

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of Viraferon. This scientific discussion has been updated until 1 August 2003. For information on changes after this date please refer to module 8B.**

### 1. Introduction

This was a full application to obtain a single European Marketing Authorisation via the centralised procedure for interferon alfa-2b. National Marketing Authorisations exist in all Member States for the use of interferon alfa-2b. Viraferon from SP Europe is indicated in the treatment of Chronic Hepatitis B, Chronic Hepatitis C.

The harmonization of the SPC for the listed indications was achieved in June 1997 through a referral under Article 11 of Council directive 75/319/EEC as amended.

The new data filed with the centralised application concerned an extension of Chronic Hepatitis B approval in adults to children (1 to 17 years of age) and the combination of interferon alfa-2b with ribavirin as first line treatment for patients with Chronic Hepatitis C.

The CPMP focused the evaluation on the new information provided in support of the centralised application.

### 2. Chemical, pharmaceutical and biological aspects

The qualitative and quantitative composition of the centrally authorised medicinal product Viraferon and of the nationally licensed Viraferon, are strictly identical. The manufacturers and the manufacturing process are those already approved for the manufacture of the nationally authorised Viraferon.

This centralised application relates to three formulations: a lyophilised powder (containing human serum albumin as stabiliser) and two solutions for injection (vials and pens) which are Human Serum Albumin (HSA) free.

The main goal of the development of the HSA-free formulation was to identify a stable interferon alfa-2b solution free of human serum albumin and remains essentially free from visible particles. An additional goal was to have a product meeting both European Pharmacopeia and USP antimicrobial preservative effectiveness criteria so that it would be suitable for worldwide marketing.

The application consisted of the full information contained in the original approved applications as well as the information submitted in the subsequent variations evaluated in the Mutual Recognition procedure. The assessment report focused in particular on the few additional changes that have been introduced in the centralised marketing authorisation application.

#### Composition and product development

The optimum pH for the formulation was determined based on a pH/stability profile of interferon alfa-2b.

Excipient screening studies were conducted to determine the compatibility of interferon alfa-2b with a variety of tonicity adjusting agents, antimicrobial preservatives, and protein stabilizers.

During the course of the formulation development program, the European Pharmacopeia adopted new criteria for antimicrobial preservative effectiveness. The solution was reformulated by changing its antimicrobial preservative system in order to meet both USP and Ph. Eur. acceptance criteria.

An ongoing stability study was performed with the m-cresol formulation filled into Type I flint glass carpoules. The package showed good compatibility with interferon alfa-2b in the formulation.

Appropriate formulation validation studies were conducted. The pH validation studies demonstrated that the product is stable in the proposed pH range.

The formulation in a vial was found not to be adversely affected by light, and it was shown to be able to withstand exposure to temperatures up to 35° for as long as seven days.

### **Active substance**

Recombinant interferon alfa-2b is a sterile, stable formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. 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 interferon is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to  $2.6 \times 10^8$  International Units (IU).

### **Other ingredients**

HSA is utilised only in the lyophilised powder formulation. It complies with the current guidelines.

### **Finished product**

The specifications and routine tests have been upgraded as compared to those previously submitted by the Company for interferon alfa-2b lyophilized powder for injection and the interferon alfa-2b injectable solution. The absence of Human Serum Albumin (HSA) in some formulations has allowed new purity test methods to be introduced.

In addition, identification and assay of the m-cresol preservative is described and the proposed efficacy of antimicrobial preservation complies with the Ph. Eur. requirements.

The other routine tests (determination of the colour and clarity of the solution, pH, bacterial endotoxins (LAL) and sterility) are performed in compliance with the Ph. Eur., and the proposed limits are acceptable for this type of product.

### **Stability**

Stability studies were conducted on different batches of interferon alfa-2b drug substance manufactured.

The available stability data justify 24 months storage at -80°C.

The following shelf lives have been accepted for the finished products:

- Viraferon powder and solvent for solution for injection: 3 years at 2-8°C;
- Viraferon solution for injection, single dose vials: 18 months at 2-8°C;
- Viraferon solution for injection multiple dose vials: 2 years at 2-8°C;
- Viraferon solution for injection multidose pen: 15 months at 2-8°C.

### 3. Toxicopharmacological aspects

Recombinant human interferon alfa-2b is a potent cytokine that possesses antiviral, immunomodulating and antiproliferative activities (Haworth, et al, 1994). It is a non-glycosylated protein. Interferon alfa-2b is produced by most cells in response to viral infection and a variety of other stimuli, including double-stranded RNA and certain cytokines (e.g. interleukin 1, interleukin 2, and tumor necrosis factor) (Hayden, 1996; DeMaeyer-Guignard, 1994). It is generally believed that interferons ameliorate viral infections by exerting direct antiviral effects and/or by modifying the immune response to infection (Hayden, 1996).

In addition to controlling infection, interferons may mediate some of the systemic symptoms associated with viral infections and contribute to immunologically mediated tissue damage in certain viral diseases. Interferons bind to specific cell surface receptor molecules signaling the cell to produce antiviral proteins (DeMaeyer-Guignard, 1994; Sen & Raanshoff, 1993). The antiviral proteins inhibit viral replication primarily through inhibition of transcription, protein processing, and virus maturation (Hayden, 1996). In addition interferons suppress cell proliferation and have immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells.

The specificity of biologic activity (Balkwill, *et al.*, 1982; Gresser & Morel-Maroger, 1976; Herberman, 1982) and the development of neutralising activity to interferon affect the testing of interferon alfa-2b, a human interferon, in laboratory animal species. Consequently, the value of studies conducted in rodents is limited. Although interferon alfa-2b does have biologic activity in monkeys, the development of neutralising antibodies may also have affected the outcome of these studies. However, there is considerable toxicologic experience with interferon alfa-2b in monkeys and most findings can be related to those observed in humans. Thus the monkey is considered to be an adequate species for characterisation of the toxicity of interferon alfa-2b.

#### Pharmacodynamics

Interferon alfa-2b has pleiotropic biologic activity. It binds to cell surface receptors and, through activation of a protein kinase signal transduction system, mediates the transcription of a set of genes called interferon-stimulated genes. Interferon alfa is immunomodulatory (increases NK cell, macrophage, neutrophil and T cell activity), antiproliferative (prolongs the cell cycle, modulates oncogene expression) and antiviral. It protects a variety of cell types, derived from a variety of species, against many RNA and DNA viruses.

#### Pharmacokinetics

Information on the absorption of interferon alfa-2b from the intramuscular route is limited to single blood samples being taken 1 hr following dose administration to rats and monkeys. Throughout the development of interferon alfa-2b, activity in serum has been measured using an antiviral cytopathic effect (CPE) inhibition assay. The CPE bioassay measures the ability of serum samples to protect a human fibroblast cell line sensitive to interferon alfa-2b from the cytopathic effects of encephalomyocarditis (EMC) virus. For more recent evaluations, a sandwich immunoassay (ELISA) has also been employed to determine concentrations of interferon alfa 2-b in serum. Pharmacokinetic parameters calculated from the data generated by the two assays were usually in good agreement leading to the same scientific interpretation. Therefore, although both sets of data were documented in the reports for the individual studies, the results from the ELISA are given in this overview. Serum neutralising antibodies to interferon alfa-2b were detected using an enzyme immunoassay (EIA) method that employed immobilised interferon alfa-2b on polystyrene beads. The CPE assay was also utilised to measure the neutralisation of the antiviral activity of interferon alfa-2b toward the EMC virus/fibroblast cell system.

Interferon alfa-2b is rapidly cleared from the circulation of animals and humans via renal metabolism. Whereas interferon alfa-2b readily induces the formation of neutralising antibodies in animals upon repeated dosing because of species specificity, this appears to occur infrequently in humans.

## Toxicology

The absence of signs of toxicity in rhesus monkeys given high single intramuscular or intravenous doses of interferon alfa-2b indicate that interferon alfa-2b has no apparent potential for causing acute toxic effects. The highest dose tested by both routes was approximately 7 times the maximum therapeutic dose and 130 times the minimum therapeutic dose of interferon alfa-2b. Although interferon alfa-2b has apparently little biologic activity in rodents, the results of single dose toxicity studies in mice and rats and the absence of effects on cardiovascular, renal and CNS function in the safety pharmacology studies support the conclusion that interferon alfa-2b has no apparent potential for causing acute toxicity.

Irritation at the injection site in repeated dose toxicity studies occurred in both rats and monkeys. The potential for irritation appeared to be mild to moderate and, at least in part, dependent on tonicity of the formulation.

Multiple dose studies for up to three months have shown no evidence of toxicity in mice, rats, or rabbits. Daily dosing of cynomolgus monkeys with  $20 \times 10^6$  IU/kg/day for three months caused no remarkable toxicity. However, toxicity was shown in monkeys administered the highest dose of  $100 \times 10^6$  IU/kg/day for three months.

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

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<sup>2</sup>. 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<sup>2</sup>). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

## 4. Clinical aspects

The harmonisation of the SPC was achieved in June 1997 through a referral under Article 11 of Council directive 75/319/EEC as amended.

During the centralised application, the assessment focused on the new data submitted and/or changes in the Summary of Product Characteristics (SPC) as compared to the Viraferon dossier reviewed by CPMP and the SmPC approved during Article 11 referral:

1. efficacy and safety of interferon alfa-2b in paediatric patients suffering from chronic hepatitis B;
2. modifications of SPC's wording relative to hepatitis C indication in order to introduce the concomitant use of ribavirin and interferon alfa-2b.

### Hepatitis B

Viral hepatitis ranks as a major public health concern in industrialised countries. Hepatitis B and Hepatitis C are both serious diseases whose complications are life threatening.

Chronic hepatitis B (CHB) is one of the leading causes of death in adults worldwide. Approximately 5% of the world population, more than 300 million people, are chronic carriers of hepatitis B surface antigen (HBsAg). An appreciable number of these people have chronic liver disease and are therefore at risk of progression to cirrhosis or hepatocellular carcinoma.

Nearly 80% of all HBV carriers are found in the Asian subcontinent, where the prevalence of HBsAg positivity ranges from 8% to 10%.

Countries in Southern Europe, the Middle East and Japan have intermediate prevalence rates (1%-3%), while the lowest rates are found in central and Northern Europe and in the United States (<0.5%).

Hepatitis B virus can be found in the blood and, to a lesser extent, in saliva, semen and other body fluids of an infected person. The symptoms of hepatitis B include fatigue, poor appetite, fever, vomiting and occasionally joint pain, hives or rash. Symptoms may appear 2 to 6 months after exposure, but usually within 3 months. Asymptomatic carriers are known. Hepatitis B may either heal slowly or leads to chronic liver disease and cirrhosis.

The majority of patients who are infected with the hepatitis B virus do not develop chronic disease.

High serum levels of HBsAg and the presence of HBeAg appear early in the infection course. When acute HBV infection heals without chronicity, these antigens are replaced with the respective antibodies anti-HBs and anti-HBe. Persistent serum levels of HBsAg indicate chronic HBV infection. However, since serum HBsAg is frequently part of incomplete viral forms rather than the complete HBV virion, some HBsAg carriers do not exhibit detectable HBV DNA in serum nor in the liver.

Generally, undetectable serum HBeAg and HBV-DNA in chronic HBsAg carriers are neither associated with abnormal liver histology nor with chronic liver disease. By contrast, detectable serum HBeAg or HBV-DNA are highly correlated with the presence of HBV virions in serum (electron microscopy), with infectivity of serum and with actively replicating HBV in liver cells.

Longitudinal studies of the natural history of chronic HBV infection indicate an annual rate of spontaneous loss of HBeAg of about 7 to 20%.

Interferon therapy is to date the only anti-viral treatment whose long-lasting efficacy has been established as a treatment of chronic hepatitis B in adults.

During harmonisation of Viraferon SmPC in the frame of the Article 11 referral, consensus was reached regarding the target population to be treated among chronic carriers of HBV. Treatment was recommended in patients with chronic hepatitis (persistently elevated serum ALT, HBsAg) showing signs of viral replication (HBeAg, HBV-DNA or DNA polymerase), and at high risk of progression towards cirrhosis (histologically proven chronic active hepatitis as assessed by the Knodell inflammatory and fibrosis score on biopsy samples).

The aim of treatment is to interrupt viral replication and reach the non-replicative phase quicker than allowed by the natural history of the disease, in order to avoid progression towards cirrhosis.

Those efficacy criteria are only surrogate markers of efficacy, and it is not known whether the risk of hepatocellular carcinoma is significantly reduced, all the more as HBsAg is rarely totally eliminated.

In adults, about 30% of patients are responders, and low pre-treatment serum HBV-DNA levels are a positive predictor of treatment success.

The data supporting the use of Viraferon in chronic hepatitis B consist of results from several randomised controlled clinical trials. Viraferon was shown to inhibit replication of the HBV. Loss of markers of viral replication occurs in 30 % to 40% of treated patients and this rate is significantly higher than the spontaneous response rate observed in untreated control patients.

The results of a single randomised placebo-controlled clinical trial in children aged 1- 17 years with chronic hepatitis B were assessed during the Centralised procedure. Patients were treated for 6 months 6 MIU/m<sup>2</sup>, followed by a 24-week observation period post-treatment. Due to a methodological flaw in

the analysis of the results, CPMP determined that an assessment of efficacy could not be made. Although the safety analysis from this study shows that the overall safety profile of interferon alfa-2b in children is essentially similar to that in adults, a safety concern was raised by CPMP due to a lower mean height gain in the 2-12 years treated subgroup compared to the untreated/control group. Therefore, the indication for treatment of hepatitis B in children was not granted, but information on the trial and safety in children is to be provided in Section 5.1 of the SPC.

## **Hepatitis C**

Viral hepatitis ranks as a major public health concern in industrialised countries. Hepatitis B and Hepatitis C are both serious diseases whose complications are life threatening.

Hepatitis C is spread by exposure to blood from an infected person, such as through a blood transfusion or sharing needles. Patients with hepatitis C may experience appetite loss, fatigue, nausea and vomiting, vague stomach pain and jaundice. Symptoms may occur from 2 weeks to 6 months after exposure but usually after 2 months. Some people carry the virus in their bloodstream and may remain contagious for years. The disease may occur in the acute form and be followed by recovery or it may become chronic and cause symptoms for years. Chronic hepatitis C accounts for a large number of cirrhosis and liver failure.

Moreover Hepatitis C Virus (HCV) infection has been identified as a risk factor for the development of hepatocellular carcinoma.

Once an individual is infected with HCV, use of antiviral therapy to prevent or reverse the chronic carrier state is the main therapeutic option.

In chronic hepatitis C Viraferon treatment produces normalisation of alanine aminotransferase (ALT) levels in 40% to 50% of treated patients. Sustained normalisation after discontinuation of treatment is seen in 15% to 20% of patients.

The optimal duration of interferon alfa-2b monotherapy in chronic hepatitis C has not been established. However, the prolongation of treatment up to 18 months might be useful in some cases of chronic hepatitis C and this has been taken into consideration in the recommendation in section 4.2 of the SPC.

### Combination therapy with ribavirin in the treatment of chronic Hepatitis C.

An application for a centralised Marketing authorisation for the use of ribavirin in association with interferon alfa-2b in the treatment of chronic hepatitis C was submitted by SP Europe in June 1998.

During the February 1999 CPMP meeting, it was recommended that a Marketing Authorisation be granted for ribavirin as associated with interferon alfa-2b in the treatment of chronic hepatitis C.

The European Commission granted a Marketing Authorisation for ribavirin (Rebetol/Cotronak) on 7 May 1999.

The data on the co-administration of interferon alfa-2b with ribavirin reviewed in the Rebetol assessment were included with the centralised application to support an extension of the interferon alfa-2b indication for hepatitis C to include combination with ribavirin as first line treatment.

## **Clinical efficacy**

Since the assessment of the clinical data made during the Article 11 referral, new technology has become available which changes the standard by which efficacy is judged for hepatitis C therapy. Previously, efficacy was based on the sustained normalisation of ALT. However, now that testing for HCV RNA has become available, the potential for discrepancies between serum HCV RNA and ALT

responses has become apparent. Therefore, efficacy is now based on the sustained virologic response defined as the loss of HCV RNA at least 6 months after the end of treatment.

The efficacy of the combination therapy was evaluated in:

- one phase II study (H095-058, Reichard *et al.*, Lancet 1998) in naïve patients (n=100),
- two phase III studies (C95-144, I95-145) in patients who relapsed after interferon treatment (n=153 and n=192),
- two phase III studies (C95-132, I95-143) in patients with chronic HCV not previously treated with interferon (n=912 and n=832).

All were double blind, placebo-controlled trials, comparing interferon alfa-2b (3 MIU t.i.w.) monotherapy with interferon alfa-2b (3 MIU t.i.w.) plus ribavirin 1,000 (for weight <75 kg) or 1,200 (for weight >75 kg) mg/day.

Dose reductions were allowed in patients with abnormal laboratory findings, who could continue on treatment if the abnormality was within the cut-off value requiring discontinuation. Ribavirin dose was reduced for abnormalities in haemoglobin (<10 g/dl) and bilirubin (>5 mg/dl); interferon dose was reduced in case of decrease of white blood cells (<1.5  $10^9/l$ ), neutrophil (<0.75  $10^9/l$ ) and platelet (<50  $10^9/l$ ) counts.

### Studies in relapse patients

The standard treatment period was 24 weeks, followed by 24 weeks of untreated follow-up. Final assessment was performed at week 48.

*Response* was defined as a composite endpoint combining virological response at week 48 (loss of detectable HCV-RNA /qPCR <100 copies/ml) with improvement in the HAI score in the 48 week liver biopsy (Knodell score for sum of categories I+II+III  $\geq 2$ ).

Overall responders showed improvement in both parameters. Patients with missing data (missing HCV-RNA, biopsy or both) were classified as non-responders. Relapsers were HCV-RNA negative at week 24 but positive at week 48.

The following secondary endpoints were also examined:

- response rate at week 24 (HCV-RNA qPCR)
- proportion of patients with normalisation of ALT at week 24 and 48
- proportion of patients with improvement in biopsy (categories I+II+III combined scores)
- change from pre-treatment in biopsy scores (categories I+II+III combined scores)

The primary endpoint (overall response) was evaluated at week 48, end of follow-up period, together with the histologic parameters. End of follow-up virological response rate after combined therapy was 48.6% ( $p < 0.0001$ ), compared with the significantly inferior rate of 4.7% for patients who received interferon alfa-2b monotherapy. Sustained improvement in Knodell score occurred in 63% of combination patients, compared to 41% of monotherapy. The overall response was 37.0% in the combination arms, 3.5 % in the monotherapy ( $p < 0.001$ ).

Some secondary endpoints were evaluated at end of therapy (week 24). The ALT response was evaluated as well at week 48. End of therapy virological response rates were significantly superior with combined therapy: rates were 81% for combined and 46% for monotherapy. ALT response was 89% for combined and 57% for monotherapy at week 24; 52% for combined and 15% for monotherapy at week 48.

Each of the two studies independently demonstrated that the addition of ribavirin to interferon alfa-2b resulted in an approximately 10-fold enhancement in efficacy compared to retreatment with interferon alfa-2b alone.

Also, response induced by the combined treatment seems to be more stable: of those patients who had a virologic response at the end of treatment, 58% (83/141) in the interferon alfa-2b+ribavirin group compared to 9% (7/80) in the interferon alfa-2b+placebo group maintained the response at the end of follow-up.

In the clinical trials, patients who failed to show virological response at week 24, failed to show sustained response at week 48 (one interferon alfa-2b + ribavirin relapse patient had PCR = 200 copies/ml and became sustained responder).

An analysis of the correlation among endpoints has been made:

- Virological response and ALT level: a sustained ALT normal level is highly correlated with the eradication of detectable HCV-RNA at the end of follow-up: the number of patients with normal ALT / number of sustained virologic responders (%) is 80/83 (96%) for interferon alfa-2b + ribavirin; 8/8 (100%) for interferon alfa-2b + placebo.
- Virological response and HAI Knodell score: the decrease in hepatic inflammation is highly correlated with the eradication of HCV-RNA whatever the treatment.
- Early relapses and genotype:
  - in HCV genotype1, sustained virologic response was obtained in 29% of interferon alfa-2b + ribavirin treated patients versus 3% interferon alfa-2b + placebo treated. In other HCV genotypes, a sustained virologic response was obtained in 74% interferon alfa-2b + ribavirin treated patients versus 6% interferon alfa-2b + placebo treated.
  - in the interferon alfa-2b+ribavirin group, relapse between the end of the treatment and the end of the follow-up occurred more frequently in patients infected with HCV genotype 1.
  - logistic regression analysis of sustained virologic response demonstrated that, in addition to treatment group, HCV genotype other than 1 was a significant predictor ( $p < 0.001$ ).
- Sustained virological response and high viral load: the combined treatment is associated with sustained virological responses (40-44% for interferon alfa-2b + ribavirin against 0-3% for interferon alfa-2b + placebo) also in patients with a high HCV-RNA level at baseline:

#### ***Predictors of sustained response***

Logistic regression analysis of the pooled data using virological response as the endpoint, showed that combined treatment (interferon alfa-2b + ribavirin), HCV genotype other than 1 and baseline high viral load were significant predictors of sustained virological response at 6 months after the end of treatment.

*Sustained Virological Response by Baseline HCV Genotype and Virus Level/Combined results for relapse patients:*

	<b>Interferon alfa-2b + Ribavirin</b>	<b>Interferon alfa-2b + Placebo</b>
<b>Other Genotypes/&lt; 2 million copies/ml</b>	95% (19/20)	18% (3/17)
<b>Other Genotypes/ &gt; 2 million copies/ml</b>	67% (36/54)	3% (2/60)
<b>Genotype 1/&lt; 2 million copies/ml</b>	44% (11/25)	13% (3/24)
<b>Genotype 1/ &gt; 2 million copies/ml</b>	24% (18/74)	0 (0/71)

The patients before therapy completed a QOL questionnaire, during therapy and six months following the end of therapy. All sustained responders had improvement of QOL, whatever their treatment.

Updated information on the durability of sustained virological response from a six month follow up of clinical trial patients is provided in section 6 of this EPAR.

#### **Studies in naïve patients**

##### **Phase II trial**

The treatment period was 24 weeks, followed by 24 weeks of untreated follow-up. Final assessment was performed at week 48.

In the evaluable population, sustained response was seen in 49% of combination and 20% of interferon alfa-2b mono-therapy patients. At 24 weeks, 68% of combination and 54% of mono therapy had normal ALT, dropping to 46 % and 28 % respectively at 48 weeks.

### **Phase III trials**

The trials (C95-132 and I95-143) evaluated the safety and efficacy of ribavirin plus interferon alfa-2b in patients with chronic HCV infection who had not previously been treated with interferon. Both trials were multicentre, double-blind and placebo-controlled.

Patients were selected according to criteria similar to those employed in the interferon-experienced patient trials except that they had no past exposure to interferon or ribavirin. Adults had to have detectable HCV-RNA by the National Genetics Institute (NGI) PCR assay, had a liver biopsy within one year which showed changes consistent with chronic hepatitis, and had elevated ALT for the past six months. Patients with decompensated cirrhosis were excluded.

Treatment regimens and dose adjustments in patients who developed laboratory abnormalities outside of the prescribed limits were as for the previous studies. The major difference was that these trials allowed for some patients to be treated for up to 48 weeks.

Patients in C95-132 were randomised to one of four treatment groups, which were balanced according to presence/absence of cirrhosis, pre-treatment HCV-RNA level and HCV genotype; 912 patients received treatment as follows:

- interferon alfa-2b plus ribavirin for 24 weeks [I/R(24)] 228 patients
- interferon alfa-2b plus ribavirin for 48 weeks [I/R(48)] 228 patients
- interferon alfa-2b plus placebo for 24 weeks [I/P(24)] 231 patients
- interferon alfa-2b plus placebo for 48 weeks [I/P(48)] 225 patients

In this study, fibrosis was graded with Knodell HAI score and METAVIR SCORE.

Patients in I95-143 were similarly randomised with balancing for the same factors as in C95-132. The difference was that the interferon alfa-2b/placebo 24-weeks group was omitted in this study since current recommendations were to give 48 weeks interferon alfa-2b in naive patients: 832 patients received treatment as follows:

- interferon alfa-2b plus ribavirin for 24 weeks [I/R(24)] 277 patients
- interferon alfa-2b plus ribavirin for 48 weeks [I/R(48)] 277 patients
- interferon alfa-2b plus placebo for 48 weeks [I/P(48)] 278 patients

In this study, fibrosis was graded with Knodell HAI score and METAVIR score.

Groups were well balanced with regard to age, sex, ALT and source and duration of infection. There were 58-70% of patients in each group who had more than 2 million copies/ml of HCV-RNA at baseline. Overall, 64-72% had HCV genotype 1 infection, while 11-17% had genotype 2, 10-20% had type 3? From biopsies 4-5% had cirrhotic changes, 15-19% showed bridging fibrosis. (These figures do not take into account the interferon alfa-2b +placebo 24 weeks group, which is not considered in the assessment of efficacy).

A 24-week post-therapy follow-up phase then ensued in all treatment groups in both trials.

The primary efficacy variable in individual study analysis was sustained virological response (undetectable HCV-RNA as measured by the NGI PCR assay, which has a cut-off limit of <100 copies/ml) at 24 weeks post-therapy.

Secondary efficacy endpoints were: improvement in liver biopsy scores at the end of follow-up, biochemical response (ALT normalisation at the end of follow-up), combined biochemical/virological response.

For the combined results, the primary efficacy endpoint was overall response, a composite endpoint defined as the association of virological and histological responses.

In both trials, there were fewer patients who completed 48 weeks therapy compared with 24 weeks therapy; however, the losses were similar for both combined and monotherapy groups and about 70% of patients assigned to 48 weeks actually completed therapy. Almost all the patients who reached the end of treatment were available for the post-therapy follow-up.

Combined results of the studies were as follows:

- End of follow-up virological response rates after combination therapy were 33% for the 24-week treatment group and 41% for the 48-week group, compared with significantly inferior rates of 6% and 16% for patients who received monotherapy for these respective treatment periods. This shows borderline superiority for 48 vs. 24 weeks in each individual study ( $p=0.053$  and  $0.055$ ), and the low percentage of sustained responders in interferon monotherapy has to be noted. The treatment difference between combination 24-week and 48-week is found to be statistically significant ( $p=0.008$ ) in the meta-analysis of both individual studies.
- End of therapy virological response rates were also significantly superior with combined therapy. In the 24-week treatment groups, rates were 55%; after 48 weeks of treatment, rates were 51%. Monotherapy rates were 29% (24 weeks and 48 weeks).
- Combination therapy with I/R decreased relapse rates compared to I/P. Extending duration with I/R (48) further decreased the relapse rate, making I/R (48) significantly more effective than I/R (24) ( $p=0.008$ ). This was true for all HCV genotypes, particularly type 1 in which relapse rates were reduced to 26% with I/R(48). Consistently higher relapse rates were noted with type 1 than with types 2 or 3.

<b>Relapse Rate by HCV Genotype (C95-132, I95-143)</b>				
	<b>I/R(24)</b>	<b>I/P(24)</b>	<b>I/R(48)</b>	<b>I/P(48)</b>
<b>All Genotypes</b>	<b>42% (118/278)<sup>a</sup></b>	<b>80% (53/66)</b>	<b>21% (55/260)</b>	<b>46% (67/147)</b>
1	62% (84/136)	89% (25/28)	26% (33/127)	56% (37/66)
2/3	21% (27/230)	76% (28/37)	15% (18/120)	37% (29/79)
4/5/6	58% (7/12)	0/1	31% (4/13)	50% (1/2)
a: Patients who had positive or missing HCV-RNA at End of FU+patients who were HCV-RNA negative at the end of treatment.				

Sustained virological response rates were markedly lower for genotype 1 HCV infections compared with all non-genotype 1, whatever the treatment or duration. However, combination therapy was still superior to interferon alfa-2b alone against genotype 1.

- A virological response to therapy at 4 weeks strongly predicted a sustained response; the likelihood of a sustained response decreased with increased duration of therapy before a finding of undetectable HCV RNA. . None of the patients who first became negative after Week 24 became sustained responders.

Sustained Virologic Response by Time to First Negative HCV–RNA/RT–PCR.				
Time to First HCV–RNA Negative	I/R(24)	I/P(24)	I/R(48)	I/P(48)
4 wks	83% (92/111) <sup>a</sup>	48% (10/21)	82% (94/115)	71% (47/66)
12 wks	44% (66/149)	9% (3/32)	66% (91/137)	35% (29/84)
24 wks	19% (8/42)	0% (0/22)	44% (20/45)	15% (6/39)
36 wks	–	–	0 (0/6)	0 (0/11)
48 wks	–	–	0 (0/2)	0 (0/2)
a: Number of sustained responders÷number of patients HCV–RNA negative for the first time in the interval.				

Nevertheless in study C95-132, of the 87 patients in the 48-week combination therapy group who had a sustained virological response, 40 first became negative for HCV-RNA at week 12, and 11 others at week 24 on therapy. Also, 15/29 responders in the 48-week monotherapy group first became negative for HCV RNA after the 4-week visit (11 at 12 weeks and 4 at 24 weeks).

Delayed viral clearance was also documented in 35/70 who received 24 weeks of combination therapy and had a sustained virological response at follow-up, including 30 first negative at 12 weeks and 5 at 24 weeks.

These findings indicate that treatment should not be interrupted in non-responders at week 12, contrarily to what is currently done under interferon monotherapy. In such late responders (first negative PCR at week 24), treatment should on the contrary be continued until week 48. On the other hand, the data suggest that it is not worth continuing treatment in patients with still detectable HCV-RNA at week 24.

- Baseline viral loads and HCV genotype influenced the sustained virologic response as follows:

Sustained Virologic Response to Treatment by HCV Genotype and Virus Levels (Naïve patients 24 weeks after the end of treatment)				
	Interferon alfa-2b + ribavirin	Interferon alfa-2b + placebo	Interferon alfa-2b + ribavirin	Interferon alfa-2b + placebo
	24 weeks	24 weeks	48 weeks	48 weeks
HCV Genotype 1 and ≤ 2 million copies/ml	32 %	4 %	33 %	25 %
HCV Genotype 1 and > 2 million copies/ml	10 %	0.9 %	27 %	3 %
HCV Genotype other than 1 and ≤ 2 million copies/ml	61 %	25 %	64 %	36 %
HCV Genotype other than 1 and > 2 million copies/ml	62 %	11 %	63 %	26 %

- Overall sustained histologic response showed for the 48 weeks therapy group a mean change in Knodell score of –2.6 in the combination groups against –1.0 in monotherapy, improvement in both groups being higher compared with 24 weeks (–1.9 and –0.6 respectively).
- The majority of the patients had disease for more than 5 years. For those patients, in study C95-132, combined therapy was clearly superior to monotherapy, but 48 weeks was not better than 24 weeks of combined treatment. In trial I95-143 response rates were markedly higher than those achieved with 24 weeks or monotherapy (61% vs 39% and 24%).

The majority of patients included were mildly injured, with fibrosis score corresponding to the F1 METAVIR quotation.. Nevertheless, due to the high number of patients included, the 5% cirrhosis (F4 stage) and the 15% bridging fibrosis (F3 stage) correspond to approximately 400 patients (100 patients per arm), which seems enough to enable efficacy evaluation in this subgroup as a whole. For naïve patients, it is proposed that only patients with liver fibrosis or high inflammatory activity be treated with the combination (see Section 4.1 of the SPC).

### **Clinical safety**

Overall, the reporting of adverse events was similar with interferon alfa-2b + ribavirin compared with interferon alfa-2b alone. The patterns of adverse events reported by both relapse and naïve populations were similar, and the combination therapy reflects the safety profiles of interferon alfa-2b and ribavirin administered alone.

The safety profile of interferon alfa-2b is well known. The side effects are generally dose related. Anaemia and decreases in haemoglobin are known to be associated with ribavirin and occurred more frequently in patients treated with the combination compared with those treated with interferon alfa-2b alone. Some cardio-vascular events were correlated with large haemoglobin drops, and severe and life-threatening cardiovascular complications occurred slightly more frequently in patients treated with the combination. Dosage modification guidelines have been defined for all patients, with additional restrictions for patients at risk for cardiovascular complications.

### **Conclusions**

The results of these trials independently demonstrated that the addition of ribavirin to interferon alfa-2b results in a significant increase in efficacy in both naïve and relapse patients compared to treatment with interferon alfa-2b alone. These studies also confirm that interferon alfa-2b as monotherapy offers clinical benefit following one year of therapy in naïve patients. However, only 5 % of relapse patient's respond to additional course of interferon alfa-2b monotherapy. Therefore, the benefit of monotherapy in relapse patients is questionable and a recommendation for combination therapy for these patients is to be included in the SPC.

As a result of the evaluation, the CPMP concluded that the benefit/risk profile for interferon alfa-2b is favourable in the treatment of chronic hepatitis C. An enhancement of efficacy is seen when interferon alfa-2b is co-administered with ribavirin and is the optimal therapy for most patients. Interferon alfa-2b as monotherapy provides potential benefit only for a subgroup of patients intolerant or contraindicated for ribavirin. Therefore, the recommended posology in the SPC is modified to show that:

- In relapse patients, interferon alfa-2b must be used in combination with ribavirin.
- In naïve patients, the optimal therapy is the combination of interferon alfa-2b + ribavirin, but interferon alfa-2b may still have a useful therapeutic role in some patients, mainly those intolerant to or contraindicated for ribavirin.

## **5. Initial conclusions and benefit/risk assessment**

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Viral Safety and batch-to-batch consistency has been documented and the relevant tests are performed according to the agreed specifications.

Taking into account both the preclinical data and the extensive human clinical exposure to interferon alfa-2b, it is concluded that the benefit/risk for the use in humans is positive. The adverse effects to patients given the therapeutic dosing regimen can be monitored and are reversible. It is the overall conclusion that patients can be safely treated for prolonged periods with interferon alfa-2b.

As far as the indication treatment of **hepatitis B** in children is concerned, the CPMP considered that the study presented major methodological concerns, and given the ADRs profile of interferon alfa-2b is not satisfactory, this indication shall not be granted. Information on the trial conducted in children is provided in Section 5.1 of the SPC.

The update of the indication “treatment of Chronic **Hepatitis C**” is acceptable, as it puts in line the prescribing information of Viraferon with the authorised indication for ribavirin.

According to the most recent international Consensus, the target population with hepatitis C should exhibit histologically proven signs of activity of the disease as demonstrated on a pre-treatment biopsy graded with the Knodell HAI score. Only histologically proven chronic hepatitis should be treated, therefore the need for biopsy is maintained in the SPC and Package Leaflet.

### **Benefit/risk assessment**

Based on the CPMP review of data on quality, safety and efficacy, (partly already assessed in the Article 11 harmonisation procedure), the CPMP considered by consensus that the benefit/risk profile of Viraferon was favourable in the treatment of:

**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 ALT and histologically proven active liver inflammation and/or fibrosis.

**Chronic Hepatitis C:** Treatment of adult patients with histologically proven chronic hepatitis C who have serum markers for virus C replication, e.g., those who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

The efficacy of interferon alfa-2b in the treatment of hepatitis C is enhanced when combined with ribavirin.

On these grounds the CPMP, during the meeting of 21 October 1999, recommended the granting of a Marketing Authorisation for Viraferon for the above-mentioned indications.

## **6. Clinical efficacy data in the indication of chronic hepatitis C submitted post authorisation**

Additional efficacy information was gathered in the indication of chronic hepatitis C from clinical trials which were still ongoing at the time of the authorisation. In this update the number of patients with chronic hepatitis C treated in clinical trials with interferon alfa-2b, alone or in combination with ribavirin, had increased to 2,522.

In trial C/198-580, the sustained response rate increased to 56% of patients receiving combination interferon alfa-2b with ribavirin who were compliant with the treatment regimen (=80% of their treatment) compared with 32% in patients who received <80%.

Additional information was provided on the sustained virological response by genotype and viral load as shown in the table below.

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

*I* Viraferon (3 MIU TIW)

*I/R* Viraferon (3 MIU TIW) + ribavirin (1,000/1,200 mg/day)

Increased efficacy of Viraferon when used in combination with ribavirin was noted

Furthermore, the CPMP decided that not all patients with chronic hepatitis C need to have a liver biopsy before treatment commences. In the Consensus statement from the French Consensus Conference on Hepatitis C, it is stated that biopsy may not be necessary if a decision to treat already has been made on other grounds and the primary objective is viral eradication. This is basically in line with the NIH Consensus Guideline and some other National Guidelines. The viral eradication rate is so high for patients with genotype 2/3, for example, that treatment is indicated in many cases even if the histology turns out to be benign. Therefore histology is not always needed.

The CPMP recommended that although the term “histologically treated” should be deleted from section 4.1 of the SPC, the following warning should be added to section 4.4: *“All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (ie patients with genotype 2 or 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.”*

The additional information led to changes to the efficacy information in the SPC. Section 5.1 of the SPC was updated to reflect that the number of patients with chronic hepatitis C treated in clinical trials with interferon alfa-2b, alone or in combination with ribavirin, had increased to 2,522. In trial C/198-580, the response rate increased with compliance with 56% of patients who had received ≥80% of their treatment having a sustained response 6 months after completion of treatment compared with 32% of patients who received <80%. Information on the increased efficacy of interferon alfa-2b when used in combination with ribavirin was also included.

## 7. Clinical safety data submitted post authorisation

Although warnings about central nervous system (CNS) effects were included the SPC at the time of authorisation, these warnings, in section 4.4, were strengthened. The adverse events of suicide and suicidal ideation added to section 4.8 to highlight the safety concerns regarding CNS reactions. Following issues raised during the initial assessment of the product and in the first Public Safety Update Report (PSUR), the MAH also proposed addition of the adverse events: peripheral ischaemia, seizure, hypertriglyceridaemia and aplastic anaemia to section 4.8 of the SPC.

Cases of patients developing cutaneous or pulmonary sarcoidosis have been reported in the literature and 11 cases were reported in the 2<sup>nd</sup> PSUR. There is also a plausible explanation as to why this may occur with the use of interferons. The CPMP agreed with the proposal of the MAH to include statements on sarcoidosis in sections 4.4 and 4.8 of the SPC.

Following a review of 82 cases of hypertriglyceridaemia, it was concluded that elevations in triglycerides occur in patients with and without other risk factors or history of dyslipidaemia. Elevations are often significant, may have clinical sequelae and may require treatment. Although hypertriglyceridaemia was already mentioned in the current SPC, the CPMP agreed that the addition of a sentence in section 4.4, recommending the monitoring of lipid levels, appeared necessary given the data.

The SPC already contained a warning in section 4.4 that patients experiencing ophthalmic symptoms during treatment with Viraferon should have an eye examination and that a baseline examination was desirable in patients with hypertension or diabetes mellitus. Following the submission of the 4<sup>th</sup> PSUR (9 Sept 2001- 8 March 2002) and a change in the US labelling for all marketed alpha interferon products, the MAH decided to strengthen the EU SPC warning with regard to ocular disorders and suggest that all patients should have baseline eye examinations. The MAH suggested that patients with other disorders associated with retinopathy be advised to have periodic eye examinations during therapy and discontinuation of Viraferon therapy should be considered in patients who develop new or worsening ophthalmological disorders.

The adverse reactions: retinopathies (including macular oedema), loss of visual acuity or visual field, optic neuritis and papilloedema were added to section 4.8.

Section 4.8 was also updated to include a statement that the common adverse reactions reported in patients receiving Viraferon in combination with ribavirin were also reported during Viraferon monotherapy.

Section 4.4 already contained a warning regarding the development of autoantibodies and autoimmune disease. This warning was strengthened with regard to the risk of developing autoimmune disorders along with a recommendation that there should be a careful evaluation of the benefit risk of continued interferon therapy in patients developing signs or symptoms compatible with autoimmune disorders.

Following discussions at the CPMP and PhVWP, a class labelling was adopted to warn of the increased risk of adverse reactions when alpha interferons and ribavirin are used in conjunction with Highly Active Anti-Retroviral Therapy in patients co-infected with HCV/HIV. This warning was incorporated into section 4.4.

The MAH reviewed all cases of erythema multiforme (EM), Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which had occurred in patients treated with either Intron A/Viraferon or Peginteron/ViraferonPeg up until 30 August 2002. Almost half of the cases involved use in combination with ribavirin. Intron A/Viraferon has been marketed for over 10 years (initially authorised nationally then as a centrally authorised product since March 2000) but ribavirin only for 4 years so it may be indicative that combination therapy carries a higher risk of EM, SJS or TEN. As a result of the review, section 4.8 was updated to add the adverse events: Stevens Johnson syndrome, toxic epidermal necrolysis and erythema multiforme.

Information on autoimmune and immune mediated disorders was also added. The MAH took the opportunity to bring section 4.8 into line with current guidelines with the consequential change of section 4.8 to a tabular format with the addition of adverse reactions occurring at the 1% level. As a consequence the following adverse reactions occurring at a frequency of 1% were added: tremor, dehydration, gingivitis, stomatitis ulcerative, hypocalcaemia, thirst, arthritis, sleep disorder, breast pain, dysmenorrhoea, vaginal disorder, bronchitis, rhinorrhoea, eczema, psoriasis (new or aggravated), skin disorder, micturition frequency, lymphadenopathy and lymphopenia.

A warning regarding the teratogenicity and embryocidicity of ribavirin was added to section 4.6 since the recommended use of Viraferon in the treatment of hepatitis C is in combination with ribavirin.

## **8. Overall Conclusions**

Viraferon treatment has been demonstrated to have a positive risk/benefit ratio in the following patient populations when used as indicated:

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 ALT and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C: 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.

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

Medicinal product no longer authorised