patient use only.

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

If adverse events develop during the course of treatment with Viraferon for any indication, modify the dosage or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dosage adjustment, or disease progresses, discontinue treatment with Viraferon. At the discretion of the physician, the patient may self-administer the dose for maintenance dosage regimens administered subcutaneously.

*Chronic Hepatitis B*: The recommended dosage is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/$mm^3$, granulocytes < 1,000/$mm^3$, thrombocytes < 100,000/$mm^3$). Treatment should be discontinued in case of severe leukopaenia (< 1,200/$mm^3$), severe neutropaenia (< 750/$mm^3$) or severe thrombocytopaenia (< 70,000/$mm^3$).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue Viraferon therapy.

*Chronic Hepatitis C*: Viraferon is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

*Children 3 years of age or older and adolescents*: Interferon alfa-2b 3 MIU/$m^2$ is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsule SPC for dose of ribavirin capsules and dosage modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC).

Relapse patients (adults):
Viraferon is given in combination with ribavirin.

Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for 6 months.

Naïve patients:
*Adults:* The efficacy of Viraferon is enhanced when given in combination with ribavirin. Viraferon should be given alone mainly in case of intolerance or contraindication to ribavirin.

Viraferon in combination with ribavirin:
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Viraferon alone:
The optimal duration of therapy with Viraferon alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with Viraferon alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

*Children and adolescents:* The efficacy and safety of Viraferon in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Virological response is defined as absence of detectable HCV-RNA at Week 12. Treatment should be discontinued in these patients.
Genotype 2/3: The recommended duration of treatment is 24 weeks.

Virological responses after 1 year of treatment and 6 months of follow-up were 36 % for genotype 1 and 81 % for genotype 2/3/4.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.

Children and adolescents:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin: Also see ribavirin SPC if interferon alfa-2b is to be administered in combination with ribavirin in patients with chronic hepatitis C.

**4.4 Special warnings and precautions for use**

*For all patients:*

Psychiatric and central nervous system (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Viraferon therapy, and even after treatment discontinuation mainly during the 6-month follow-up periodand in the follow-up period. Among children and adolescents treated with Viraferon in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others), confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric

symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Viraferon be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of or history of severe psychiatric conditions:*
If a treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases, termination of Viraferon therapy. Any patient developing liver function abnormalities during treatment with Viraferon must be monitored closely and treatment discontinued if signs and symptoms progress.

Hypotension may occur during Viraferon therapy or up to two days post-therapy and may require supportive treatment.

Adequate hydration must be maintained in patients undergoing Viraferon therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Viraferon must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instance after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with Viraferon, must have a prompt and complete eye examination. Periodic visual examinations during Viraferon therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of Viraferon should be considered in patients who develop new or worsening ophthalmological disorders.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of Viraferon.

Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require Viraferon therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of Viraferon therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of Viraferon in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Discontinue treatment with Viraferon in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decompensation.

Chronic Hepatitis C:
Combination therapy with ribavirin: Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy: Infrequently, adult patients treated for chronic hepatitis C with Viraferon developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using Viraferon therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which Viraferon may alter thyroid status is unknown. Prior to initiation of Viraferon therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of Viraferon therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, Viraferon treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of

Viraferon therapy has not reversed thyroid dysfunction occurring during treatment (also see Children and adolescents, Thyroid monitoring).

*Supplemental monitoring specific for children and adolescents*
Thyroid Monitoring: Approximately 12 % of children treated with interferon alfa-2b and ribavirin developed increase in TSH. Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of Viraferon therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Growth and Development: During a 1-year course of therapy there was a decrease in the rate of linear growth (mean percentile decrease of 9 %) and a decrease in the rate of weight gain (mean percentile decrease of 13 %). A general reversal of these trends was noted during the 6 months follow-up post treatment. However, based on interim data from a long-term follow-up study, 12 (14 %) of 84 children had a > 15 percentile decrease in rate of linear growth, of whom 5 (6 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In addition, preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3). Therefore, the risk/benefit of the combined use of interferon alfa-2b and ribavirin should be assessed in young children prior to the initiation of therapy. Physicians are advised to monitor the growth of children taking ribavirin in combination with interferon alfa-2b. There are no data on long term effects on growth and development and on sexual maturation.

HCV/HIV Coinfection**:** Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Viraferon and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders**:** Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Viraferon and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests:
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with Viraferon.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during Viraferon therapy to greater than or equal to 2 times baseline, Viraferon therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, liver function tests: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin must be monitored at two-week intervals.

Effect on fertility: Interferon may impair fertility (see section 4.6 and section 5.3).

## 4.5 Interaction with other medicinal products and other forms of interaction

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with Viraferon.

Interactions between Viraferon and other medicinal products have not been fully evaluated. Caution must be exercised when administering Viraferon in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dosage adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

(Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C).

## 4.6 Pregnancy and lactation

Women of childbearing potential have to use effective contraception during treatment. Viraferon must be used with caution in fertile men. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Viraferon is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

Combination therapy with ribavirin: Ribavirin causes serious birth defects when administered during pregnancy. Ribavirin therapy is contraindicated in women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking Viraferon in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

## 4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with Viraferon, and therefore it is recommended that they avoid driving or operating machinery.

## 4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/$m^2$/week in hairy cell leukaemia up to 100 MIU/$m^2$/week in melanoma), the most commonly reported undesirable effects were fever, fatigue, headache and myalgia. Fever and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

In clinical trials conducted in the hepatitis C population, patients were treated with Viraferon alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of Viraferon three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10); rarely (≥1/10,000, <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1.** Adverse reactions reported during clinical trials or following the marketing use of Viraferon alone or in combination with ribavirin

| System Organ Class | Adverse Reactions |
|---|---|
| **Infections and infestations** | |
| Very common: | Pharyngitis*, infection viral* |
| Common: | Bronchitis, sinusitis, herpes simplex (resistance), rhinitis |
| Rarely: | Pneumonia§ |
| **Blood and lymphatic system disorders** | |
| Very common: | Leukopaenia |
| Common: | Thrombocytopaenia, lymphadenopathy, lymphopenia |
| Very rarely: | Aplastic anaemia |
| Not known**:** | Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura |
| **Immune system disorders**§ | |
| Very rarely: | Sarcoidosis, exacerbation of sarcoidosis |
| Not known: | Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis§ |
| **Endocrine disorders** | |
| Common: | Hypothyroidism§, hyperthyroidism§ |
| Very rarely: | Diabetes, aggravated diabetes |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcaemia, dehydration, hyperuricemia, thirst |
| Very rarely: | Hyperglycaemia, hypertriglyceridaemia§, increased appetite |
| **Psychiatric disorders**§ | |
| Very common: | Depression, insomnia, anxiety, emotional lability*, agitation, nervousness |
| Common: | Confusion, sleep disorder, libido decreased |
| Rarely: | Suicide ideation |
| Very rarely: | Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations |
| Not known: | Mental status change§ |
| **Nervous system disorders**§ | |
| Very common: | Dizziness, headache, concentration impaired, mouth dry |
| Common: | Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion |
| Very rarely: | Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy, neuropathy, polyneuropathy |
| Not known: | Mononeuropathies, coma§ |
| **Eye disorders** | |

| | |
|---|---|
| Very common:<br>Common:<br><br>Rarely: | Vision blurred<br>Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain<br>Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§] |
| **Ear and labyrinth**<br>Common:<br>Very rarely: | <br>Vertigo, tinnitus<br>Hearing loss, hearing disorder |
| **Cardiac disorders**<br>Common:<br>Rarely:<br>Very rarely:<br>Not known: | <br>Palpitation, tachycardia<br>Cardiomyopathy<br>Myocardial infarction, cardiac ischaemia<br>Arrhythmia |
| **Vascular disorders**<br>Common:<br>Very rarely: | <br>Hypertension<br>Peripheral ischaemia, hypotension[§] |
| **Respiratory, thoracic and mediastinal disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br><br>Dyspnoea*, coughing*<br>Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive<br>Pulmonary infiltrates[§], pneumonitis[§] |
| **Gastrointestinal disorders**<br>Very common:<br><br>Common:<br><br>Very rarely:<br><br>Not known: | <br>Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia<br>Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools<br>Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding<br>Periodontal disorder NOS, dental disorder NOS[§] |
| **Hepatobiliary disorders**<br>Common:<br>Very rarely: | <br>Hepatomegaly<br>Hepatotoxicity, (including fatality) |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br>Alopecia, pruritus*, skin dry*, rash*, sweating increased<br>Psoriasis (new or aggravated)[§], rash maculopapular, rash erythematous, eczema, erythema, skin disorder<br>Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders**<br>Very common:<br>Common:<br>Very rarely: | <br>Myalgia, arthralgia, musculoskeletal pain<br>Arthritis<br>Rhabdomyolysis, myositis, leg cramps, back pain |
| **Renal and urinary disorders**<br>Common:<br>Very rarely: | <br>Micturition frequency<br>Renal failure, renal insufficiency, nephrotic syndrome |
| **Reproductive system and breast disorders**<br>Common: | <br>Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder |
| **General disorders and administration** | |

| | |
|---|---|
| **site conditions**<br>Very common:<br><br><br>Common:<br>Very rarely: | <br>Injection site inflammation, injection site reaction*, fatigue, rigors, fever§, flu-like symptoms§, asthenia, irritability, chest pain, malaise<br>Injection site pain<br>Injection site necrosis, face oedema |
| **Investigations**<br>Very common: | <br>Weight decrease |

*These events were only common with Viraferon alone
§See section 4.4

These undesirable effects have also been reported with Viraferon alone.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

**Paediatric population**

*Children and adolescents – Chronic Hepatitis C*
In clinical trials of 118 children or adolescents 3 to 16 years of age, 6 % discontinued therapy due to adverse events. In general, the adverse event profile in the limited paediatric population studied was similar to that observed in adults, although there is a paediatric specific concern regarding growth inhibition as decrease in height (mean percentile decrease of growth velocity of 9 %) and weight (mean percentile decrease of 13 %) percentile were observed during treatment (see section 4.4). Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from paediatric clinical trials.
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 2** Adverse reactions very commonly and commonly reported in paediatric clinical trials
Very common (≥1/10) - Common (≥1/100, <1/10)

| System Organ Class | Adverse Reactions |
|---|---|
| **Infection and infestations**<br>Very common: | <br>Viral infection, pharyngitis |

| | |
|---|---|
| Common: | Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)**<br>Common: | Neoplasm (unspecified) |
| **Blood and lymphatic system disorders**<br>Very common:<br>Common: | Anaemia, neutropaenia<br>Thrombocytopaenia, lymphadenopathy |
| **Endocrine disorders**<br>Very common:<br>Common: | Hypothyroidism[§],<br>Hyperthyroidism[§], virilism |
| **Metabolism and nutrition disorders**<br>Very common:<br>Common: | Anorexia<br>Hypertriglyceridemia[§], hyperuricemia, increased appetite |
| **Psychiatric disorders**[§]<br>Very common:<br>Common: | Depression, emotional lability, insomnia<br>Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy |
| **Nervous system disorders**[§]<br>Very common:<br>Common: | Headache, dizziness<br>Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence |
| **Eye disorders**<br>Common: | Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder |
| **Vascular disorders**<br>Common: | Raynaud's disease, flushing, pallor |
| **Respiratory, thoracic and mediastinal disorders**<br>Common: | Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing |
| **Gastrointestinal disorders**<br>Very common:<br>Common: | Diarrhoea, vomiting, nausea, abdominal pain<br>Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder |
| **Hepatobiliary disorders**<br>Common: | Hepatic function abnormal |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common: | Alopecia, rash<br>Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased |
| **Musculoskeletal and connective tissue disorders**<br>Very common: | Arthralgia, myalgia, musculoskeletal pain |
| **Renal and urinary disorders**<br>Common: | Enuresis, micturition disorder, urinary incontinence |

| | |
|---|---|
| **Reproductive system and breast disorders**<br>Common: | <br><br>Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder<br>Male: testicular pain |
| **General disorders and administration site conditions**<br>Very common:<br><br>Common: | <br><br>Injection site inflammation, injection site reaction, fatigue, rigors, fever[§], influenza-like symptoms[§], malaise, irritability<br>Chest pain, asthenia, oedema, injection site pain |
| **Investigations**<br>Very common: | <br>Growth rate decrease (height and/or weight decrease for age)[§] |
| **Injury and poisoning**<br>Common: | <br>Skin laceration |

[§]See section 4.4

### 4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, cytokines and immunomodulators, interferons, interferon alfa-2b, ATC code: L03A B05

Viraferon is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of Viraferon is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $l0^8$ IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. Viraferon has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B:
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/$m^2$ 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C:
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

Adult patients: Viraferon alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of Viraferon used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/ml), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Viraferon was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with Viraferon alone or in combination with ribavirin (from two studies) are shown in **Table 3**.

Co-administration of Viraferon with ribavirin increased the efficacy of Viraferon by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of Viraferon + ribavirin, compared with Viraferon alone, is maintained across all subgroups. The relative benefit of combination therapy with Viraferon + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received Viraferon in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained

response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

**Table 3** Sustained virologic response rates with Viraferon + ribavirin (one year of treatment) by genotype and viral load

| **HCV Genotype** | **I N=503 C95-132/I95-143** | **I/R N=505 C95-132/I95-143** | **I/R N=505 C/I98-580** |
|---|---|---|---|
| **All Genotypes** | **16 %** | **41 %** | **47 %** |
| **Genotype 1** | 9 % | 29 % | 33 % |
| Genotype 1 ≤ 2 million copies/ml | 25 % | 33 % | 45 % |
| Genotype 1 > 2 million copies/ml | 3 % | 27 % | 29 % |
| **Genotype 2/3** | 31 % | 65 % | 79 % |

I Viraferon (3 MIU 3 times a week)
I/R Viraferon (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

*HCV/HIV Co-infected patients*
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received Viraferon plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or Viraferon (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or Viraferon (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

**Table 4** Sustained virological response based on genotype after Viraferon in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients

| | **Study 1**[1] | | | **Study 2**[2] | | |
|---|---|---|---|---|---|---|
| | pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg) | Viraferon (3 MIU TIW) + ribavirin (800 mg) | p value[a] | pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Viraferon (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |

| | | | | | | |
|---|---|---|---|---|---|---|
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients: A total of 345 interferon alpha relapse patients were treated in two clinical trials with Viraferon monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to Viraferon increased by as much as 10-fold the efficacy of Viraferon used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/ml by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non pegylated interferon alfa-2b or non pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Clinical trials in paediatric patients with chronic hepatitis C:
Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received Viraferon 3 MIU/$m^2$ 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. Sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

**Table 5.** Virological response in previously untreated paediatric patients

| | **Viraferon 3 MIU/$m^2$** 3 times a week<br>+<br>**ribavirin 15 mg/kg/day** |
|---|---|
| Overall Response[1] (n=118) | 54 (46 %)* |

| | |
|---|---|
| Genotype 1 (n=92) | 33 (36 %)* |
| Genotype 2/3/4 (n=26) | 21 (81 %)* |

*Number (%) of patients
1. Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

## 5.2 Pharmacokinetic properties

The pharmacokinetics of Viraferon were studied in healthy volunteers following single 5 million IU/$m^2$ and 10 million IU doses administered subcutaneously, at 5 million IU/$m^2$ administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. $C_{max}$ occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/ml) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

*Children and adolescents*: Multiple-dose pharmacokinetic properties for Viraferon injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 6**. The pharmacokinetics of Viraferon and ribavirin (dose-normalized) are similar in adults and children or adolescents.

**Table 6.** Mean (% CV) multiple-dose pharmacokinetic parameters for Viraferon and ribavirin capsules when administered to children or adolescents with chronic hepatitis C

| **Parameter** | **Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17) | **Viraferon** 3 MIU/$m^2$ 3 times a week (n = 54) |
|---|---|---|
| $T_{max}$ (hr) | 1.9 (83) | 5.9 (36) |
| $C_{max}$ (ng/ml) | 3,275 (25) | 51 (48) |
| AUC* | 29,774 (26) | 622 (48) |
| Apparent clearance l/hr/kg | 0.27 (27) | Not done |

*$AUC_{12}$ (ng.hr/ml) for ribavirin; $AUC_{0-24}$ (IU.hr/ml) for Viraferon

Interferon neutralising factor assays were performed on serum samples of patients who received Viraferon in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

## 5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x $10^6$ IU/kg/day

for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x $10^6$ IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour (see section 4.4 and Rebetol SPC if Viraferon is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Disodium phosphate anhydrous,
Sodium dihydrogen phosphate monohydrate,
Edetate disodium,
Sodium chloride,
M-cresol,
Polysorbate 80,
Water for injections q.s.

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

15 months

Chemical and physical in-use stability has been demonstrated for 27 days at 2ºC – 8ºC.
From a microbiological point of view, once opened, the product may be stored for a maximum of 27 days at 2ºC – 8ºC. Other in-use storage times and conditions are the responsibility of the user.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.

### 6.5 Nature and contents of container

1.2 ml of solution (corresponding to 30 MIU) in a pen made of a cartridge (type I glass) sealed at one end with an cap (aluminium) containing a liner (bromobutyl rubber) and at the other end by a plunger (bromobutyl rubber)
with 12 injection needles and12 cleansing swabs
Pack sizes of 1, 2 or 8
Not all pack sizes may be marketed.

The pen is designed to deliver its contents of 30 million IU in doses ranging from 2.5 to 10 million IU. The pen will deliver a maximum of 12 doses of 2.5 million IU over a period not to exceed 4 weeks.

### 6.6 Special precautions for disposal

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

Viraferon, solution for injection, multidose pen is injected subcutaneously after attaching an injection needle and dialing the prescribed dose.

Remove the pen from the refrigerator approximately 30 minutes before administration to allow the injectable solution to reach room temperature (not more than 25°C).

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to "How to self inject Viraferon").

Each pen is intended for a maximum four-week use period and must then be discarded. A new injection needle must be used for each dose. After each use, the injection needle must be discarded safely and the pen must be returned immediately to the refrigerator. A maximum of 48 hours (two days) of exposure to 25°C is permitted over the four-week use period to cover accidental delays in returning the pen to the refrigerator. Sufficient needles and swabs are provided to use the Viraferon pen for administering the smallest measurable doses. Instruct the patient that any extra needles and swabs that remain after the final dose has been taken from the pen, must be discarded appropriately and safely.

As with all parenteral medicinal products, prior to administration inspect Viraferon, solution for injection, visually for particulate matter and discolouration. The solution should be clear and colourless.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/99/128/032
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Date of last renewal : 23 May 2005

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 60 million IU solution for injection, multidose pen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One cartridge contains 60 million IU of recombinant interferon alfa-2b produced in *E.coli* by recombinant DNA technology, in 1.2 ml.

One ml contains 50 million IU of interferon alfa-2b.

The pen is designed to deliver its contents of 60 million IU in doses ranging from 5 to 20 million IU. The pen will deliver a maximum of 12 doses of 5 million IU over a period not to exceed 4 weeks.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection
Solution is clear and colourless.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C:
*Adult patients:*
Viraferon is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section 4.4).

The best way to use Viraferon in this indication is in combination with ribavirin.

*Chidren and adolescents:*
Viraferon is intended for use, in a combination regimen with ribavirin, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials (see sections 4.4, 4.8 and 5.1).

### 4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Multidose presentations must be for individual patient use only.

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

If adverse events develop during the course of treatment with Viraferon for any indication, modify the dosage or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dosage adjustment, or disease progresses, discontinue treatment with Viraferon. At the discretion of the physician, the patient may self-administer the dose for maintenance dosage regimens administered subcutaneously.

*Chronic Hepatitis B*: The recommended dosage is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/$mm^3$, granulocytes < 1,000/$mm^3$, thrombocytes < 100,000/$mm^3$). Treatment should be discontinued in case of severe leukopaenia (< 1,200/$mm^3$), severe neutropaenia (< 750/$mm^3$) or severe thrombocytopaenia (< 70,000/$mm^3$).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue Viraferon therapy.

*Chronic Hepatitis C*: Viraferon is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

*Children 3 years of age or older and adolescents*: Interferon alfa-2b 3 MIU/$m^2$ is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsule SPC for dose of ribavirin capsules and dosage modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC).

Relapse patients (adults):
Viraferon is given in combination with ribavirin.

Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for 6 months.

Naïve patients:
*Adults:* The efficacy of Viraferon is enhanced when given in combination with ribavirin. Viraferon should be given alone mainly in case of intolerance or contraindication to ribavirin.

Viraferon in combination with ribavirin:
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with Viraferon in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Viraferon alone:
The optimal duration of therapy with Viraferon alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with Viraferon alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

*Children and adolescents:* The efficacy and safety of Viraferon in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Virological response is defined as absence of detectable HCV-RNA at Week 12. Treatment should be discontinued in these patients.
Genotype 2/3: The recommended duration of treatment is 24 weeks.

Virological responses after 1 year of treatment and 6 months of follow-up were 36 % for genotype 1 and 81 % for genotype 2/3/4.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.

Children and adolescents:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin: Also see ribavirin SPC if interferon alfa-2b is to be administered in combination with ribavirin in patients with chronic hepatitis C.

**4.4 Special warnings and precautions for use**

*For all patients:*

Psychiatric and central nervous system (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Viraferon therapy, and even after treatment discontinuation mainly during the 6-month follow-up periodand in the follow-up period. Among children and adolescents treated with Viraferon in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others), confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric

symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Viraferon be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of or history of severe psychiatric conditions:*
If a treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Viraferon therapy. If such a reaction develops, discontinue the medication and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases, termination of Viraferon therapy. Any patient developing liver function abnormalities during treatment with Viraferon must be monitored closely and treatment discontinued if signs and symptoms progress.

Hypotension may occur during Viraferon therapy or up to two days post-therapy and may require supportive treatment.

Adequate hydration must be maintained in patients undergoing Viraferon therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Viraferon must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instance after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with Viraferon, must have a prompt and complete eye examination. Periodic visual examinations during Viraferon therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of Viraferon should be considered in patients who develop new or worsening ophthalmological disorders.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of Viraferon.

Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require Viraferon therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of Viraferon therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of Viraferon in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Discontinue treatment with Viraferon in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decompensation.

<u>Chronic Hepatitis C:</u>
Combination therapy with ribavirin: Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy: Infrequently, adult patients treated for chronic hepatitis C with Viraferon developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using Viraferon therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which Viraferon may alter thyroid status is unknown. Prior to initiation of Viraferon therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of Viraferon therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, Viraferon treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of

Viraferon therapy has not reversed thyroid dysfunction occurring during treatment (also see Children and adolescents, Thyroid monitoring).

*Supplemental monitoring specific for children and adolescents*
Thyroid Monitoring**:** Approximately 12 % of children treated with interferon alfa-2b and ribavirin developed increase in TSH. Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of Viraferon therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Viraferon therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Growth and Development: During a 1-year course of therapy there was a decrease in the rate of linear growth (mean percentile decrease of 9 %) and a decrease in the rate of weight gain (mean percentile decrease of 13 %). A general reversal of these trends was noted during the 6 months follow-up post treatment. However, based on interim data from a long-term follow-up study, 12 (14 %) of 84 children had a > 15 percentile decrease in rate of linear growth, of whom 5 (6 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In addition, preclicinal juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3). Therefore, the risk/benefit of the combined use of interferon alfa-2b and ribavirin should be assessed in young children prior to the initiation of therapy. Physicians are advised to monitor the growth of children taking ribavirin in combination with interferon alfa-2b. There are no data on long term effects on growth and development and on sexual maturation.

HCV/HIV Coinfection**:** Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Viraferon and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders**:** Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Viraferon and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests:
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with Viraferon.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during Viraferon therapy to greater than or equal to 2 times baseline, Viraferon therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, liver function tests: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin must be monitored at two-week intervals.

Effect on fertility: Interferon may impair fertility (see section 4.6 and section 5.3).

### 4.5 Interaction with other medicinal products and other forms of interaction

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with Viraferon.

Interactions between Viraferon and other medicinal products have not been fully evaluated. Caution must be exercised when administering Viraferon in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dosage adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with Viraferon. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

(Also see ribavirin SPC if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C).

## 4.6 Pregnancy and lactation

Women of childbearing potential have to use effective contraception during treatment. Viraferon must be used with caution in fertile men. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Viraferon is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

Combination therapy with ribavirin: Ribavirin causes serious birth defects when administered during pregnancy. Ribavirin therapy is contraindicated in women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking Viraferon in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

## 4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with Viraferon, and therefore it is recommended that they avoid driving or operating machinery.

## 4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if Viraferon is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/$m^2$/week in hairy cell leukaemia up to 100 MIU/$m^2$/week in melanoma), the most commonly reported undesirable effects were fever, fatigue, headache and myalgia. Fever and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

In clinical trials conducted in the hepatitis C population, patients were treated with Viraferon alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of Viraferon three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10); rarely (≥1/10,000, <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1.** Adverse reactions reported during clinical trials or following the marketing use of Viraferon alone or in combination with ribavirin

| System Organ Class | Adverse Reactions |
|---|---|
| **Infections and infestations** | |
| Very common: | Pharyngitis*, infection viral* |
| Common: | Bronchitis, sinusitis, herpes simplex (resistance), rhinitis |
| Rarely: | Pneumonia§ |
| **Blood and lymphatic system disorders** | |
| Very common: | Leukopaenia |
| Common: | Thrombocytopaenia, lymphadenopathy, lymphopenia |
| Very rarely: | Aplastic anaemia |
| Not known**:** | Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura |
| **Immune system disorders**§ | |
| Very rarely: | Sarcoidosis, exacerbation of sarcoidosis |
| Not known: | Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis§ |
| **Endocrine disorders** | |
| Common: | Hypothyroidism§, hyperthyroidism§ |
| Very rarely: | Diabetes, aggravated diabetes |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcaemia, dehydration, hyperuricemia, thirst |
| Very rarely: | Hyperglycaemia, hypertriglyceridaemia§, increased appetite |
| **Psychiatric disorders**§ | |
| Very common: | Depression, insomnia, anxiety, emotional lability*, agitation, nervousness |
| Common: | Confusion, sleep disorder, libido decreased |
| Rarely: | Suicide ideation |
| Very rarely: | Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations |
| Not known: | Mental status change§ |
| **Nervous system disorders**§ | |
| Very common: | Dizziness, headache, concentration impaired, mouth dry |
| Common: | Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion |
| Very rarely: | Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy, neuropathy, polyneuropathy |
| Not known: | Mononeuropathies, coma§ |
| **Eye disorders** | |
| Very common: | Vision blurred |

| | |
|---|---|
| Common:<br><br>Rarely: | Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain<br>Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§] |
| **Ear and labyrinth**<br>Common:<br>Very rarely: | <br>Vertigo, tinnitus<br>Hearing loss, hearing disorder |
| **Cardiac disorders**<br>Common:<br>Rarely:<br>Very rarely:<br>Not known: | <br>Palpitation, tachycardia<br>Cardiomyopathy<br>Myocardial infarction, cardiac ischaemia<br>Arrhythmia |
| **Vascular disorders**<br>Common:<br>Very rarely: | <br>Hypertension<br>Peripheral ischaemia, hypotension[§] |
| **Respiratory, thoracic and mediastinal disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br><br>Dyspnoea*, coughing*<br>Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive<br>Pulmonary infiltrates[§], pneumonitis[§] |
| **Gastrointestinal disorders**<br>Very common:<br><br>Common:<br><br>Very rarely:<br><br>Not known: | <br>Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia<br>Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools<br>Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding<br>Periodontal disorder NOS, dental disorder NOS[§] |
| **Hepatobiliary disorders**<br>Common:<br>Very rarely: | <br>Hepatomegaly<br>Hepatotoxicity, (including fatality) |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common:<br><br>Very rarely: | <br>Alopecia, pruritus*, skin dry*, rash*, sweating increased<br>Psoriasis (new or aggravated)[§], rash maculopapular, rash erythematous, eczema, erythema, skin disorder<br>Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders**<br>Very common:<br>Common:<br>Very rarely: | <br><br>Myalgia, arthralgia, musculoskeletal pain<br>Arthritis<br>Rhabdomyolysis, myositis, leg cramps, back pain |
| **Renal and urinary disorders**<br>Common:<br>Very rarely: | <br>Micturition frequency<br>Renal failure, renal insufficiency, nephrotic syndrome |
| **Reproductive system and breast disorders**<br>Common: | <br><br>Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder |
| **General disorders and administration site conditions** | |

| | |
|---|---|
| Very common:<br><br><br>Common:<br>Very rarely: | Injection site inflammation, injection site reaction*, fatigue, rigors, fever[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise<br>Injection site pain<br>Injection site necrosis, face oedema |
| **Investigations**<br>Very common: | <br>Weight decrease |

*These events were only common with Viraferon alone
[§]See section 4.4

These undesirable effects have also been reported with Viraferon alone.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

**Paediatric population**

*Children and adolescents – Chronic Hepatitis C*
In clinical trials of 118 children or adolescents 3 to 16 years of age, 6 % discontinued therapy due to adverse events. In general, the adverse event profile in the limited paediatric population studied was similar to that observed in adults, although there is a paediatric specific concern regarding growth inhibition as decrease in height (mean percentile decrease of growth velocity of 9 %) and weight (mean percentile decrease of 13 %) percentile were observed during treatment (see section 4.4). Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from paediatric clinical trials.
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 2** Adverse reactions very commonly and commonly reported in paediatric clinical trials
Very common (≥1/10) - Common (≥1/100, <1/10)

| System Organ Class | Adverse Reactions |
|---|---|
| **Infection and infestations** | |
| Very common: | Viral infection, pharyngitis |
| Common: | Fungal infection, bacterial infection, pulmonary infection, otitis |

| | |
|---|---|
| | media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)**<br>Common: | Neoplasm (unspecified) |
| **Blood and lymphatic system disorders**<br>Very common:<br>Common: | Anaemia, neutropaenia<br>Thrombocytopaenia, lymphadenopathy |
| **Endocrine disorders**<br>Very common:<br>Common: | Hypothyroidism[§],<br>Hyperthyroidism[§], virilism |
| **Metabolism and nutrition disorders**<br>Very common:<br>Common: | Anorexia<br>Hypertriglyceridemia[§], hyperuricemia, increased appetite |
| **Psychiatric disorders**[§]<br>Very common:<br>Common: | Depression, emotional lability, insomnia<br>Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy |
| **Nervous system disorders**[§]<br>Very common:<br>Common: | Headache, dizziness<br>Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence |
| **Eye disorders**<br>Common: | Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder |
| **Vascular disorders**<br>Common: | Raynaud's disease, flushing, pallor |
| **Respiratory, thoracic and mediastinal disorders**<br>Common: | Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing |
| **Gastrointestinal disorders**<br>Very common:<br>Common: | Diarrhoea, vomiting, nausea, abdominal pain<br>Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder |
| **Hepatobiliary disorders**<br>Common: | Hepatic function abnormal |
| **Skin and subcutaneous tissue disorders**<br>Very common:<br>Common: | Alopecia, rash<br>Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased |
| **Musculoskeletal and connective tissue disorders**<br>Very common: | Arthralgia, myalgia, musculoskeletal pain |
| **Renal and urinary disorders**<br>Common: | Enuresis, micturition disorder, urinary incontinence |
| **Reproductive system and** | |

| | |
|---|---|
| **breast disorders**<br>Common: | <br>Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder<br>Male: testicular pain |
| **General disorders and administration site conditions**<br>Very common:<br><br>Common: | <br><br>Injection site inflammation, injection site reaction, fatigue, rigors, fever[§], influenza-like symptoms[§], malaise, irritability<br>Chest pain, asthenia, oedema, injection site pain |
| **Investigations**<br>Very common: | <br>Growth rate decrease (height and/or weight decrease for age)[§] |
| **Injury and poisoning**<br>Common: | <br>Skin laceration |

[§]See section 4.4

### 4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, cytokines and immunomodulators, interferons, interferon alfa-2b, ATC code: L03A B05

Viraferon is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of Viraferon is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $10^8$ IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. Viraferon has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B:
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/$m^2$ 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C:
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

Adult patients: Viraferon alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of Viraferon used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/ml), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Viraferon was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with Viraferon alone or in combination with ribavirin (from two studies) are shown in **Table 3.**

Co-administration of Viraferon with ribavirin increased the efficacy of Viraferon by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of Viraferon + ribavirin, compared with Viraferon alone, is maintained across all subgroups. The relative benefit of combination therapy with Viraferon + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received Viraferon in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained

response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

**Table 3** Sustained virologic response rates with Viraferon + ribavirin (one year of treatment) by genotype and viral load

| HCV Genotype | I N=503 C95-132/I95-143 | I/R N=505 C95-132/I95-143 | I/R N=505 C/I98-580 |
|---|---|---|---|
| **All Genotypes** | **16 %** | **41 %** | **47 %** |
| **Genotype 1** | 9 % | 29 % | 33 % |
| Genotype 1 ≤ 2 million copies/ml | 25 % | 33 % | 45 % |
| Genotype 1 > 2 million copies/ml | 3 % | 27 % | 29 % |
| **Genotype 2/3** | 31 % | 65 % | 79 % |

I Viraferon (3 MIU 3 times a week)
I/R Viraferon (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

*HCV/HIV Co-infected patients*
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received Viraferon plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or Viraferon (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or Viraferon (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

**Table 4** Sustained virological response based on genotype after Viraferon in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients

| | **Study 1**[1] | | | **Study 2**[2] | | |
|---|---|---|---|---|---|---|
| | pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg) | Viraferon (3 MIU TIW) + ribavirin (800 mg) | p value[a] | pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Viraferon (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |

| | | | | | | |
|---|---|---|---|---|---|---|
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients: A total of 345 interferon alpha relapse patients were treated in two clinical trials with Viraferon monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to Viraferon increased by as much as 10-fold the efficacy of Viraferon used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/ml by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non pegylated interferon alfa-2b or non pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Clinical trials in paediatric patients with chronic hepatitis C:
Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received Viraferon 3 MIU/$m^2$ 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. Sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

**Table 5.** Virological response in previously untreated paediatric patients

| | **Viraferon 3 MIU/$m^2$** 3 times a week<br>+<br>**ribavirin 15 mg/kg/day** |
|---|---|
| Overall Response[1] (n=118) | 54 (46 %)* |

| | |
|---|---|
| Genotype 1 (n=92) | 33 (36 %)* |
| Genotype 2/3/4 (n=26) | 21 (81 %)* |

*Number (%) of patients
1. Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

## 5.2 Pharmacokinetic properties

The pharmacokinetics of Viraferon were studied in healthy volunteers following single 5 million IU/$m^2$ and 10 million IU doses administered subcutaneously, at 5 million IU/$m^2$ administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. $C_{max}$ occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/ml) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

*Children and adolescents*: Multiple-dose pharmacokinetic properties for Viraferon injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 6**. The pharmacokinetics of Viraferon and ribavirin (dose-normalized) are similar in adults and children or adolescents.

**Table 6.** Mean (% CV) multiple-dose pharmacokinetic parameters for Viraferon and ribavirin capsules when administered to children or adolescents with chronic hepatitis C

| **Parameter** | **Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17) | **Viraferon** 3 MIU/$m^2$ 3 times a week (n = 54) |
|---|---|---|
| $T_{max}$ (hr) | 1.9 (83) | 5.9 (36) |
| $C_{max}$ (ng/ml) | 3,275 (25) | 51 (48) |
| AUC* | 29,774 (26) | 622 (48) |
| Apparent clearance l/hr/kg | 0.27 (27) | Not done |

*$AUC_{12}$ (ng.hr/ml) for ribavirin; $AUC_{0-24}$ (IU.hr/ml) for Viraferon

Interferon neutralising factor assays were performed on serum samples of patients who received Viraferon in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

## 5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x $10^6$ IU/kg/day

for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x $10^6$ IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/$m^2$). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour (see section 4.4 and Rebetol SPC if Viraferon is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Disodium phosphate anhydrous,
Sodium dihydrogen phosphate monohydrate,
Edetate disodium,
Sodium chloride,
M-cresol,
Polysorbate 80,
Water for injections q.s.

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

15 months

Chemical and physical in-use stability has been demonstrated for 27 days at 2ºC – 8ºC.
From a microbiological point of view, once opened, the product may be stored for a maximum of 27 days at 2ºC – 8ºC. Other in-use storage times and conditions are the responsibility of the user.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.

### 6.5 Nature and contents of container

1.2 ml of solution (corresponding to 60 MIU) in a pen made of a cartridge (type I glass) sealed at one end with an cap (aluminium) containing a liner (bromobutyl rubber) and at the other end by a plunger (bromobutyl rubber)
with 12 injection needles and12 cleansing swabs
Pack sizes of 1, 2 or 8
Not all pack sizes may be marketed.

The pen is designed to deliver its contents of 60 million IU in doses ranging from 5 to 20 million IU. The pen will deliver a maximum of 12 doses of 5 million IU over a period not to exceed 4 weeks.

### 6.6 Special precautions for disposal

Not all dosage forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

Viraferon, solution for injection, multidose pen is injected subcutaneously after attaching an injection needle and dialing the prescribed dose.

Remove the pen from the refrigerator approximately 30 minutes before administration to allow the injectable solution to reach room temperature (not more than 25°C).

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to "How to self inject Viraferon").

Each pen is intended for a maximum four-week use period and must then be discarded. A new injection needle must be used for each dose. After each use, the injection needle must be discarded safely and the pen must be returned immediately to the refrigerator. A maximum of 48 hours (two days) of exposure to 25°C is permitted over the four-week use period to cover accidental delays in returning the pen to the refrigerator. Sufficient needles and swabs are provided to use the Viraferon pen for administering the smallest measurable doses. Instruct the patient that any extra needles and swabs that remain after the final dose has been taken from the pen, must be discarded appropriately and safely.

As with all parenteral medicinal products, prior to administration inspect Viraferon, solution for injection, visually for particulate matter and discolouration. The solution should be clear and colourless.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/99/128/035
EU/1/99/128/036
EU/1/99/128/037

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 9 March 2000
Date of last renewal : 23 May 2005

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

# ANNEX II

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OF THE MARKETING AUTHORISATION**

## A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

SP (Brinny) Company
Innishannon - County Cork
Ireland

Name and address of the manufacturer responsible for batch release

SP Labo N.V.
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

## B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE OF THE MEDICINAL PRODUCT**

Not applicable.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

**A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 1 million IU/ml powder and solvent for solution for injection
interferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 1 million IU of interferon alfa-2b and provides 1 million IU per ml of interferon alfa-2b when reconstituted as recommended.

## 3. LIST OF EXCIPIENTS

Excipients: glycine, disodium phosphate anhydrous, Sodium dihydrogen phosphate monohydrate, and human albumin solution
One ampoule of solvent contains 1 ml of water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

1 million IU/ml powder and solvent for solution for injection
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/128/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Viraferon 1 MIU powder

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Vial label**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Viraferon 1 million IU/ml powder for injection
interferon alfa-2b
SC

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

1 million IU/ml

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 3 million IU/ml powder and solvent for solution for injection
interferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 3 million IU of interferon alfa-2b and provides 3 million IU per ml of interferon alfa-2b when reconstituted as recommended.

## 3. LIST OF EXCIPIENTS

Excipients: glycine, disodium phosphate anhydrous sodium dihydrogen phosphate monohydrate, and human albumin solution
One ampoule of solvent contains 1 ml of water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

3 million IU/ml powder and solvent for solution for injection
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
6 vials of powder and 6 ampoules of solvent

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator. Do not freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

After withdrawal of the dose, any remaining solution must be discarded.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/99/128/002 1 vial of powder
EU/1/99/128/003 6 vials of powder

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Viraferon 3 MIU powder

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Vial label**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Viraferon 3 million IU/ml powder for injection
interferon alfa-2b
SC

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

3 million IU/ml

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

**1. NAME OF THE MEDICINAL PRODUCT**

Viraferon 5 million IU/ml powder and solvent for solution for injection
interferon alfa-2b

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial of powder contains 5 million IU of interferon alfa-2b and provides 5 million IU per ml of interferon alfa-2b when reconstituted as recommended.

**3. LIST OF EXCIPIENTS**

Excipients: glycine, disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, and human albumin solution
One ampoule of solvent contains 1 ml of water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 million IU/ml powder and solvent for solution for injection
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
6 vials of powder and 6 ampoules of solvent

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous use.
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/128/004 1 vial of powder
EU/1/99/128/005 6 vials of powder

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Viraferon 5 MIU powder

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Vial label**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Viraferon 5 million IU/ml powder for injection
interferon alfa-2b
SC

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

5 million IU/ml

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 10 million IU/ml powder and solvent for solution for injection
interferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 10 million IU of interferon alfa-2b and provides 10 million IU per ml of interferon alfa-2b when reconstituted as recommended.

## 3. LIST OF EXCIPIENTS

Excipients: glycine, disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, and human albumin solution
One ampoule of solvent contains 1 ml of water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

10 million IU/ml powder and solvent for solution for injection
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
6 vials of powder and 6 ampoules of solvent
10 vials of powder, 10 ampoules of solvent, 10 injection syringes, 20 injection needles and 10 cleansing swabs

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a

refrigerator (2°C - 8°C).

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/128/006 1 vial of powder
EU/1/99/128/007 6 vials of powder
EU/1/99/128/008 10 vials of powder

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Viraferon 10 MIU powder

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Vial label**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Viraferon 10 million IU/ml powder for injection
interferon alfa-2b
SC

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

10 million IU/ml

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Vial label, ampoule of solvent**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Viraferon
Water for injections

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

**1. NAME OF THE MEDICINAL PRODUCT**

Viraferon 3 million IU/0.5 ml solution for injection
interferon alfa-2b

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 3 million IU of interferon alfa-2b in 0.5 ml of solution.

**3. LIST OF EXCIPIENTS**

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections

**4. PHARMACEUTICAL FORM AND CONTENTS**

3 million IU/0.5 ml solution for injection
1 single dose vial
1 single dose vial, 1 injection syringe, 1 injection needle and 1 cleansing swab
6 single dose vials, 6 injection syringes, 6 injection needles and 6 cleansing swabs
12 single dose vials, 12 injection syringes, 12 injection needles and 12 cleansing swabs

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous use.
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/128/009 1 single dose vial
EU/1/99/128/010 1 single dose vial, 1 injection syringe, 1 injection needle and 1 cleansing swab
EU/1/99/128/011 6 single dose vials
EU/1/99/128/012 12 single dose vials

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Viraferon 3 MIU solution

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Vial label**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Viraferon 3 million IU/0.5 ml solution for injection
interferon alfa-2b
SC

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

3 million IU/0.5 ml

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

**1. NAME OF THE MEDICINAL PRODUCT**

Viraferon 5 million IU/0.5 ml solution for injection
interferon alfa-2b

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 5 million IU of interferon alfa-2b in 0.5 ml of solution.

**3. LIST OF EXCIPIENTS**

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 million IU/0.5 ml solution for injection
1 single dose vial
1 single dose vial, 1 injection syringe, 1 injection needle and 1 cleansing swab
6 single dose vials, 6 injection syringes, 6 injection needles and 6 cleansing swabs
12 single dose vials, 12 injection syringes, 12 injection needles and 12 cleansing swabs

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous use.
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/128/013 1 single dose vial
EU/1/99/128/014 1 single dose vial, 1 injection syringe, 1 injection needle and 1 cleansing swab
EU/1/99/128/015 6 single dose vials
EU/1/99/128/016 12 single dose vials

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Viraferon 5 MIU solution

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Vial label**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Viraferon 5 million IU/0.5 ml solution for injection
interferon alfa-2b
SC

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

5 million IU/0.5 ml

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 10 million IU/ml solution for injection
interferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 10 million IU of interferon alfa-2b in 1 ml of solution.

## 3. LIST OF EXCIPIENTS

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections

## 4. PHARMACEUTICAL FORM AND CONTENTS

10 million IU/ml solution for injection
1 single dose vial
1 single dose vial, 1 injection syringe, 1 injection needle and 1 cleansing swab
6 single dose vials, 6 injection syringes, 6 injection needles and 6 cleansing swabs
12 single dose vials, 12 injection syringes, 12 injection needles and 12 cleansing swabs

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/128/017 1 single dose vial
EU/1/99/128/018 1 single dose vial, 1 injection syringe, 1 injection needle and 1 cleansing swab
EU/1/99/128/019 6 single dose vials
EU/1/99/128/020 12 single dose vials

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Viraferon 10 MIU solution

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Vial label**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Viraferon 10 million IU/ml solution for injection
interferon alfa-2b
SC

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

10 million IU/1 ml

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

**1. NAME OF THE MEDICINAL PRODUCT**

Viraferon 18 million IU/3 ml solution for injection
interferon alfa-2b

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 18 million IU of interferon alfa-2b in 3 ml of solution.

**3. LIST OF EXCIPIENTS**

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections

**4. PHARMACEUTICAL FORM AND CONTENTS**

18 million IU/3 ml solution for injection
1 multiple dose vial
1 multiple dose vial, 6 injection syringes, 6 injection needles and 12 cleansing swabs
2 multiple dose vials
12 multiple dose vials

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous use.
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/128/021 1 multiple dose vial
EU/1/99/128/022 1 multiple dose vial, 6 injection syringes, 6 injection needles and 12 cleansing swabs
EU/1/99/128/023 2 multiple dose vials
EU/1/99/128/024 12 multiple dose vials

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Viraferon 18 MIU solution

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Vial label**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Viraferon 18 million IU/3 ml solution for injection
interferon alfa-2b
SC

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

18 million IU/3 ml

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

**1. NAME OF THE MEDICINAL PRODUCT**

Viraferon 25 million IU/2.5 ml solution for injection
interferon alfa-2b

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 25 million IU of interferon alfa-2b in 2.5 ml of solution.

**3. LIST OF EXCIPIENTS**

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections

**4. PHARMACEUTICAL FORM AND CONTENTS**

25 million IU/2.5 ml solution for injection
1 multiple dose vial
1 multiple dose vial, 6 injection syringes, 6 injection needles and 12 cleansing swabs
2 multiple dose vials
12 multiple dose vials

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous use.
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/128/025 1 multiple dose vial
EU/1/99/128/026 1 multiple dose vial, 6 injection syringes, 6 injection needles and 12 cleansing swabs
EU/1/99/128/027 2 multiple dose vials
EU/1/99/128/028 12 multiple dose vials

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Viraferon 25 MIU solution

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Vial label**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Viraferon 25 million IU/2.5 ml solution for injection
interferon alfa-2b
SC

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

25 million IU/2.5 ml

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 18 million IU solution for injection multidose pen
interferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pen contains 18 million IU of interferon alfa-2b in 1.2 ml of solution.

## 3. LIST OF EXCIPIENTS

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections

## 4. PHARMACEUTICAL FORM AND CONTENTS

18 million IU solution for injection multidose pen
1 pen, 12 injection needles and 12 cleansing swabs
2 pens, 24 injection needles and 24 cleansing swabs
8 pens, 96 injection needles and 96 cleansing swabs

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/99/128/029 1 pen
EU/1/99/128/030 2 pens
EU/1/99/128/031 8 pens

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Viraferon 18 MIU pen

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Pen label**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Viraferon 18 million IU solution for injection multidose pen
interferon alfa-2b
Subcutaneous use

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

18 million IU/pen

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 30 million IU solution for injection multidose pen
interferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pen contains 30 million IU of interferon alfa-2b in 1.2 ml of solution.

## 3. LIST OF EXCIPIENTS

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections

## 4. PHARMACEUTICAL FORM AND CONTENTS

30 million IU solution for injection multidose pen
1 pen, 12 injection needles and 12 cleansing swabs
2 pens, 24 injection needles and 24 cleansing swabs
8 pens, 96 injection needles and 96 cleansing swabs

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/99/128/032 1 pen
EU/1/99/128/033 2 pens
EU/1/99/128/034 8 pens

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Viraferon 30 MIU pen

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Pen label**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Viraferon 30 million IU solution for injection multidose pen
interferon alfa-2b
Subcutaneous use

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

30 million IU/pen

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

## 1. NAME OF THE MEDICINAL PRODUCT

Viraferon 60 million IU solution for injection multidose pen
interferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pen contains 60 million IU of interferon alfa-2b in 1.2 ml of solution.

## 3. LIST OF EXCIPIENTS

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections

## 4. PHARMACEUTICAL FORM AND CONTENTS

60 million IU solution for injection multidose pen
1 pen, 12 injection needles and 12 cleansing swabs
2 pens, 24 injection needles and 24 cleansing swabs
8 pens, 96 injection needles and 96 cleansing swabs

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/99/128/035 1 pen
EU/1/99/128/036 2 pens
EU/1/99/128/037 8 pens

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Viraferon 60 MIU pen

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Pen label**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Viraferon 60 million IU solution for injection multidose pen
interferon alfa-2b
Subcutaneous use

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

60 million IU/pen

**6. OTHER**

**B. PACKAGE LEAFLET**

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Viraferon, 1 million IU/ml powder and solvent for solution for injection**
Interferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:


## 1. WHAT VIRAFERON IS AND WHAT IT IS USED FOR

Viraferon (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases. Viraferon is used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

Viraferon is used in combination with ribavirin in children and adolescents 3 years of age and older who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE VIRAFERON

**Do not use Viraferon**
- if you are allergic (hypersensitive) to interferon or any of the other ingredients of Viraferon.
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medications that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with Viraferon**
- if you are pregnant or planning to become pregnant (see Pregnancy).
- if you have had a severe nervous or mental disorder. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see "Do not use Viraferon")
- if you have ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) while on treatment with Viraferon (see section 4).

- if you have psoriasis, it may get worse during treatment with Viraferon.
- when receiving Viraferon, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication seek medical help immediately.
- if you are also being treated for HIV, please see **Using other medicines.**
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Viraferon with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During the one year of treatment, many children did not grow or gain weight as much as expected. However, during the 6 months after treatment, this trend was generally reversed, although a few children did not return to their previous rate of growth within the first year after completing treatment.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide.

Be sure to tell your doctor if you are taking the Chinese herbal medication Shosaikoto.

**Using other medicines**
Viraferon will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medications.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medication you are taking, or have taken recently, even those not prescribed, as the dose of some medications may have to be adjusted while you are treated with Viraferon.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Viraferon and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Using Viraferon with food and drink**
While being treated with Viraferon, your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed Viraferon in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Viraferon. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

**Driving and using machines**
Do not drive or use machinery if you become drowsy, tired, or confused from this medicine.

**Important information about some of the ingredients of Viraferon**
Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived albumin.

This medicine contains human albumin solution as an excipient. When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

There are no reports of virus infections with albumin manufactured to European Pharmacopoeia specifications by established processes.

It is strongly recommended that every time you receive a dose of Viraferon the name and batch number of the product are recorded in order to maintain a record of the batches used.

## 3. HOW TO USE VIRAFERON

Your doctor has prescribed Viraferon specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of Viraferon according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting Viraferon yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/$m^2$ 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Your doctor may prescribe a different dose of Viraferon alone or in combination with other medicines (e.g. ribavirin). If you are prescribed Viraferon in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of Viraferon is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:
Viraferon is usually intended for subcutaneous use. This means that Viraferon is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see HOW TO SELF INJECT VIRAFERON at the end of the leaflet).

One dose of Viraferon is given on each scheduled day. Viraferon is given three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use Viraferon exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take Viraferon for as long as prescribed.

**If you use more Viraferon than you should**
Contact your doctor or healthcare professional as soon as possible.

**If you forget to take Viraferon**
If you are self-administering treatment, or if you are the caregiver of a child taking Viraferon in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this product every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Viraferon can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Some people get depressed when taking Viraferon alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Paediatric Use: Children are particularly prone to develop depression when being treated with Viraferon and ribavirin. Immediately contact the doctor or seek emergency care if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

If any of the following side effects happen, stop taking Viraferon and tell your doctor immediately or go to the casualty department at your nearest hospital:

- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Viraferon. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:

- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.

These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

At the beginning of treatment with Viraferon, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Other side effects that may occur include:

Very commonly reported side effects (at least 1 in every 10 patients):
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects (at least 1 in every 100 patients, but less than 1 in every 10 patients):
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, fingers and toes very sensitive to cold, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Rarely reported side effects (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):
pneumonia

Very rarely reported side effects (less than 1 in every 10,000 patients):
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production

of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord) has been reported with Viraferon use.

Other side effects not listed above may also occur in some patients. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE VIRAFERON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For short term travelling, the non-reconstituted product can be kept out of the refrigerator at or below 25°C for a period up to four weeks before use. If the product is not used during this four-week period, it should be discarded.

The solution should be used immediately after reconstitution. If not used immediately, it must be stored at 2°C - 8°C in the refrigerator and used within 24 hours.

Do not use Viraferon after the expiry date which is stated on the package.

Do not use Viraferon if you notice changes in the appearance of Viraferon.

Any unused product must be discarded after withdrawal of the dose.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What Viraferon contains**

- The active substance is recombinant interferon alfa-2b, 1 million IU/ml.
- The other ingredients are glycine, disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, and human albumin solution.
- Solvent: water for injections 1 ml/ampoule

**What Viraferon looks like and contents of the pack**

Viraferon is presented as a powder and solvent for solution for injection
The white to cream coloured powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule with 1 injection syringe, 2 injection needles and 1 cleansing swab.

Not all pack sizes may be marketed.

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SP Europe
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**Manufacturer:**
SP Labo N.V.
Industriepark 30
B-2220 Heist-op-den-Berg
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For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last approved on**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site:
http://www.emea.europa.eu/

HOW TO SELF INJECT VIRAFERON

The following instructions explain how to inject Viraferon yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject Viraferon. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of Viraferon powder for injection;
- an ampoule of solvent for Viraferon (water for injections 1 ml);
- a 2 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the Viraferon powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting Viraferon powder for injection
Remove the protective cap from the Viraferon vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly onto the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

To prepare the Viraferon solution insert the needle through the rubber top of the Viraferon vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.
Slowly inject the diluent, aiming the stream of liquid at the glass wall of the vial in order to avoid production of air bubbles. Do not aim the stream at the white powder at the bottom of the vial. To dissolve the white contents, swirl the Viraferon vial with a gentle rotary motion leaving the syringe needle in the vial, until the contents are completely dissolved. Do not shake. If air bubbles do form, wait until the solution has settled and all bubbles have risen to the top of the solution and disappeared before withdrawing your dose from the vial. The solution should be used immediately after reconstitution. If not used immediately, it must be stored at 2°C - 8°C in the refrigerator and used within 24 hours.

Measuring the dose of Viraferon from the reconstituted powder for injection
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the Viraferon reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.
Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly onto the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the reconstituted solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.

Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard.With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently.

Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Viraferon, 3 million IU/ml powder and solvent for solution for injection**
Interferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:


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- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
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- if you have a history of seizures (convulsions).
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- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with Viraferon**
- if you are pregnant or planning to become pregnant (see Pregnancy).
- if you have had a severe nervous or mental disorder. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see "Do not use Viraferon")
- if you have ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) while on treatment with Viraferon (see section 4).

- if you have psoriasis, it may get worse during treatment with Viraferon.
- when receiving Viraferon, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication seek medical help immediately.
- if you are also being treated for HIV, please see **Using other medicines.**
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Viraferon with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

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Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide.

Be sure to tell your doctor if you are taking the Chinese herbal medication Shosaikoto.

**Using other medicines**
Viraferon will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medications.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medication you are taking, or have taken recently, even those not prescribed, as the dose of some medications may have to be adjusted while you are treated with Viraferon.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Viraferon and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Using Viraferon with food and drink**
While being treated with Viraferon, your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed Viraferon in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Viraferon. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

**Driving and using machines**
Do not drive or use machinery if you become drowsy, tired, or confused from this medicine.

**Important information about some of the ingredients of Viraferon**
Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived albumin.

This medicine contains human albumin solution as an excipient. When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

There are no reports of virus infections with albumin manufactured to European Pharmacopoeia specifications by established processes.

It is strongly recommended that every time you receive a dose of Viraferon the name and batch number of the product are recorded in order to maintain a record of the batches used.

## 3. HOW TO USE VIRAFERON

Your doctor has prescribed Viraferon specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of Viraferon according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting Viraferon yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/$m^2$ 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Your doctor may prescribe a different dose of Viraferon alone or in combination with other medicines (e.g. ribavirin). If you are prescribed Viraferon in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of Viraferon is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:
Viraferon is usually intended for subcutaneous use. This means that Viraferon is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see HOW TO SELF INJECT VIRAFERON at the end of the leaflet).

One dose of Viraferon is given on each scheduled day. Viraferon is given three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use Viraferon exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take Viraferon for as long as prescribed.

**If you use more Viraferon than you should**
Contact your doctor or healthcare professional as soon as possible.

**If you forget to take Viraferon**
If you are self-administering treatment, or if you are the caregiver of a child taking Viraferon in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this product every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Viraferon can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Some people get depressed when taking Viraferon alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Paediatric Use: Children are particularly prone to develop depression when being treated with Viraferon and ribavirin. Immediately contact the doctor or seek emergency care if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

If any of the following side effects happen, stop taking Viraferon and tell your doctor immediately or go to the casualty department at your nearest hospital:

- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Viraferon. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:

- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.

These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

At the beginning of treatment with Viraferon, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Other side effects that may occur include:

Very commonly reported side effects (at least 1 in every 10 patients):
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects (at least 1 in every 100 patients, but less than 1 in every 10 patients):
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, fingers and toes very sensitive to cold, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Rarely reported side effects (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):
pneumonia

Very rarely reported side effects (less than 1 in every 10,000 patients):
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production

of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord) has been reported with Viraferon use.

Other side effects not listed above may also occur in some patients. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE VIRAFERON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For short term travelling, the non-reconstituted product can be kept out of the refrigerator at or below 25°C for a period up to four weeks before use. If the product is not used during this four-week period, it should be discarded.

The solution should be used immediately after reconstitution. If not used immediately, it must be stored at 2°C - 8°C in the refrigerator and used within 24 hours.

Do not use Viraferon after the expiry date which is stated on the package.

Do not use Viraferon if you notice changes in the appearance of Viraferon.

Any unused product must be discarded after withdrawal of the dose.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What Viraferon contains**

- The active substance is recombinant interferon alfa-2b, 3 million IU/ml.
- The other ingredients are glycine, disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, and human albumin solution.
- Solvent: water for injections 1 ml/ampoule

**What Viraferon looks like and contents of the pack**

Viraferon is presented as a powder and solvent for solution for injection
The white to cream coloured powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

Viraferon is available in two different pack sizes:
- Pack of 1 vial of powder for solution for injection, 1 ampoule of water for injections, 1 injection syringe, 2 injection needles and 1 cleansing swab
- Pack of 6 vials of powder for solution for injection and 6 ampoules of water for injections

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

**Manufacturer:**
SP Labo N.V.
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last approved on**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HOW TO SELF INJECT VIRAFERON

The following instructions explain how to inject Viraferon yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject Viraferon. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of Viraferon powder for injection;
- an ampoule of solvent for Viraferon (water for injections 1 ml);
- a 2 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the Viraferon powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting Viraferon powder for injection
Remove the protective cap from the Viraferon vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly onto the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

To prepare the Viraferon solution insert the needle through the rubber top of the Viraferon vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.
Slowly inject the diluent, aiming the stream of liquid at the glass wall of the vial in order to avoid production of air bubbles. Do not aim the stream at the white powder at the bottom of the vial. To dissolve the white contents, swirl the Viraferon vial with a gentle rotary motion leaving the syringe needle in the vial, until the contents are completely dissolved. Do not shake. If air bubbles do form, wait until the solution has settled and all bubbles have risen to the top of the solution and disappeared before withdrawing your dose from the vial. The solution should be used immediately after reconstitution. If not used immediately, it must be stored at 2°C - 8°C in the refrigerator and used within 24 hours.

Measuring the dose of Viraferon from the reconstituted powder for injection
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the Viraferon reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.
Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly onto the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the reconstituted solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.

Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard.With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently.

Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Viraferon, 5 million IU/ml powder and solvent for solution for injection**
Interferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:


## 1. WHAT VIRAFERON IS AND WHAT IT IS USED FOR

Viraferon (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases. Viraferon is used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

Viraferon is used in combination with ribavirin in children and adolescents 3 years of age and older who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE VIRAFERON

**Do not use Viraferon**
- if you are allergic (hypersensitive) to interferon or any of the other ingredients of Viraferon.
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medications that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with Viraferon**
- if you are pregnant or planning to become pregnant (see Pregnancy).
- if you have had a severe nervous or mental disorder. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see "Do not use Viraferon")
- if you have ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) while on treatment with Viraferon (see section 4).

- if you have psoriasis, it may get worse during treatment with Viraferon.
- when receiving Viraferon, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication seek medical help immediately.
- if you are also being treated for HIV, please see **Using other medicines.**
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Viraferon with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During the one year of treatment, many children did not grow or gain weight as much as expected. However, during the 6 months after treatment, this trend was generally reversed, although a few children did not return to their previous rate of growth within the first year after completing treatment.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide.

Be sure to tell your doctor if you are taking the Chinese herbal medication Shosaikoto.

**Using other medicines**
Viraferon will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medications.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medication you are taking, or have taken recently, even those not prescribed, as the dose of some medications may have to be adjusted while you are treated with Viraferon.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Viraferon and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Using Viraferon with food and drink**
While being treated with Viraferon, your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed Viraferon in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Viraferon. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

**Driving and using machines**
Do not drive or use machinery if you become drowsy, tired, or confused from this medicine.

**Important information about some of the ingredients of Viraferon**
Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived albumin.

This medicine contains human albumin solution as an excipient. When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

There are no reports of virus infections with albumin manufactured to European Pharmacopoeia specifications by established processes.

It is strongly recommended that every time you receive a dose of Viraferon the name and batch number of the product are recorded in order to maintain a record of the batches used.

## 3. HOW TO USE VIRAFERON

Your doctor has prescribed Viraferon specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of Viraferon according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting Viraferon yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/$m^2$ 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Your doctor may prescribe a different dose of Viraferon alone or in combination with other medicines (e.g. ribavirin). If you are prescribed Viraferon in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of Viraferon is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:
Viraferon is usually intended for subcutaneous use. This means that Viraferon is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see HOW TO SELF INJECT VIRAFERON at the end of the leaflet).

One dose of Viraferon is given on each scheduled day. Viraferon is given three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use Viraferon exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take Viraferon for as long as prescribed.

**If you use more Viraferon than you should**
Contact your doctor or healthcare professional as soon as possible.

**If you forget to take Viraferon**
If you are self-administering treatment, or if you are the caregiver of a child taking Viraferon in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this product every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Viraferon can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Some people get depressed when taking Viraferon alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Paediatric Use: Children are particularly prone to develop depression when being treated with Viraferon and ribavirin. Immediately contact the doctor or seek emergency care if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

If any of the following side effects happen, stop taking Viraferon and tell your doctor immediately or go to the casualty department at your nearest hospital:

- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Viraferon. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:

- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.

These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

At the beginning of treatment with Viraferon, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Other side effects that may occur include:

Very commonly reported side effects (at least 1 in every 10 patients):
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects (at least 1 in every 100 patients, but less than 1 in every 10 patients):
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, fingers and toes very sensitive to cold, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Rarely reported side effects (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):
pneumonia

Very rarely reported side effects (less than 1 in every 10,000 patients):
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production

of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord) has been reported with Viraferon use.

Other side effects not listed above may also occur in some patients. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE VIRAFERON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For short term travelling, the non-reconstituted product can be kept out of the refrigerator at or below 25°C for a period up to four weeks before use. If the product is not used during this four-week period, it should be discarded.

The solution should be used immediately after reconstitution. If not used immediately, it must be stored at 2°C - 8°C in the refrigerator and used within 24 hours.

Do not use Viraferon after the expiry date which is stated on the package.

Do not use Viraferon if you notice changes in the appearance of Viraferon.

Any unused product must be discarded after withdrawal of the dose.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What Viraferon contains**

- The active substance is recombinant interferon alfa-2b, 5 million IU/ml.
- The other ingredients are glycine, disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, and human albumin solution.
- Solvent: water for injections 1 ml/ampoule

**What Viraferon looks like and contents of the pack**

Viraferon is presented as a powder and solvent for solution for injection
The white to cream coloured powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

Viraferon is available in two different pack sizes:
- Pack of 1 vial of powder for solution for injection, 1 ampoule of water for injections, 1 injection syringe, 2 injection needles and 1 cleansing swab
- Pack of 6 vials of powder for solution for injection and 6 ampoules of water for injections

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

**Manufacturer:**
SP Labo N.V.
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last approved on**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HOW TO SELF INJECT VIRAFERON

The following instructions explain how to inject Viraferon yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject Viraferon. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of Viraferon powder for injection;
- an ampoule of solvent for Viraferon (water for injections 1 ml);
- a 2 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the Viraferon powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting Viraferon powder for injection
Remove the protective cap from the Viraferon vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly onto the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

To prepare the Viraferon solution insert the needle through the rubber top of the Viraferon vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.
Slowly inject the diluent, aiming the stream of liquid at the glass wall of the vial in order to avoid production of air bubbles. Do not aim the stream at the white powder at the bottom of the vial. To dissolve the white contents, swirl the Viraferon vial with a gentle rotary motion leaving the syringe needle in the vial, until the contents are completely dissolved. Do not shake. If air bubbles do form, wait until the solution has settled and all bubbles have risen to the top of the solution and disappeared before withdrawing your dose from the vial. The solution should be used immediately after reconstitution. If not used immediately, it must be stored at 2°C - 8°C in the refrigerator and used within 24 hours.

Measuring the dose of Viraferon from the reconstituted powder for injection
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the Viraferon reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.
Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly onto the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the reconstituted solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.

Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard.With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently.

Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Viraferon, 10 million IU/ml powder and solvent for solution for injection**
Interferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:


## 1. WHAT VIRAFERON IS AND WHAT IT IS USED FOR

Viraferon (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases. Viraferon is used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

Viraferon is used in combination with ribavirin in children and adolescents 3 years of age and older who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE VIRAFERON

**Do not use Viraferon**
- if you are allergic (hypersensitive) to interferon or any of the other ingredients of Viraferon.
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medications that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with Viraferon**
- if you are pregnant or planning to become pregnant (see Pregnancy).
- if you have had a severe nervous or mental disorder. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see "Do not use Viraferon")
- if you have ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) while on treatment with Viraferon (see section 4).

- if you have psoriasis, it may get worse during treatment with Viraferon.
- when receiving Viraferon, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication seek medical help immediately.
- if you are also being treated for HIV, please see **Using other medicines.**
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Viraferon with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During the one year of treatment, many children did not grow or gain weight as much as expected. However, during the 6 months after treatment, this trend was generally reversed, although a few children did not return to their previous rate of growth within the first year after completing treatment.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide.

Be sure to tell your doctor if you are taking the Chinese herbal medication Shosaikoto.

**Using other medicines**
Viraferon will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medications.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medication you are taking, or have taken recently, even those not prescribed, as the dose of some medications may have to be adjusted while you are treated with Viraferon.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Viraferon and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Using Viraferon with food and drink**
While being treated with Viraferon, your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed Viraferon in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Viraferon. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

**Driving and using machines**
Do not drive or use machinery if you become drowsy, tired, or confused from this medicine.

**Important information about some of the ingredients of Viraferon**
Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived albumin.

This medicine contains human albumin solution as an excipient. When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

There are no reports of virus infections with albumin manufactured to European Pharmacopoeia specifications by established processes.

It is strongly recommended that every time you receive a dose of Viraferon the name and batch number of the product are recorded in order to maintain a record of the batches used.

## 3. HOW TO USE VIRAFERON

Your doctor has prescribed Viraferon specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of Viraferon according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting Viraferon yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/$m^2$ 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Your doctor may prescribe a different dose of Viraferon alone or in combination with other medicines (e.g. ribavirin). If you are prescribed Viraferon in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of Viraferon is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:
Viraferon is usually intended for subcutaneous use. This means that Viraferon is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see HOW TO SELF INJECT VIRAFERON at the end of the leaflet).

One dose of Viraferon is given on each scheduled day. Viraferon is given three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use Viraferon exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take Viraferon for as long as prescribed.

**If you use more Viraferon than you should**
Contact your doctor or healthcare professional as soon as possible.

**If you forget to take Viraferon**
If you are self-administering treatment, or if you are the caregiver of a child taking Viraferon in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this product every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Viraferon can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Some people get depressed when taking Viraferon alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Paediatric Use: Children are particularly prone to develop depression when being treated with Viraferon and ribavirin. Immediately contact the doctor or seek emergency care if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

If any of the following side effects happen, stop taking Viraferon and tell your doctor immediately or go to the casualty department at your nearest hospital:

- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Viraferon. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:

- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.

These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

At the beginning of treatment with Viraferon, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Other side effects that may occur include:

Very commonly reported side effects (at least 1 in every 10 patients):
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects (at least 1 in every 100 patients, but less than 1 in every 10 patients):
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, fingers and toes very sensitive to cold, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Rarely reported side effects (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):
pneumonia

Very rarely reported side effects (less than 1 in every 10,000 patients):
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production

of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord) has been reported with Viraferon use.

Other side effects not listed above may also occur in some patients. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE VIRAFERON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For short term travelling, the non-reconstituted product can be kept out of the refrigerator at or below 25°C for a period up to four weeks before use. If the product is not used during this four-week period, it should be discarded.

The solution should be used immediately after reconstitution. If not used immediately, it must be stored at 2°C - 8°C in the refrigerator and used within 24 hours.

Do not use Viraferon after the expiry date which is stated on the package.

Do not use Viraferon if you notice changes in the appearance of Viraferon.

Any unused product must be discarded after withdrawal of the dose.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What Viraferon contains**

- The active substance is recombinant interferon alfa-2b, 10 million IU/ml.
- The other ingredients are glycine, disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, and human albumin solution.
- Solvent: water for injections 1 ml/ampoule

**What Viraferon looks like and contents of the pack**

Viraferon is presented as a powder and solvent for solution for injection
The white to cream coloured powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

Viraferon is available in three different pack sizes:
- Pack of 1 vial of powder for solution for injection, 1 ampoule of water for injections, 1 injection syringe, 2 injection needles and 1 cleansing swab
- Pack of 6 vials of powder for solution for injection and 6 ampoules of water for injections
- Pack of 10 vials of powder for solution for injection, 10 ampoules of water for injections, 10 injection syringes, 20 injection needles and 10 cleansing swabs

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

**Manufacturer:**
SP Labo N.V.
Industriepark 30
B-2220 Heist-op-den-Berg
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For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last approved on**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HOW TO SELF INJECT VIRAFERON

The following instructions explain how to inject Viraferon yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject Viraferon. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of Viraferon powder for injection;
- an ampoule of solvent for Viraferon (water for injections 1 ml);
- a 2 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the Viraferon powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting Viraferon powder for injection
Remove the protective cap from the Viraferon vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly onto the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

To prepare the Viraferon solution insert the needle through the rubber top of the Viraferon vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.
Slowly inject the diluent, aiming the stream of liquid at the glass wall of the vial in order to avoid production of air bubbles. Do not aim the stream at the white powder at the bottom of the vial. To dissolve the white contents, swirl the Viraferon vial with a gentle rotary motion leaving the syringe needle in the vial, until the contents are completely dissolved. Do not shake. If air bubbles do form, wait until the solution has settled and all bubbles have risen to the top of the solution and disappeared before withdrawing your dose from the vial. The solution should be used immediately after reconstitution. If not used immediately, it must be stored at 2°C - 8°C in the refrigerator and used within 24 hours.

Measuring the dose of Viraferon from the reconstituted powder for injection
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the Viraferon reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.
Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly onto the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the reconstituted solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.

Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard.With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently.

Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Viraferon, 3 million IU/0.5 ml solution for injection**
Interferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:


## 1. WHAT VIRAFERON IS AND WHAT IT IS USED FOR

Viraferon (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases. Viraferon is used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

Viraferon is used in combination with ribavirin in children and adolescents 3 years of age and older who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE VIRAFERON

**Do not use Viraferon**
- if you are allergic (hypersensitive) to interferon or any of the other ingredients of Viraferon.
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medications that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with Viraferon**
- if you are pregnant or planning to become pregnant (see Pregnancy).
- if you have had a severe nervous or mental disorder. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see "Do not use Viraferon")
- if you have ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) while on treatment with Viraferon (see section 4).

- if you have psoriasis, it may get worse during treatment with Viraferon.
- when receiving Viraferon, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication seek medical help immediately.
- if you are also being treated for HIV, please see **Using other medicines.**
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Viraferon with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During the one year of treatment, many children did not grow or gain weight as much as expected. However, during the 6 months after treatment, this trend was generally reversed, although a few children did not return to their previous rate of growth within the first year after completing treatment.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide.

Be sure to tell your doctor if you are taking the Chinese herbal medication Shosaikoto.

**Using other medicines**
Viraferon will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medications.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medication you are taking, or have taken recently, even those not prescribed, as the dose of some medications may have to be adjusted while you are treated with Viraferon.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Viraferon and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Using Viraferon with food and drink**
While being treated with Viraferon, your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed Viraferon in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Viraferon. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

**Driving and using machines**
Do not drive or use machinery if you become drowsy, tired, or confused from this medicine.

## 3. HOW TO USE VIRAFERON

Your doctor has prescribed Viraferon specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of Viraferon according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting Viraferon yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/$m^2$ 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Your doctor may prescribe a different dose of Viraferon alone or in combination with other medicines (e.g. ribavirin). If you are prescribed Viraferon in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of Viraferon is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:

Viraferon is usually intended for subcutaneous use. This means that Viraferon is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see HOW TO SELF INJECT VIRAFERON at the end of the leaflet).

One dose of Viraferon is given on each scheduled day. Viraferon is given three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use Viraferon exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take Viraferon for as long as prescribed.

**If you use more Viraferon than you should**
Contact your doctor or healthcare professional as soon as possible.

**If you forget to take Viraferon**
If you are self-administering treatment, or if you are the caregiver of a child taking Viraferon in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this product every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Viraferon can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Some people get depressed when taking Viraferon alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Paediatric Use: Children are particularly prone to develop depression when being treated with Viraferon and ribavirin. Immediately contact the doctor or seek emergency care if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

If any of the following side effects happen, stop taking Viraferon and tell your doctor immediately or go to the casualty department at your nearest hospital:

- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Viraferon. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:

- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of

treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.
These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

At the beginning of treatment with Viraferon, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Other side effects that may occur include:

Very commonly reported side effects (at least 1 in every 10 patients):
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects (at least 1 in every 100 patients, but less than 1 in every 10 patients):
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, fingers and toes very sensitive to cold, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Rarely reported side effects (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):
pneumonia

Very rarely reported side effects (less than 1 in every 10,000 patients):
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord) has been reported with Viraferon use.

Other side effects not listed above may also occur in some patients. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE VIRAFERON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For short term travelling, the solution can be kept out of the refrigerator at or below 25°C for a period up to seven days before use. Viraferon can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it should be discarded.

Do not use Viraferon after the expiry date which is stated on the package.

Do not use Viraferon if you notice changes in the appearance of Viraferon.

Any unused product must be discarded after withdrawal of the dose.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What Viraferon contains**

- The active substance is recombinant interferon alfa-2b, 3 million IU in a single dose vial
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

**What Viraferon looks like and contents of the pack**

Viraferon is presented as a solution for injection
- The clear and colourless solution is contained in a glass vial with 1 injection syringe, 1 injection needle and 1 cleansing swab. Pack of 1, 6 or 12. Vial alone is also available.

Not all pack sizes may be marketed.

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**This leaflet was last approved on**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HOW TO SELF INJECT VIRAFERON

The following instructions explain how to inject Viraferon yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject Viraferon. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of Viraferon solution for injection;
- a 1 ml syringe;
- a needle for the subcutaneous injection (for example 0.4 × 13 mm [27 gauge 0.5 inch]);
- a cleansing swab.

Wash your hands carefully.

Measuring the dose of Viraferon
Remove the cap from the vial. If this is a multidose vial, you will only have to remove the cap when preparing the first dose. Clean the rubber stopper on the top of the vial containing the Viraferon solution with a cleansing swab.
Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the needle and place it firmly onto the tip of the syringe.
Remove the needle guard without touching the needle, and fill the syringe with air by pulling the plunger to the level that represents your dose as prescribed by your doctor.
Hold the Viraferon vial upright without touching the cleaned top of the vial with your hands.
Insert the needle into the vial containing the Viraferon solution and inject air into the vial.
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the Viraferon solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.
Remove the needle from the vial and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently. Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial and injection materials intended for single use must be discarded. Dispose of the syringe and needle safely in a closed container. For multidose vials, be sure to return the vial to the refrigerator.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Viraferon, 5 million IU/0.5 ml solution for injection**
Interferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:


## 1. WHAT VIRAFERON IS AND WHAT IT IS USED FOR

Viraferon (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases. Viraferon is used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

Viraferon is used in combination with ribavirin in children and adolescents 3 years of age and older who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE VIRAFERON

**Do not use Viraferon**
- if you are allergic (hypersensitive) to interferon or any of the other ingredients of Viraferon.
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medications that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with Viraferon**
- if you are pregnant or planning to become pregnant (see Pregnancy).
- if you have had a severe nervous or mental disorder. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see "Do not use Viraferon")
- if you have ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) while on treatment with Viraferon (see section 4).

- if you have psoriasis, it may get worse during treatment with Viraferon.
- when receiving Viraferon, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication seek medical help immediately.
- if you are also being treated for HIV, please see **Using other medicines.**
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Viraferon with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During the one year of treatment, many children did not grow or gain weight as much as expected. However, during the 6 months after treatment, this trend was generally reversed, although a few children did not return to their previous rate of growth within the first year after completing treatment.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide.

Be sure to tell your doctor if you are taking the Chinese herbal medication Shosaikoto.

**Using other medicines**
Viraferon will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medications.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medication you are taking, or have taken recently, even those not prescribed, as the dose of some medications may have to be adjusted while you are treated with Viraferon.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Viraferon and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Using Viraferon with food and drink**
While being treated with Viraferon, your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed Viraferon in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Viraferon. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

**Driving and using machines**
Do not drive or use machinery if you become drowsy, tired, or confused from this medicine.

## 3. HOW TO USE VIRAFERON

Your doctor has prescribed Viraferon specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of Viraferon according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting Viraferon yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/$m^2$ 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Your doctor may prescribe a different dose of Viraferon alone or in combination with other medicines (e.g. ribavirin). If you are prescribed Viraferon in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of Viraferon is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:

Viraferon is usually intended for subcutaneous use. This means that Viraferon is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see HOW TO SELF INJECT VIRAFERON at the end of the leaflet).

One dose of Viraferon is given on each scheduled day. Viraferon is given three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use Viraferon exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take Viraferon for as long as prescribed.

**If you use more Viraferon than you should**
Contact your doctor or healthcare professional as soon as possible.

**If you forget to take Viraferon**
If you are self-administering treatment, or if you are the caregiver of a child taking Viraferon in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this product every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Viraferon can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Some people get depressed when taking Viraferon alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Paediatric Use: Children are particularly prone to develop depression when being treated with Viraferon and ribavirin. Immediately contact the doctor or seek emergency care if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

If any of the following side effects happen, stop taking Viraferon and tell your doctor immediately or go to the casualty department at your nearest hospital:

- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Viraferon. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:

- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of

treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.
These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

At the beginning of treatment with Viraferon, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Other side effects that may occur include:

Very commonly reported side effects (at least 1 in every 10 patients):
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects (at least 1 in every 100 patients, but less than 1 in every 10 patients):
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, fingers and toes very sensitive to cold, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Rarely reported side effects (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):
pneumonia

Very rarely reported side effects (less than 1 in every 10,000 patients):
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord) has been reported with Viraferon use.

Other side effects not listed above may also occur in some patients. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE VIRAFERON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For short term travelling, the solution can be kept out of the refrigerator at or below 25°C for a period up to seven days before use. Viraferon can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it should be discarded.

Do not use Viraferon after the expiry date which is stated on the package.

Do not use Viraferon if you notice changes in the appearance of Viraferon.

Any unused product must be discarded after withdrawal of the dose.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What Viraferon contains**

- The active substance is recombinant interferon alfa-2b, 5 million IU in a single dose vial
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

**What Viraferon looks like and contents of the pack**

Viraferon is presented as a solution for injection
- The clear and colourless solution is contained in a glass vial with 1 injection syringe, 1 injection needle and 1 cleansing swab. Pack of 1, 6 or 12. Vial alone is also available.

Not all pack sizes may be marketed.

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**This leaflet was last approved on**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HOW TO SELF INJECT VIRAFERON

The following instructions explain how to inject Viraferon yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject Viraferon. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of Viraferon solution for injection;
- a 1 ml syringe;
- a needle for the subcutaneous injection (for example 0.4 × 13 mm [27 gauge 0.5 inch]);
- a cleansing swab.

Wash your hands carefully.

Measuring the dose of Viraferon
Remove the cap from the vial. If this is a multidose vial, you will only have to remove the cap when preparing the first dose. Clean the rubber stopper on the top of the vial containing the Viraferon solution with a cleansing swab.
Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the needle and place it firmly onto the tip of the syringe.
Remove the needle guard without touching the needle, and fill the syringe with air by pulling the plunger to the level that represents your dose as prescribed by your doctor.
Hold the Viraferon vial upright without touching the cleaned top of the vial with your hands.
Insert the needle into the vial containing the Viraferon solution and inject air into the vial.
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the Viraferon solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.
Remove the needle from the vial and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently. Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial and injection materials intended for single use must be discarded. Dispose of the syringe and needle safely in a closed container. For multidose vials, be sure to return the vial to the refrigerator.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Viraferon, 10 million IU/ml solution for injection**
Interferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:


## 1. WHAT VIRAFERON IS AND WHAT IT IS USED FOR

Viraferon (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases. Viraferon is used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

Viraferon is used in combination with ribavirin in children and adolescents 3 years of age and older who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE VIRAFERON

**Do not use Viraferon**
- if you are allergic (hypersensitive) to interferon or any of the other ingredients of Viraferon.
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medications that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with Viraferon**
- if you are pregnant or planning to become pregnant (see Pregnancy).
- if you have had a severe nervous or mental disorder. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see "Do not use Viraferon")
- if you have ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) while on treatment with Viraferon (see section 4).

- if you have psoriasis, it may get worse during treatment with Viraferon.
- when receiving Viraferon, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication seek medical help immediately.
- if you are also being treated for HIV, please see **Using other medicines.**
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Viraferon with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During the one year of treatment, many children did not grow or gain weight as much as expected. However, during the 6 months after treatment, this trend was generally reversed, although a few children did not return to their previous rate of growth within the first year after completing treatment.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide.

Be sure to tell your doctor if you are taking the Chinese herbal medication Shosaikoto.

**Using other medicines**
Viraferon will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medications.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medication you are taking, or have taken recently, even those not prescribed, as the dose of some medications may have to be adjusted while you are treated with Viraferon.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Viraferon and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Using Viraferon with food and drink**
While being treated with Viraferon, your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed Viraferon in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Viraferon. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

**Driving and using machines**
Do not drive or use machinery if you become drowsy, tired, or confused from this medicine.

## 3. HOW TO USE VIRAFERON

Your doctor has prescribed Viraferon specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of Viraferon according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting Viraferon yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/$m^2$ 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Your doctor may prescribe a different dose of Viraferon alone or in combination with other medicines (e.g. ribavirin). If you are prescribed Viraferon in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of Viraferon is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:

Viraferon is usually intended for subcutaneous use. This means that Viraferon is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see HOW TO SELF INJECT VIRAFERON at the end of the leaflet).

One dose of Viraferon is given on each scheduled day. Viraferon is given three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use Viraferon exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take Viraferon for as long as prescribed.

**If you use more Viraferon than you should**
Contact your doctor or healthcare professional as soon as possible.

**If you forget to take Viraferon**
If you are self-administering treatment, or if you are the caregiver of a child taking Viraferon in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this product every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Viraferon can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Some people get depressed when taking Viraferon alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Paediatric Use: Children are particularly prone to develop depression when being treated with Viraferon and ribavirin. Immediately contact the doctor or seek emergency care if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

If any of the following side effects happen, stop taking Viraferon and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Viraferon. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:
- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of

treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.
These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

At the beginning of treatment with Viraferon, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Other side effects that may occur include:

Very commonly reported side effects (at least 1 in every 10 patients):
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects (at least 1 in every 100 patients, but less than 1 in every 10 patients):
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, fingers and toes very sensitive to cold, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Rarely reported side effects (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):
pneumonia

Very rarely reported side effects (less than 1 in every 10,000 patients):
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord) has been reported with Viraferon use.

Other side effects not listed above may also occur in some patients. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE VIRAFERON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For short term travelling, the solution can be kept out of the refrigerator at or below 25°C for a period up to seven days before use. Viraferon can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it should be discarded.

Do not use Viraferon after the expiry date which is stated on the package.

Do not use Viraferon if you notice changes in the appearance of Viraferon

Any unused product must be discarded after withdrawal of the dose.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What Viraferon contains**

- The active substance is recombinant interferon alfa-2b, 10 million IU in a single dose vial
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

**What Viraferon looks like and contents of the pack**

Viraferon is presented as a solution for injection
- The clear and colourless solution is contained in a glass with 1 injection syringe, 1 injection needle and 1 cleansing swab. Pack of 1, 6 or 12. Vial alone is also available.

Not all pack sizes may be marketed.

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**Manufacturer:**
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Industriepark 30
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HOW TO SELF INJECT VIRAFERON

The following instructions explain how to inject Viraferon yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject Viraferon. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of Viraferon solution for injection;
- a 2 ml syringe;
- a needle for the subcutaneous injection (for example 0.4 × 13 mm [27 gauge 0.5 inch]);
- a cleansing swab.

Wash your hands carefully.

Measuring the dose of Viraferon
Remove the cap from the vial. If this is a multidose vial, you will only have to remove the cap when preparing the first dose. Clean the rubber stopper on the top of the vial containing the Viraferon solution with a cleansing swab.
Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the needle and place it firmly onto the tip of the syringe.
Remove the needle guard without touching the needle, and fill the syringe with air by pulling the plunger to the level that represents your dose as prescribed by your doctor.
Hold the Viraferon vial upright without touching the cleaned top of the vial with your hands.
Insert the needle into the vial containing the Viraferon solution and inject air into the vial.
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the Viraferon solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.
Remove the needle from the vial and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently. Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial and injection materials intended for single use must be discarded. Dispose of the syringe and needle safely in a closed container. For multidose vials, be sure to return the vial to the refrigerator.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Viraferon, 18 million IU/3 ml solution for injection**
Interferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:


## 1. WHAT VIRAFERON IS AND WHAT IT IS USED FOR

Viraferon (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases. Viraferon is used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

Viraferon is used in combination with ribavirin in children and adolescents 3 years of age and older who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE VIRAFERON

**Do not use Viraferon**
- if you are allergic (hypersensitive) to interferon or any of the other ingredients of Viraferon.
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medications that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with Viraferon**
- if you are pregnant or planning to become pregnant (see Pregnancy).
- if you have had a severe nervous or mental disorder. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see "Do not use Viraferon")
- if you have ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) while on treatment with Viraferon (see section 4).

- if you have psoriasis, it may get worse during treatment with Viraferon.
- when receiving Viraferon, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication seek medical help immediately.
- if you are also being treated for HIV, please see **Using other medicines.**
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Viraferon with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During the one year of treatment, many children did not grow or gain weight as much as expected. However, during the 6 months after treatment, this trend was generally reversed, although a few children did not return to their previous rate of growth within the first year after completing treatment.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide.

Be sure to tell your doctor if you are taking the Chinese herbal medication Shosaikoto.

**Using other medicines**
Viraferon will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medications.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medication you are taking, or have taken recently, even those not prescribed, as the dose of some medications may have to be adjusted while you are treated with Viraferon.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Viraferon and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Using Viraferon with food and drink**
While being treated with Viraferon, your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed Viraferon in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Viraferon. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

**Driving and using machines**
Do not drive or use machinery if you become drowsy, tired, or confused from this medicine.

## 3. HOW TO USE VIRAFERON

Your doctor has prescribed Viraferon specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of Viraferon according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting Viraferon yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/$m^2$ 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Your doctor may prescribe a different dose of Viraferon alone or in combination with other medicines (e.g. ribavirin). If you are prescribed Viraferon in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of Viraferon is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:

Viraferon is usually intended for subcutaneous use. This means that Viraferon is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see HOW TO SELF INJECT VIRAFERON at the end of the leaflet).

One dose of Viraferon is given on each scheduled day. Viraferon is given three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use Viraferon exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take Viraferon for as long as prescribed.

**If you use more Viraferon than you should**
Contact your doctor or healthcare professional as soon as possible.

**If you forget to take Viraferon**
If you are self-administering treatment, or if you are the caregiver of a child taking Viraferon in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this product every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Viraferon can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Some people get depressed when taking Viraferon alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Paediatric Use: Children are particularly prone to develop depression when being treated with Viraferon and ribavirin. Immediately contact the doctor or seek emergency care if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

If any of the following side effects happen, stop taking Viraferon and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Viraferon. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:
- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of

treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.
These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

At the beginning of treatment with Viraferon, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Other side effects that may occur include:

Very commonly reported side effects (at least 1 in every 10 patients):
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects (at least 1 in every 100 patients, but less than 1 in every 10 patients):
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, fingers and toes very sensitive to cold, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Rarely reported side effects (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):
pneumonia

Very rarely reported side effects (less than 1 in every 10,000 patients):
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord) has been reported with Viraferon use.

Other side effects not listed above may also occur in some patients. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE VIRAFERON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For short term travelling, the solution can be kept out of the refrigerator at or below 25°C for a period up to seven days before use. Viraferon can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it should be discarded.

Once opened, the product may be stored for a maximum of 28 days at 2ºC – 8ºC.

Do not use Viraferon after the expiry date which is stated on the package.

Do not use Viraferon if you notice changes in the appearance of Viraferon.

## 6. FURTHER INFORMATION

**What Viraferon contains**

- The active substance is recombinant interferon alfa-2b, 18 million IU in a multiple dose vial
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.
- One ml of solution contains 6 million IU of interferon alfa-2b

**What Viraferon looks like and contents of the pack**

Viraferon is presented as a solution for injection
The clear and colourless solution is contained in a glass vial.

Viraferon is available in four different pack sizes:
- Pack of 1 vial
- Pack of 1 vial, 6 injection syringes, 6 injection needles and 12 cleansing swabs
- Pack of 2 vials
- Pack of 12 vials

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

**Manufacturer:**
SP Labo N.V.
Industriepark 30
B-2220 Heist-op-den-Berg
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For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last approved on**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HOW TO SELF INJECT VIRAFERON

The following instructions explain how to inject Viraferon yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject Viraferon. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation

Collect necessary items before you begin:

- a vial of Viraferon solution for injection;
- a 1 ml syringe;
- a needle for the subcutaneous injection (for example 0.4 × 13 mm [27 gauge 0.5 inch]);
- a cleansing swab.

Wash your hands carefully.

Measuring the dose of Viraferon

Remove the cap from the vial. If this is a multidose vial, you will only have to remove the cap when preparing the first dose. Clean the rubber stopper on the top of the vial containing the Viraferon solution with a cleansing swab.

Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the needle and place it firmly onto the tip of the syringe.

Remove the needle guard without touching the needle, and fill the syringe with air by pulling the plunger to the level that represents your dose as prescribed by your doctor.

Hold the Viraferon vial upright without touching the cleaned top of the vial with your hands.

Insert the needle into the vial containing the Viraferon solution and inject air into the vial.

Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the Viraferon solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.

Remove the needle from the vial and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose.

Volume to be withdrawn according to the dose:

| Volume (ml) | Corresponding dose (million IU) using Viraferon 18 million IU/3 ml solution for injection |
|---|---|
| 0.25 | 1.5 |
| 0.1 | 0.6 |
| 0.5 | 3 |
| 1 | 6 |
| 1.5 | 9 |
| 2 | 12 |
| 2.5 | 15 |
| 3 | 18 |

Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently. Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial and injection materials intended for single use must be discarded. Dispose of the syringe and needle safely in a closed container. For multidose vials, be sure to return the vial to the refrigerator.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Viraferon, 25 million IU/2.5 ml solution for injection**
Interferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:


## 1. WHAT VIRAFERON IS AND WHAT IT IS USED FOR

Viraferon (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases. Viraferon is used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

Viraferon is used in combination with ribavirin in children and adolescents 3 years of age and older who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE VIRAFERON

**Do not use Viraferon**
- if you are allergic (hypersensitive) to interferon or any of the other ingredients of Viraferon.
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medications that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with Viraferon**
- if you are pregnant or planning to become pregnant (see Pregnancy).
- if you have had a severe nervous or mental disorder. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see "Do not use Viraferon")
- if you have ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) while on treatment with Viraferon (see section 4).

- if you have psoriasis, it may get worse during treatment with Viraferon.
- when receiving Viraferon, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication seek medical help immediately.
- if you are also being treated for HIV, please see **Using other medicines.**
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Viraferon with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During the one year of treatment, many children did not grow or gain weight as much as expected. However, during the 6 months after treatment, this trend was generally reversed, although a few children did not return to their previous rate of growth within the first year after completing treatment.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide.

Be sure to tell your doctor if you are taking the Chinese herbal medication Shosaikoto.

**Using other medicines**
Viraferon will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medications.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medication you are taking, or have taken recently, even those not prescribed, as the dose of some medications may have to be adjusted while you are treated with Viraferon.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Viraferon and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Using Viraferon with food and drink**
While being treated with Viraferon, your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed Viraferon in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Viraferon. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

**Driving and using machines**
Do not drive or use machinery if you become drowsy, tired, or confused from this medicine.

## 3. HOW TO USE VIRAFERON

Your doctor has prescribed Viraferon specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of Viraferon according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting Viraferon yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/$m^2$ 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Your doctor may prescribe a different dose of Viraferon alone or in combination with other medicines (e.g. ribavirin). If you are prescribed Viraferon in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of Viraferon is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:

Viraferon is usually intended for subcutaneous use. This means that Viraferon is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see HOW TO SELF INJECT VIRAFERON at the end of the leaflet).

One dose of Viraferon is given on each scheduled day. Viraferon is given three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use Viraferon exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take Viraferon for as long as prescribed.

**If you use more Viraferon than you should**
Contact your doctor or healthcare professional as soon as possible.

**If you forget to take Viraferon**
If you are self-administering treatment, or if you are the caregiver of a child taking Viraferon in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this product every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Viraferon can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Some people get depressed when taking Viraferon alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Paediatric Use: Children are particularly prone to develop depression when being treated with Viraferon and ribavirin. Immediately contact the doctor or seek emergency care if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

If any of the following side effects happen, stop taking Viraferon and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Viraferon. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:
- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of

treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.
These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

At the beginning of treatment with Viraferon, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Other side effects that may occur include:

Very commonly reported side effects (at least 1 in every 10 patients):
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects (at least 1 in every 100 patients, but less than 1 in every 10 patients):
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, fingers and toes very sensitive to cold, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Rarely reported side effects (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):
pneumonia

Very rarely reported side effects (less than 1 in every 10,000 patients):
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord) has been reported with Viraferon use.

Other side effects not listed above may also occur in some patients. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE VIRAFERON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For short term travelling, the solution can be kept out of the refrigerator at or below 25°C for a period up to seven days before use. Viraferon can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it should be discarded.

Once opened, the product may be stored for a maximum of 28 days at 2ºC – 8ºC.

Do not use Viraferon after the expiry date which is stated on the package.

Do not use Viraferon if you notice changes in the appearance of Viraferon.

## 6. FURTHER INFORMATION

**What Viraferon contains**

- The active substance is recombinant interferon alfa-2b, 25 million IU in a multiple dose vial
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.
- One ml of solution contains 10 million IU of interferon alfa-2b

**What Viraferon looks like and contents of the pack**

Viraferon is presented as a solution for injection
The clear and colourless solution is contained in a glass vial.

Viraferon is available in four different pack sizes:
- Pack of 1 vial
- Pack of 1 vial, 6 injection syringes, 6 injection needles and 12 cleansing swabs
- Pack of 2 vials
- Pack of 12 vials

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

**Manufacturer:**
SP Labo N.V.
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last approved on**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HOW TO SELF INJECT VIRAFERON

The following instructions explain how to inject Viraferon yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject Viraferon. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of Viraferon solution for injection;
- a 1 ml syringe;
- a needle for the subcutaneous injection (for example 0.4 × 13 mm [27 gauge 0.5 inch]);
- a cleansing swab.

Wash your hands carefully.

Measuring the dose of Viraferon
Remove the cap from the vial. If this is a multidose vial, you will only have to remove the cap when preparing the first dose. Clean the rubber stopper on the top of the vial containing the Viraferon solution with a cleansing swab.
Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the needle and place it firmly onto the tip of the syringe.
Remove the needle guard without touching the needle, and fill the syringe with air by pulling the plunger to the level that represents your dose as prescribed by your doctor.
Hold the Viraferon vial upright without touching the cleaned top of the vial with your hands.
Insert the needle into the vial containing the Viraferon solution and inject air into the vial.
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the Viraferon solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.
Remove the needle from the vial and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose.

Volume to be withdrawn according to the dose:

| Volume (ml) | Corresponding dose (million IU) using Viraferon 25 million IU/2.5 ml solution for injection |
|---|---|
| 0.25 | 2.5 |
| 0.1 | 1 |
| 0.5 | 5 |
| 1 | 10 |
| 1.5 | 15 |
| 2 | 20 |
| 2.5 | 25 |

Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your

palms. Examine the solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently. Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial and injection materials intended for single use must be discarded. Dispose of the syringe and needle safely in a closed container. For multidose vials, be sure to return the vial to the refrigerator.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Viraferon, 18 million IU solution for injection, multidose pen**
Interferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:


## 1. WHAT VIRAFERON IS AND WHAT IT IS USED FOR

Viraferon (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases. Viraferon is used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

Viraferon is used in combination with ribavirin in children and adolescents 3 years of age and older who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE VIRAFERON

**Do not use Viraferon**
- if you are allergic (hypersensitive) to interferon or any of the other ingredients of Viraferon.
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medications that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with Viraferon**
- if you are pregnant or planning to become pregnant (see Pregnancy).
- if you have had a severe nervous or mental disorder. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see "Do not use Viraferon")
- if you have ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) while on treatment with Viraferon (see section 4).

- if you have psoriasis, it may get worse during treatment with Viraferon.
- when receiving Viraferon, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication seek medical help immediately.
- if you are also being treated for HIV, please see **Using other medicines.**
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Viraferon with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During the one year of treatment, many children did not grow or gain weight as much as expected. However, during the 6 months after treatment, this trend was generally reversed, although a few children did not return to their previous rate of growth within the first year after completing treatment.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide.

Be sure to tell your doctor if you are taking the Chinese herbal medication Shosaikoto.

**Using other medicines**
Viraferon will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medications.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medication you are taking, or have taken recently, even those not prescribed, as the dose of some medications may have to be adjusted while you are treated with Viraferon.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Viraferon and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Using Viraferon with food and drink**
While being treated with Viraferon, your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed Viraferon in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Viraferon. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

**Driving and using machines**
Do not drive or use machinery if you become drowsy, tired, or confused from this medicine.

## 3. HOW TO USE VIRAFERON

Your doctor has prescribed Viraferon specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of Viraferon according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting Viraferon yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/$m^2$ 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Your doctor may prescribe a different dose of Viraferon alone or in combination with other medicines (e.g. ribavirin). If you are prescribed Viraferon in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of Viraferon is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:

Viraferon is usually intended for subcutaneous use. This means that Viraferon is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see HOW TO SELF INJECT VIRAFERON at the end of the leaflet).

One dose of Viraferon is given on each scheduled day. Viraferon is given three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use Viraferon exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take Viraferon for as long as prescribed.

**If you use more Viraferon than you should**
Contact your doctor or healthcare professional as soon as possible.

**If you forget to take Viraferon**
If you are self-administering treatment, or if you are the caregiver of a child taking Viraferon in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this product every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Viraferon can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Some people get depressed when taking Viraferon alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Paediatric Use: Children are particularly prone to develop depression when being treated with Viraferon and ribavirin. Immediately contact the doctor or seek emergency care if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

If any of the following side effects happen, stop taking Viraferon and tell your doctor immediately or go to the casualty department at your nearest hospital:

- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Viraferon. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:

- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of

treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.
These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

At the beginning of treatment with Viraferon, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Other side effects that may occur include:

Very commonly reported side effects (at least 1 in every 10 patients):
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects (at least 1 in every 100 patients, but less than 1 in every 10 patients):
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, fingers and toes very sensitive to cold, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Rarely reported side effects (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):
pneumonia

Very rarely reported side effects (less than 1 in every 10,000 patients):
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord) has been reported with Viraferon use.

Other side effects not listed above may also occur in some patients. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE VIRAFERON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Each pen is intended for a maximum four-week use period and must then be discarded. A maximum of 48 hours (two days) of exposure to 25°C is permitted over the four-week period to cover accidental delays in returning the pen to the refrigerator.

Depending upon your dose, you may have extra needles and swabs left in the pack. Please discard these appropriately and safely.

Do not use Viraferon after the expiry date which is stated on the package.

Do not use Viraferon if you notice changes in the appearance of Viraferon.

## 6. FURTHER INFORMATION

**What Viraferon contains**

- The active substance is recombinant interferon alfa-2b, 18 million IU/pen
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

**What Viraferon looks like and contents of the pack**

Viraferon is presented as a solution for injection
The clear and colourless solution is contained in a glass cartridge.
The pen is designed to deliver its contents of 18 million IU in doses ranging from 1.5 to 6 million IU. The pen will deliver a maximum of 12 doses of 1.5 million IU over a period not to exceed 4 weeks.

Viraferon is available in three different pack sizes:
Viraferon, 18 million IU/pen, solution for injection:
- Pack of 1 pen, 12 injection needles and 12 cleansing swabs
- Pack of 2 pens, 24 injection needles and 24 cleansing swabs
- Pack of 8 pens, 96 injection needles and 96 cleansing swabs

Not all pack sizes may be marketed.

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**Manufacturer:**
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Industriepark 30
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**This leaflet was last approved on**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HOW TO SELF INJECT VIRAFERON

The following instructions explain how to inject Viraferon yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject Viraferon. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation

Collect necessary items before you begin:

- the Viraferon multidose pen;
- a needle for subcutaneous injection (provided in the packaging);
- a cleansing swab.

Wash your hands carefully. Use the injection needles provided in the packaging only for Viraferon. Use a new injection needle for each dose. Be sure the solution is at room temperature at the time of injection.

Diagrams A and B show you all the different parts of the pen and the injection needle. The most important parts to note are as follows:

- The push button scale tells you what dose has been set.
- The colour coding strip brown and the push button are at the bottom of the pen as it is held cap up.
- The pen can only be fully capped when the triangle on the cap scale is aligned with the dosage indicator on the barrel.

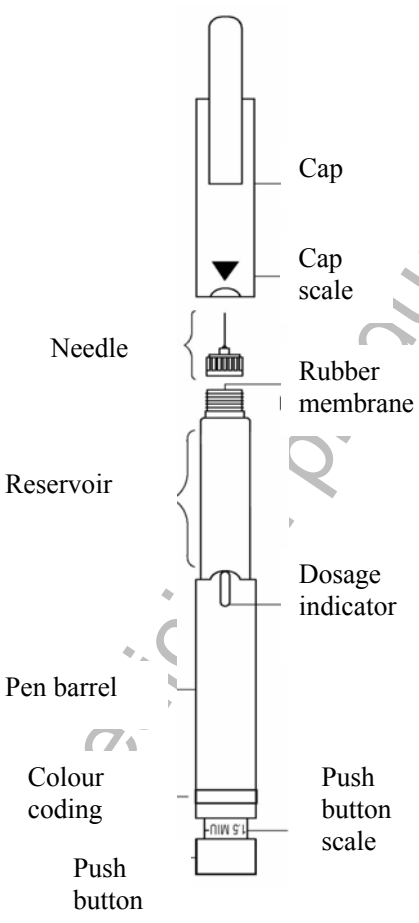


Diagram A

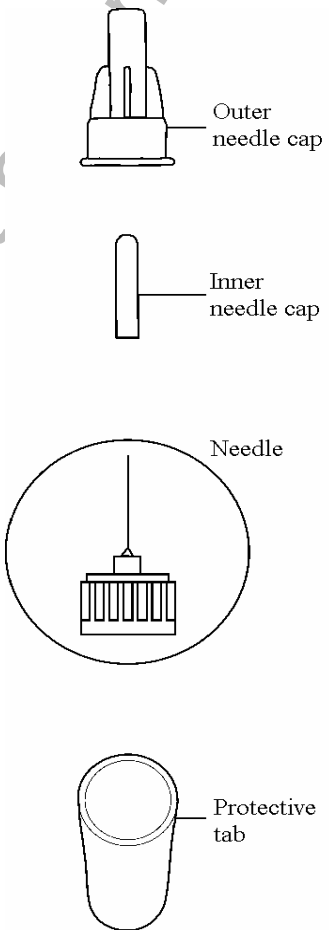


Diagram B

Measuring the dose of Viraferon

Take the pen out of the refrigerator about one-half hour before administering the dose so that the solution in the pen is at room temperature when it is injected.

When you are ready to give your injection prepare your pen as follows:

Check that Viraferon, solution for injection, is clear and colourless in appearance prior to use. If it does not have a clear uniform appearance or if it contains any particles, do not use.

Pull off the cap of the pen and disinfect the rubber membrane (see Diagram C) with one cleansing swab.

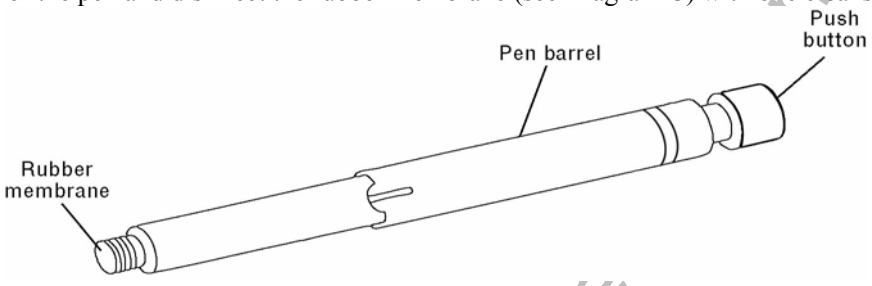


Diagram C

Remove the protective tab from the injection needle. Note that the rear portion of the injection needle is revealed once the protective tab is removed (see Diagram D).

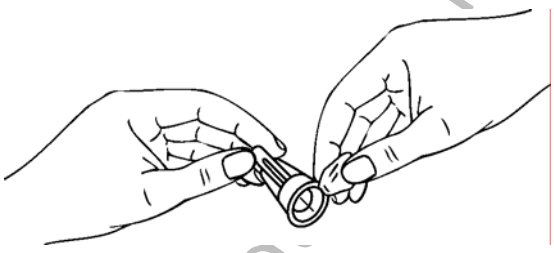

Diagram D

Gently push the injection needle onto the pen as shown in Diagram E. (Notice that the rear portion of the injection needle will pierce through the rubber membrane that you disinfected previously). Now screw the injection needle onto the pen securely by turning it in a clockwise direction (see Diagram F).

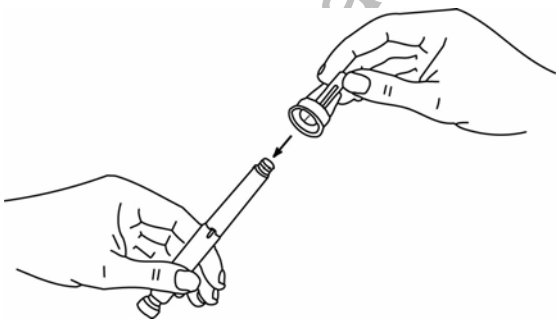

Diagram E

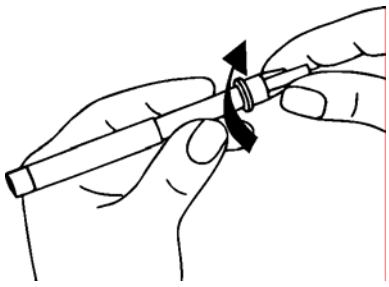

Diagram F

First, pull off the outer injection needle cap (Diagram G). Then, pull off the inner injection needle cap carefully, bearing in mind that the injection needle will now be exposed (Diagram H). Keep the outer injection needle cap for later use.

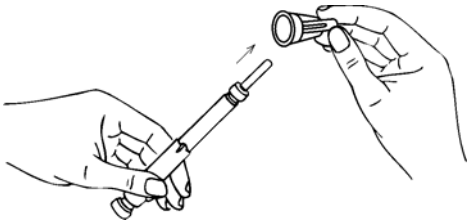

Diagram G

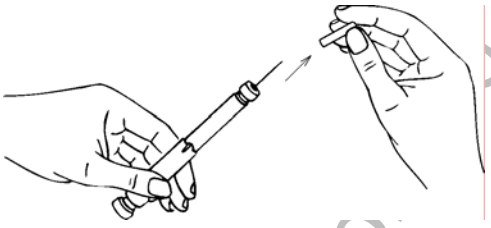

Diagram H

The pen is now ready to use. Since a small amount of air may collect in the injection needle and reservoir during storage, the next step is to remove any air bubbles. This is called performing the Air-Shot.

Hold the Viraferon, solution for injection, multidose pen with the injection needle point upwards.

Tap the reservoir with your finger so that any air bubbles rise to the top of the reservoir, just below the injection needle (Diagram I).

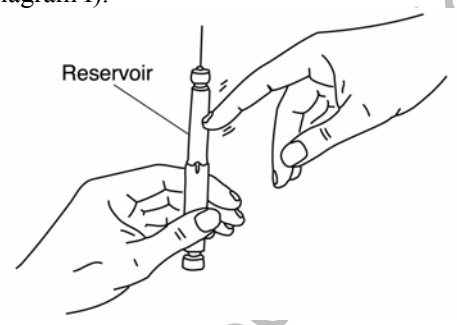


Diagram I

Hold the pen by the barrel and turn the reservoir in the direction as indicated by the arrow in Diagram J (clockwise) until you feel it click.

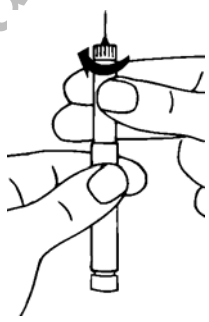

Diagram J

Keeping the pen pointing upwards, press the push button up fully and see if a drop of Viraferon, solution for injection, appears at the injection needle tip (Notice the drop at the tip of injection needle in Diagram K below).

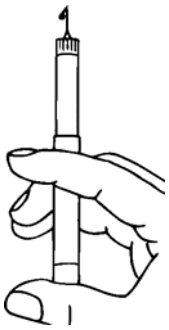

Diagram K

If no drop appears, use a different pen, and return the faulty pen to your provider.

Note: some air may remain in the pen, but this is not important as you have removed the air from the injection needle and the dose will be accurate.

Replace the Viraferon, solution for injection, multidose pen cap with the 'triangle' opposite the dosage indicator as seen in Diagram L.

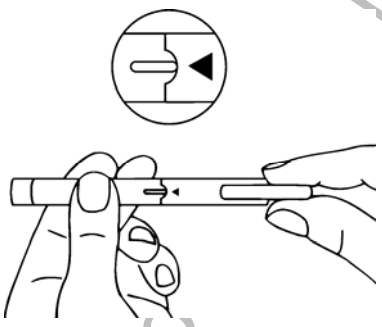

Diagram L

The pen is now ready to set the dose. For the next step hold the pen in the middle of the barrel. This will allow the push button to move freely, ensuring that the correct dose is set.

To set the required dose, hold the pen horizontally by the barrel with one hand. With the other hand, turn the cap in a clockwise direction indicated by the arrow in Diagram M. You will observe the push button rising, indicating the dose set. To set the correct dose, turn the cap as many times as indicated as follows:

| Number of "turns" and "clicks" | Corresponding doses (million IU) using Viraferon, solution for injection, multidose pen 18 million IU/pen |
|---|---|
| 1 full turn (5 clicks) | 1.5 |
| 6 clicks | 1.8 |
| 7 clicks | 2.1 |
| 8 clicks | 2.4 |
| 9 clicks | 2.7 |
| 2 full turns (10 clicks) | 3 |
| 11 clicks | 3.3 |
| 12 clicks | 3.6 |
| 13 clicks | 3.9 |
| 14 clicks | 4.2 |
| 3 full turns (15 clicks) | 4.5 |
| 16 clicks | 4.8 |
| 17 clicks | 5.1 |
| 18 clicks | 5.4 |
| 19 clicks | 5.7 |
| 4 full turns (20 clicks)* | 6 |

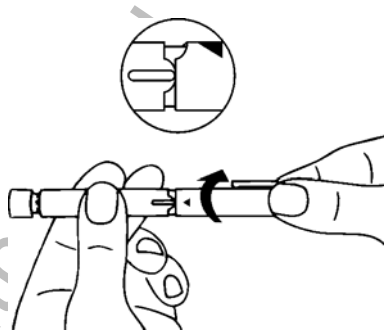

Diagram M

*4 full turns correspond to the maximum dose to be administered in one injection. The pen is designed to deliver its contents of 18 million IU in doses ranging from 1.5 to 6 million IU. The pen will deliver a maximum of 12 doses of 1.5 million IU over a period not to exceed 4 weeks.

The push button scale will show you the dose set (see Diagram N below). For doses corresponding to full turns, the scale should line up with the correct dose marking. For doses corresponding to clicks intermediate between full turns, the scale should line up between the two appropriate full-turn dose markings. At that point check that you have the correct dose.

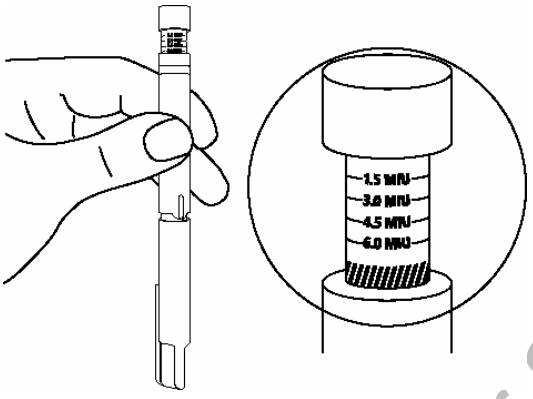


Diagram N

After each complete turn make sure that the triangle is opposite the dosage indicator (see Diagram O). If you have set a wrong dose, simply turn the cap back (anti-clockwise) as far as you can until the push button is fully home and start again. Once the correct dose is set you are ready to give the injection.

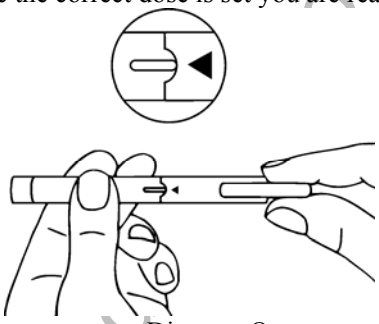

Diagram O

Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection. Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry.
With one hand, pinch a fold of loose skin. With your other hand, pick up the pen and hold it as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°.

Then press the push button down fully (see Diagram P).

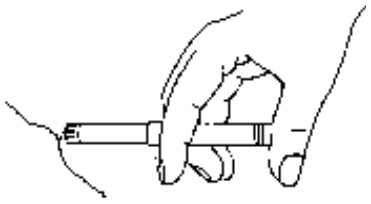

Diagram P

Keeping the push button down, leave the injection needle in place for a few seconds to allow the Viraferon, solution for injection, to distribute under the skin, then remove.

Carefully replace the outer injection needle cap (See Diagram Q).

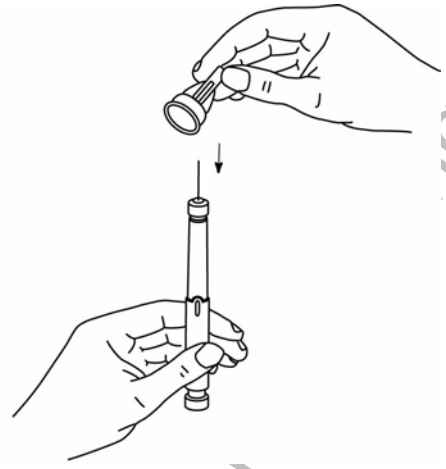

Diagram Q

Completely unscrew the injection needle assembly using an anti-clockwise turning motion as shown in Diagram R. Then carefully lift it off the pen and discard the capped injection needle (see Diagram S).

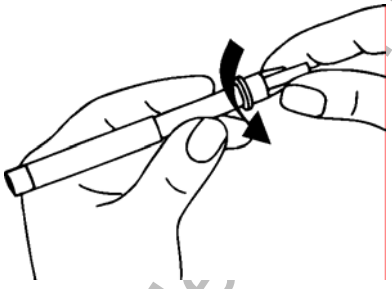

Diagram R

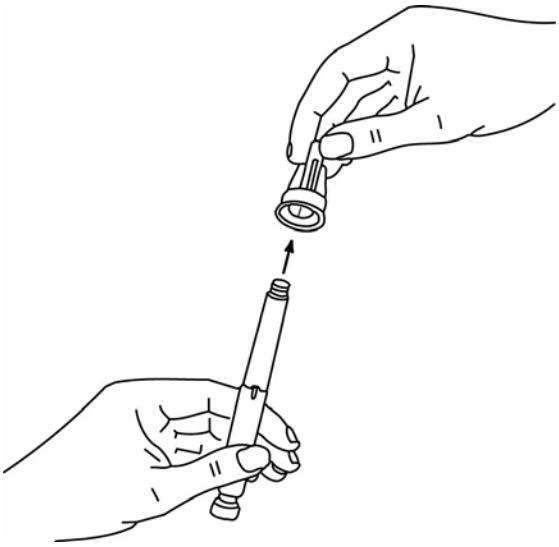

Diagram S

Replace the pen cap with the triangle once again opposite the dosage indicator as shown in Diagram T. Then return the pen to the refrigerator.

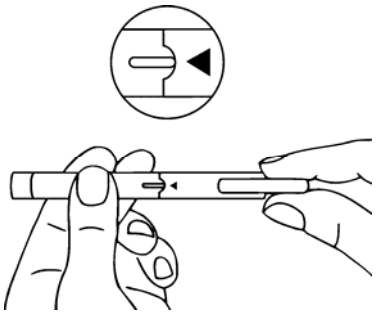

Diagram T

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Viraferon, 30 million IU solution for injection, multidose pen**
Interferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:


## 1. WHAT VIRAFERON IS AND WHAT IT IS USED FOR

Viraferon (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases. Viraferon is used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

Viraferon is used in combination with ribavirin in children and adolescents 3 years of age and older who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE VIRAFERON

**Do not use Viraferon**
- if you are allergic (hypersensitive) to interferon or any of the other ingredients of Viraferon.
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medications that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with Viraferon**
- if you are pregnant or planning to become pregnant (see Pregnancy).
- if you have had a severe nervous or mental disorder. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see "Do not use Viraferon")
- if you have ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) while on treatment with Viraferon (see section 4).

- if you have psoriasis, it may get worse during treatment with Viraferon.
- when receiving Viraferon, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication seek medical help immediately.
- if you are also being treated for HIV, please see **Using other medicines.**
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Viraferon with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During the one year of treatment, many children did not grow or gain weight as much as expected. However, during the 6 months after treatment, this trend was generally reversed, although a few children did not return to their previous rate of growth within the first year after completing treatment.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide.

Be sure to tell your doctor if you are taking the Chinese herbal medication Shosaikoto.

**Using other medicines**
Viraferon will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medications.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medication you are taking, or have taken recently, even those not prescribed, as the dose of some medications may have to be adjusted while you are treated with Viraferon.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Viraferon and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Using Viraferon with food and drink**
While being treated with Viraferon, your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed Viraferon in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Viraferon. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

**Driving and using machines**
Do not drive or use machinery if you become drowsy, tired, or confused from this medicine.

## 3. HOW TO USE VIRAFERON

Your doctor has prescribed Viraferon specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of Viraferon according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting Viraferon yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/$m^2$ 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Your doctor may prescribe a different dose of Viraferon alone or in combination with other medicines (e.g. ribavirin). If you are prescribed Viraferon in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of Viraferon is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:

Viraferon is usually intended for subcutaneous use. This means that Viraferon is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see HOW TO SELF INJECT VIRAFERON at the end of the leaflet).

One dose of Viraferon is given on each scheduled day. Viraferon is given three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use Viraferon exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take Viraferon for as long as prescribed.

**If you use more Viraferon than you should**
Contact your doctor or healthcare professional as soon as possible.

**If you forget to take Viraferon**
If you are self-administering treatment, or if you are the caregiver of a child taking Viraferon in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this product every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Viraferon can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Some people get depressed when taking Viraferon alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Paediatric Use: Children are particularly prone to develop depression when being treated with Viraferon and ribavirin. Immediately contact the doctor or seek emergency care if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

If any of the following side effects happen, stop taking Viraferon and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Viraferon. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:
- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of

treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.
These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

At the beginning of treatment with Viraferon, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Other side effects that may occur include:

Very commonly reported side effects (at least 1 in every 10 patients):
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects (at least 1 in every 100 patients, but less than 1 in every 10 patients):
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, fingers and toes very sensitive to cold, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Rarely reported side effects (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):
pneumonia

Very rarely reported side effects (less than 1 in every 10,000 patients):
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord) has been reported with Viraferon use.

Other side effects not listed above may also occur in some patients. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE VIRAFERON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Each pen is intended for a maximum four-week use period and must then be discarded. A maximum of 48 hours (two days) of exposure to 25°C is permitted over the four-week period to cover accidental delays in returning the pen to the refrigerator.

Depending upon your dose, you may have extra needles and swabs left in the pack. Please discard these appropriately and safely.

Do not use Viraferon after the expiry date which is stated on the package.

Do not use Viraferon if you notice changes in the appearance of Viraferon.

## 6. FURTHER INFORMATION

**What Viraferon contains**

- The active substance is recombinant interferon alfa-2b, 30 million IU/pen
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

**What Viraferon looks like and contents of the pack**

Viraferon is presented as a solution for injection
The clear and colourless solution is contained in a glass cartridge.
The pen is designed to deliver its contents of 30 million IU in doses ranging from 2.5 to 10 million IU. The pen will deliver a maximum of 12 doses of 2.5 million IU over a period not to exceed 4 weeks.

Viraferon is available in three different pack sizes:
Viraferon, 30 million IU/pen, solution for injection:
- Pack of 1 pen, 12 injection needles and 12 cleansing swabs
- Pack of 2 pens, 24 injection needles and 24 cleansing swabs
- Pack of 8 pens, 96 injection needles and 96 cleansing swabs

Not all pack sizes may be marketed.

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**Manufacturer:**
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Industriepark 30
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**This leaflet was last approved on**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HOW TO SELF INJECT VIRAFERON

The following instructions explain how to inject Viraferon yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject Viraferon. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation

Collect necessary items before you begin:

- the Viraferon multidose pen;
- a needle for subcutaneous injection (provided in the packaging);
- a cleansing swab.

Wash your hands carefully. Use the injection needles provided in the packaging only for Viraferon. Use a new injection needle for each dose. Be sure the solution is at room temperature at the time of injection.

Diagrams A and B show you all the different parts of the pen and the injection needle. The most important parts to note are as follows:

- The push button scale tells you what dose has been set.
- The colour coding strip blue and the push button are at the bottom of the pen as it is held cap up.
- The pen can only be fully capped when the triangle on the cap scale is aligned with the dosage indicator on the barrel.

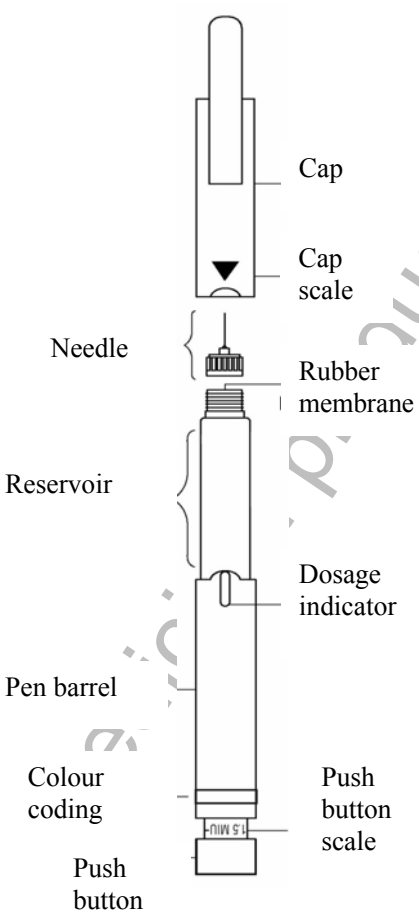


Diagram A

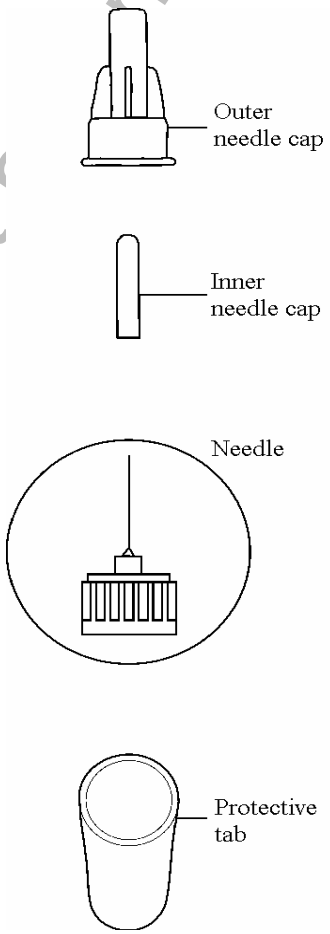


Diagram B

Measuring the dose of Viraferon

Take the pen out of the refrigerator about one-half hour before administering the dose so that the solution in the pen is at room temperature when it is injected.

When you are ready to give your injection prepare your pen as follows:

Check that Viraferon, solution for injection, is clear and colourless in appearance prior to use. If it does not have a clear uniform appearance or if it contains any particles, do not use.

Pull off the cap of the pen and disinfect the rubber membrane (see Diagram C) with one cleansing swab.

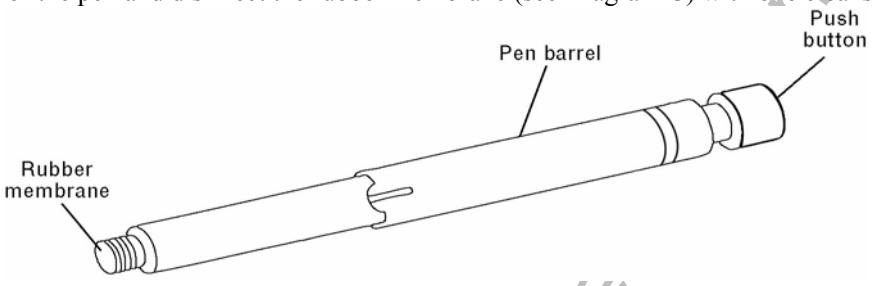


Diagram C

Remove the protective tab from the injection needle. Note that the rear portion of the injection needle is revealed once the protective tab is removed (see Diagram D).

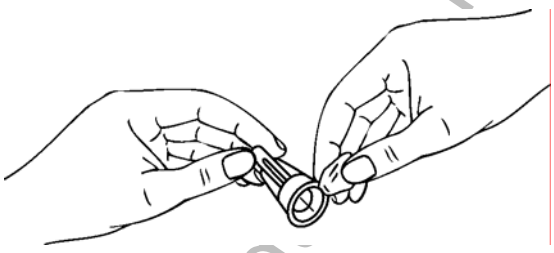

Diagram D

Gently push the injection needle onto the pen as shown in Diagram E. (Notice that the rear portion of the injection needle will pierce through the rubber membrane that you disinfected previously). Now screw the injection needle onto the pen securely by turning it in a clockwise direction (see Diagram F).

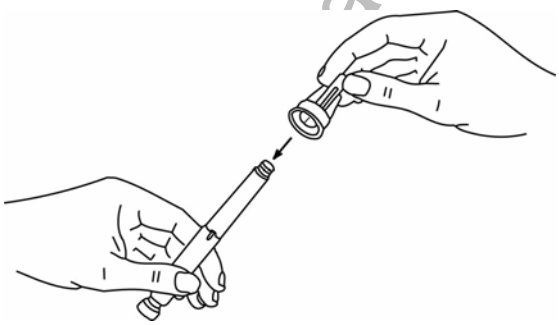

Diagram E

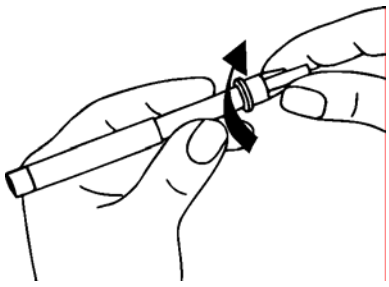

Diagram F

First, pull off the outer injection needle cap (Diagram G). Then, pull off the inner injection needle cap carefully, bearing in mind that the injection needle will now be exposed (Diagram H). Keep the outer injection needle cap for later use.

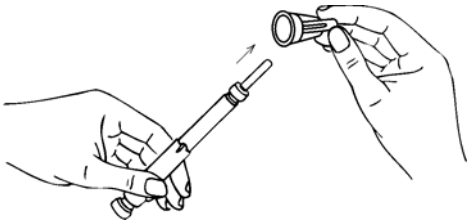

Diagram G

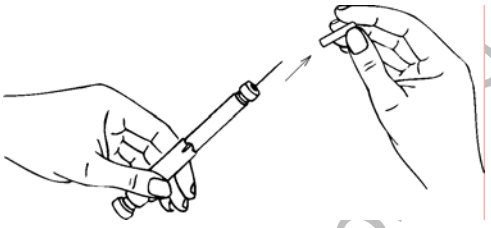

Diagram H

The pen is now ready to use. Since a small amount of air may collect in the injection needle and reservoir during storage, the next step is to remove any air bubbles. This is called performing the Air-Shot.

Hold the Viraferon, solution for injection, multidose pen with the injection needle point upwards.

Tap the reservoir with your finger so that any air bubbles rise to the top of the reservoir, just below the injection needle (Diagram I).

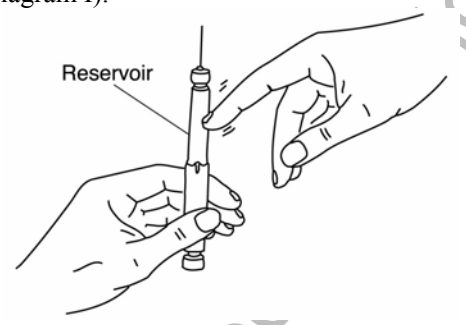


Diagram I

Hold the pen by the barrel and turn the reservoir in the direction as indicated by the arrow in Diagram J (clockwise) until you feel it click.

Diagram J

Keeping the pen pointing upwards, press the push button up fully and see if a drop of Viraferon, solution for injection, appears at the injection needle tip (Notice the drop at the tip of injection needle in Diagram K below).

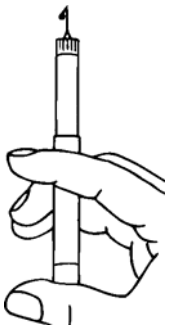

Diagram K

If no drop appears, use a different pen, and return the faulty pen to your provider.

Note: some air may remain in the pen, but this is not important as you have removed the air from the injection needle and the dose will be accurate.

Replace the Viraferon, solution for injection, multidose pen cap with the 'triangle' opposite the dosage indicator as seen in Diagram L.

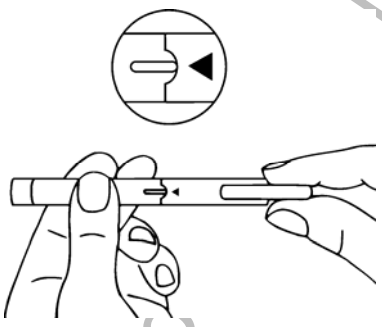

Diagram L

The pen is now ready to set the dose. For the next step hold the pen in the middle of the barrel. This will allow the push button to move freely, ensuring that the correct dose is set.

To set the required dose, hold the pen horizontally by the barrel with one hand. With the other hand, turn the cap in a clockwise direction indicated by the arrow in Diagram M. You will observe the push button rising, indicating the dose set. To set the correct dose, turn the cap as many times as indicated as follows:

| Number of "turns" and "clicks" | Corresponding doses (million IU) using Viraferon, solution for injection, multidose pen 30 million IU/pen: |
|---|---|
| 1 full turn (5 clicks) | 2.5 |
| 6 clicks | 3 |
| 7 clicks | 3.5 |
| 8 clicks | 4 |
| 9 clicks | 4.5 |
| 2 full turns (10 clicks) | 5 |
| 11 clicks | 5.5 |
| 12 clicks | 6 |
| 13 clicks | 6.5 |
| 14 clicks | 7 |
| 3 full turns (15 clicks) | 7.5 |
| 16 clicks | 8 |
| 17 clicks | 8.5 |
| 18 clicks | 9 |
| 19 clicks | 9.5 |
| 4 full turns (20 clicks)* | 10 |

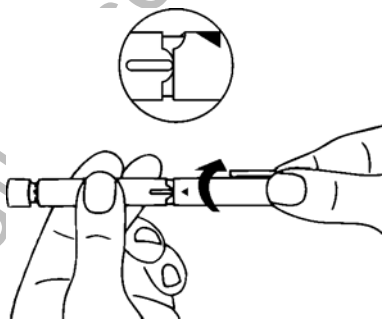

Diagram M

* 4 full turns correspond to the maximum dose to be administered in one injection. The pen is designed to deliver its contents of 30 million IU in doses ranging from 2.5 to 10 million IU. The pen will deliver a maximum of 12 doses of 2.5 million IUover a period not to exceed 4 weeks.

The push button scale will show you the dose set (see Diagram N below). For doses corresponding to full turns, the scale should line up with the correct dose marking. For doses corresponding to clicks intermediate between full turns, the scale should line up between the two appropriate full-turn dose markings. At that point check that you have the correct dose.

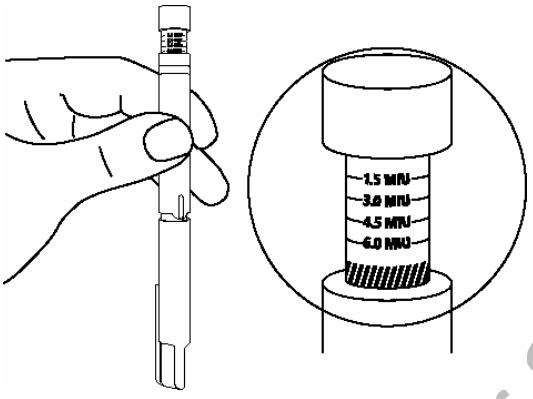


Diagram N

After each complete turn make sure that the triangle is opposite the dosage indicator (see Diagram O). If you have set a wrong dose, simply turn the cap back (anti-clockwise) as far as you can until the push button is fully home and start again. Once the correct dose is set you are ready to give the injection.

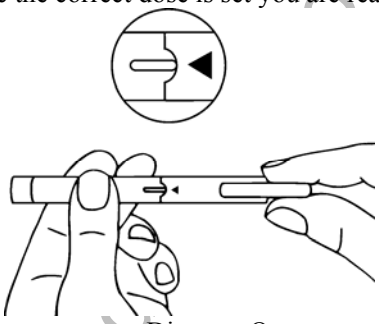

Diagram O

Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection. Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry.
With one hand, pinch a fold of loose skin. With your other hand, pick up the pen and hold it as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°.

Then press the push button down fully (see Diagram P).

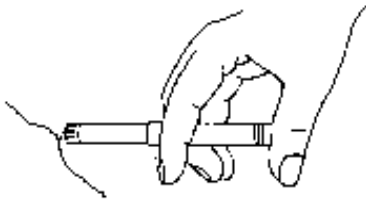

Diagram P

Keeping the push button down, leave the injection needle in place for a few seconds to allow the Viraferon, solution for injection, to distribute under the skin, then remove.

Carefully replace the outer injection needle cap (See Diagram Q).

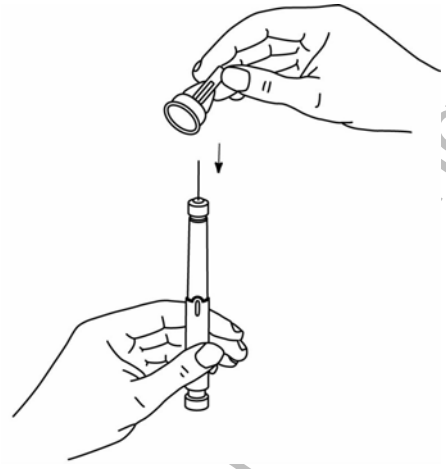

Diagram Q

Completely unscrew the injection needle assembly using an anti-clockwise turning motion as shown in Diagram R. Then carefully lift it off the pen and discard the capped injection needle (see Diagram S).

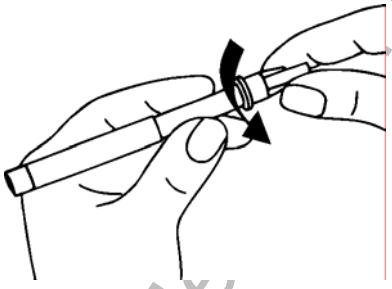

Diagram R

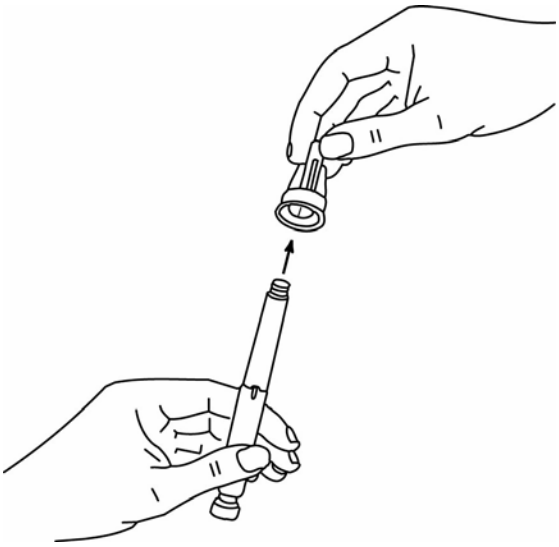

Diagram S

Replace the pen cap with the triangle once again opposite the dosage indicator as shown in Diagram T. Then return the pen to the refrigerator.

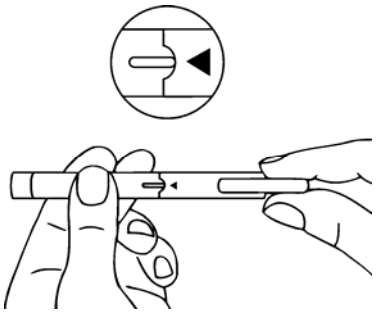

Diagram T

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Viraferon, 60 million IU solution for injection, multidose pen**
Interferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:


## 1. WHAT VIRAFERON IS AND WHAT IT IS USED FOR

Viraferon (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases. Viraferon is used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

Viraferon is used in combination with ribavirin in children and adolescents 3 years of age and older who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE VIRAFERON

**Do not use Viraferon**
- if you are allergic (hypersensitive) to interferon or any of the other ingredients of Viraferon.
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medications that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with Viraferon**
- if you are pregnant or planning to become pregnant (see Pregnancy).
- if you have had a severe nervous or mental disorder. The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see "Do not use Viraferon")
- if you have ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) while on treatment with Viraferon (see section 4).

- if you have psoriasis, it may get worse during treatment with Viraferon.
- when receiving Viraferon, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication seek medical help immediately.
- if you are also being treated for HIV, please see **Using other medicines.**
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Viraferon and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Viraferon with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During the one year of treatment, many children did not grow or gain weight as much as expected. However, during the 6 months after treatment, this trend was generally reversed, although a few children did not return to their previous rate of growth within the first year after completing treatment.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide.

Be sure to tell your doctor if you are taking the Chinese herbal medication Shosaikoto.

**Using other medicines**
Viraferon will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medications.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medication you are taking, or have taken recently, even those not prescribed, as the dose of some medications may have to be adjusted while you are treated with Viraferon.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Viraferon and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with Viraferon and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Using Viraferon with food and drink**
While being treated with Viraferon, your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed Viraferon in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Viraferon. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

**Driving and using machines**
Do not drive or use machinery if you become drowsy, tired, or confused from this medicine.

## 3. HOW TO USE VIRAFERON

Your doctor has prescribed Viraferon specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of Viraferon according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting Viraferon yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/$m^2$ 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Your doctor may prescribe a different dose of Viraferon alone or in combination with other medicines (e.g. ribavirin). If you are prescribed Viraferon in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of Viraferon is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:

Viraferon is usually intended for subcutaneous use. This means that Viraferon is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see HOW TO SELF INJECT VIRAFERON at the end of the leaflet).

One dose of Viraferon is given on each scheduled day. Viraferon is given three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use Viraferon exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take Viraferon for as long as prescribed.

**If you use more Viraferon than you should**
Contact your doctor or healthcare professional as soon as possible.

**If you forget to take Viraferon**
If you are self-administering treatment, or if you are the caregiver of a child taking Viraferon in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this product every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Viraferon can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Some people get depressed when taking Viraferon alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Paediatric Use: Children are particularly prone to develop depression when being treated with Viraferon and ribavirin. Immediately contact the doctor or seek emergency care if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

If any of the following side effects happen, stop taking Viraferon and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Viraferon. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:
- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of

treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.
These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

At the beginning of treatment with Viraferon, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Other side effects that may occur include:

Very commonly reported side effects (at least 1 in every 10 patients):
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects (at least 1 in every 100 patients, but less than 1 in every 10 patients):
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, fingers and toes very sensitive to cold, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Rarely reported side effects (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):
pneumonia

Very rarely reported side effects (less than 1 in every 10,000 patients):
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord) has been reported with Viraferon use.

Other side effects not listed above may also occur in some patients. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE VIRAFERON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Each pen is intended for a maximum four-week use period and must then be discarded. A maximum of 48 hours (two days) of exposure to 25°C is permitted over the four-week period to cover accidental delays in returning the pen to the refrigerator.

Depending upon your dose, you may have extra needles and swabs left in the pack. Please discard these appropriately and safely.

Do not use Viraferon after the expiry date which is stated on the package.

Do not use Viraferon if you notice changes in the appearance of Viraferon.

## 6. FURTHER INFORMATION

**What Viraferon contains**

- The active substance is recombinant interferon alfa-2b, 60 million IU/pen
- The other ingredients are disodium phosphate anhydrous, Sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

**What Viraferon looks like and contents of the pack**

Viraferon is presented as a solution for injection
The clear and colourless solution is contained in a glass cartridge.
The pen is designed to deliver its contents of 60 million IU in doses ranging from 5 to 20 million IU. The pen will deliver a maximum of 12 doses of 5 million IU over a period not to exceed 4 weeks.

Viraferon is available in three different pack sizes:
Viraferon, 60 million IU/pen, solution for injection:
- Pack of 1 pen, 12 injection needles and 12 cleansing swabs
- Pack of 2 pens, 24 injection needles and 24 cleansing swabs
- Pack of 8 pens, 96 injection needles and 96 cleansing swabs

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
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**Manufacturer:**
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Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HOW TO SELF INJECT VIRAFERON

The following instructions explain how to inject Viraferon yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject Viraferon. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation

Collect necessary items before you begin:

- the Viraferon multidose pen;
- a needle for subcutaneous injection (provided in the packaging);
- a cleansing swab.

Wash your hands carefully. Use the injection needles provided in the packaging only for Viraferon. Use a new injection needle for each dose. Be sure the solution is at room temperature at the time of injection.

Diagrams A and B show you all the different parts of the pen and the injection needle. The most important parts to note are as follows:

- The push button scale tells you what dose has been set.
- The colour coding strip pink and the push button are at the bottom of the pen as it is held cap up.
- The pen can only be fully capped when the triangle on the cap scale is aligned with the dosage indicator on the barrel.

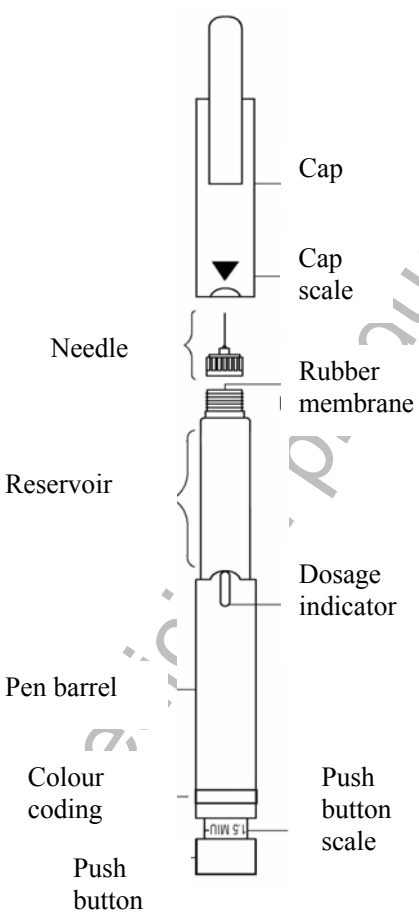


Diagram A

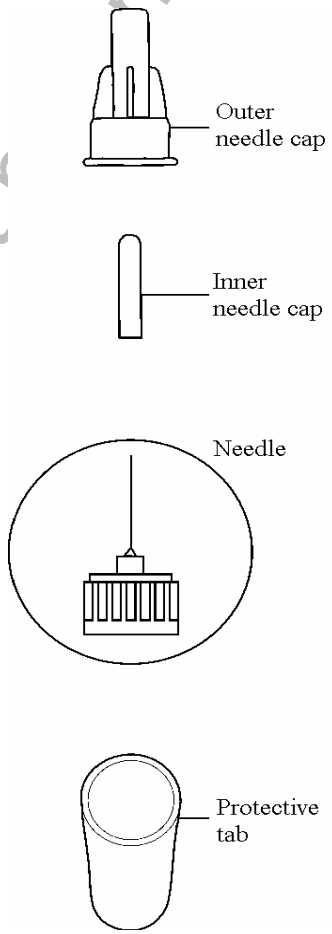


Diagram B

Measuring the dose of Viraferon

Take the pen out of the refrigerator about one-half hour before administering the dose so that the solution in the pen is at room temperature when it is injected.

When you are ready to give your injection prepare your pen as follows:

Check that Viraferon, solution for injection, is clear and colourless in appearance prior to use. If it does not have a clear uniform appearance or if it contains any particles, do not use.

Pull off the cap of the pen and disinfect the rubber membrane (see Diagram C) with one cleansing swab.

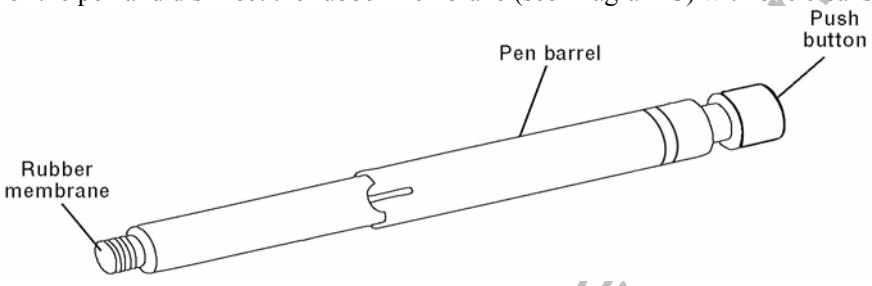


Diagram C

Remove the protective tab from the injection needle. Note that the rear portion of the injection needle is revealed once the protective tab is removed (see Diagram D).

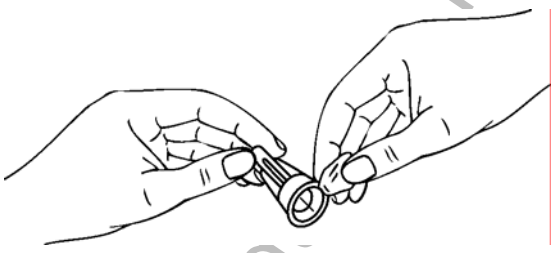

Diagram D

Gently push the injection needle onto the pen as shown in Diagram E. (Notice that the rear portion of the injection needle will pierce through the rubber membrane that you disinfected previously). Now screw the injection needle onto the pen securely by turning it in a clockwise direction (see Diagram F).

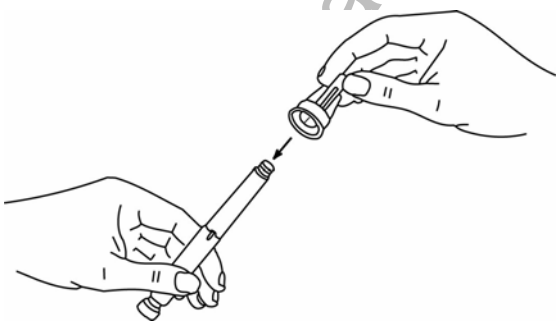

Diagram E

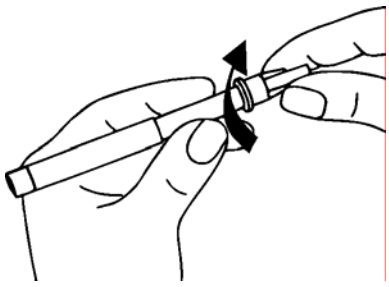

Diagram F

First, pull off the outer injection needle cap (Diagram G). Then, pull off the inner injection needle cap carefully, bearing in mind that the injection needle will now be exposed (Diagram H). Keep the outer injection needle cap for later use.

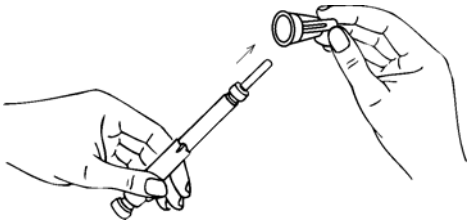

Diagram G

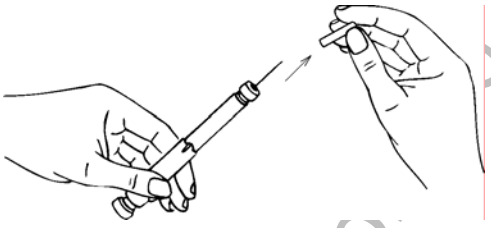

Diagram H

The pen is now ready to use. Since a small amount of air may collect in the injection needle and reservoir during storage, the next step is to remove any air bubbles. This is called performing the Air-Shot.

Hold the Viraferon, solution for injection, multidose pen with the injection needle point upwards.

Tap the reservoir with your finger so that any air bubbles rise to the top of the reservoir, just below the injection needle (Diagram I).

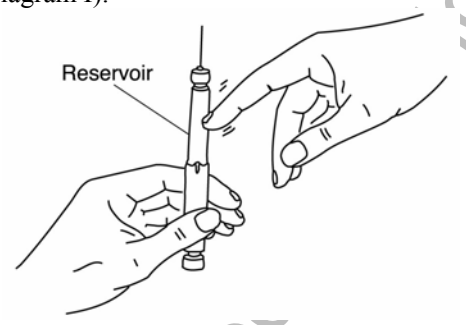


Diagram I

Hold the pen by the barrel and turn the reservoir in the direction as indicated by the arrow in Diagram J (clockwise) until you feel it click.

Diagram J

Keeping the pen pointing upwards, press the push button up fully and see if a drop of Viraferon, solution for injection, appears at the injection needle tip (Notice the drop at the tip of injection needle in Diagram K below).

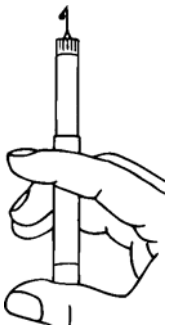

Diagram K

If no drop appears, use a different pen, and return the faulty pen to your provider.

Note: some air may remain in the pen, but this is not important as you have removed the air from the injection needle and the dose will be accurate.

Replace the Viraferon, solution for injection, multidose pen cap with the 'triangle' opposite the dosage indicator as seen in Diagram L.

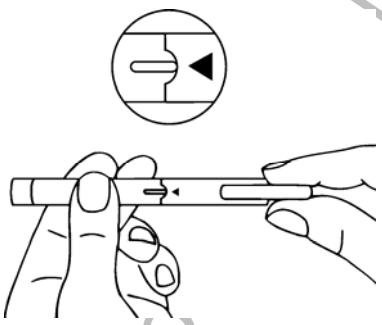

Diagram L

The pen is now ready to set the dose. For the next step hold the pen in the middle of the barrel. This will allow the push button to move freely, ensuring that the correct dose is set.

To set the required dose, hold the pen horizontally by the barrel with one hand. With the other hand, turn the cap in a clockwise direction indicated by the arrow in Diagram M. You will observe the push button rising, indicating the dose set. To set the correct dose, turn the cap as many times as indicated as follows:

| Number of "turns" and "clicks" | Corresponding doses (million IU) using Viraferon, solution for injection, multidose pen 60 million IU/pen: |
|---|---|
| 1 full turn (5 clicks) | 5 |
| 6 clicks | 6 |
| 7 clicks | 7 |
| 8 clicks | 8 |
| 9 clicks | 9 |
| 2 full turns (10 clicks) | 10 |
| 11 clicks | 11 |
| 12 clicks | 12 |
| 13 clicks | 13 |
| 14 clicks | 14 |
| 3 full turns (15 clicks) | 15 |
| 16 clicks | 16 |
| 17 clicks | 17 |
| 18 clicks | 18 |
| 19 clicks | 19 |
| 4 full turns (20 clicks)* | 20 |

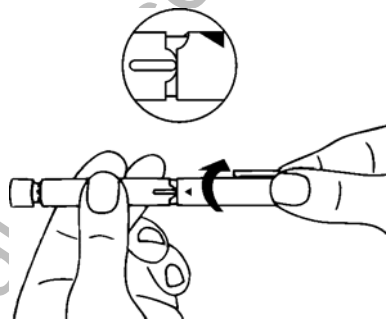

Diagram M

*4 full turns correspond to the maximum dose to be administered in one injection. The pen is designed to deliver its contents of 60 million IU in doses ranging from 5 to 20 million IU. The pen will deliver a maximum of 12 doses of 5 million IU over a period not to exceed 4 weeks.

The push button scale will show you the dose set (see Diagram N below). For doses corresponding to full turns, the scale should line up with the correct dose marking. For doses corresponding to clicks intermediate between full turns, the scale should line up between the two appropriate full-turn dose markings. At that point check that you have the correct dose.

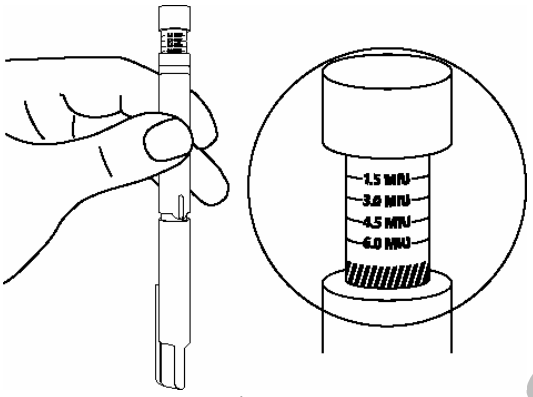


Diagram N

After each complete turn make sure that the triangle is opposite the dosage indicator (see Diagram O). If you have set a wrong dose, simply turn the cap back (anti-clockwise) as far as you can until the push button is fully home and start again. Once the correct dose is set you are ready to give the injection.

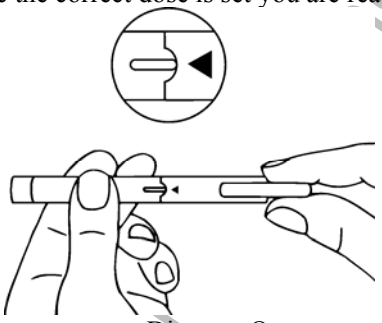

Diagram O

Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection. Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry.
With one hand, pinch a fold of loose skin. With your other hand, pick up the pen and hold it as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°.

Then press the push button down fully (see Diagram P).

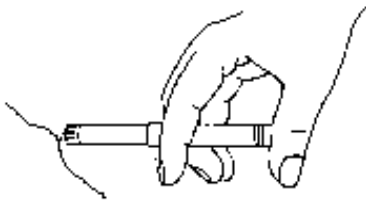

Diagram P

Keeping the push button down, leave the injection needle in place for a few seconds to allow the Viraferon, solution for injection, to distribute under the skin, then remove.

Carefully replace the outer injection needle cap (See Diagram Q).

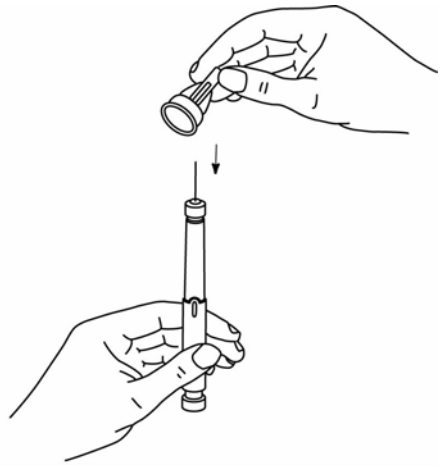

Diagram Q

Completely unscrew the injection needle assembly using an anti-clockwise turning motion as shown in Diagram R. Then carefully lift it off the pen and discard the capped injection needle (see Diagram S).

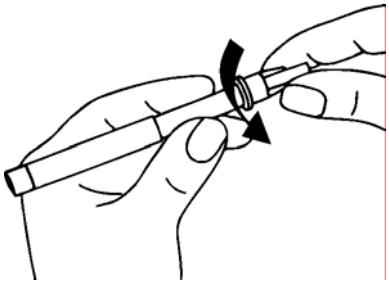

Diagram R

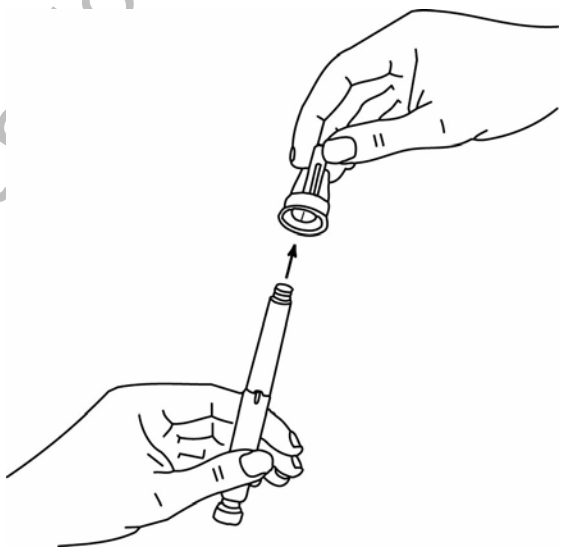

Diagram S

Replace the pen cap with the triangle once again opposite the dosage indicator as shown in Diagram T. Then return the pen to the refrigerator.

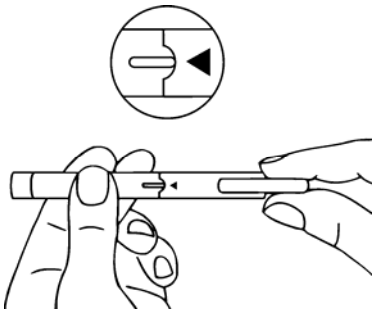

Diagram T