Viraferon

Procedural steps taken and scientific information after the authorisation
Changes made after 01/08/2003

For procedures finalised before 01/08/2003, please refer to module 8A

MAJOR CHANGES[1]

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
II/0059	Update of Summary of Product Characteristics and Package Leaflet Update of section 5.1 of the SPC with the results of the development programme in HIV/HCV co-infected patients treated with pegylated interferon/ribavarin further to a request of the CHMP made in the context of the 5 year renewal of Viraferon. The details of the Romanian local representative are updated in the Package leaflet.	18/03/2008	22/04/2008	SPC, PL	In the context of the 5 year renewal of Viraferon the MAH was requested to update the product information with the results of the development programme in HIV/HCV co-infected patients with pegylated interferon/ribavarin. Extensions of indication to include treatment of HCV in HIV/HCV co-infected patients were granted by the CHMP for the alfa 2b pegylated interferons and Rebetol in June 2007 based on the results of 2 clinical trials conducted in patients co-infected with HIV and HCV. The results of these two studies are now reflected in the SPC of the standard interferons. Additionally it is mentioned that in both studies, patients who received standard interferon alfa-2b plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin.
II/0058	Change(s) to the test method(s) and/or specifications for the active substance	21/02/2008	26/02/2008		
II/0057	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.4. and 4.8 of the SPC with the adverse reaction Vogt-Koyanagi-Harada syndrome. Section 4.8 is also updated in line with the SPC guideline further to a request from the CHMP. The	13/12/2007	28/01/2008	SPC, PL	A cumulative review carried out by the Marketing Authorisation Holder identified 11 cases of Vogt-Koyanagi-Harada syndrome associated with interferon alfa therapy. In all cases, the role of alfa interferon could not be totally ruled out. However it is now well-recognized that Hepatitis C infection itself can be involved in the development of auto-immune disorders. The CHMP considered that the very rare frequency and the seriousness of this hardly known disease must be taken into account and therefore the adverse reaction

[1] Major changes e.g. Type II variations, Annex II applications, Renewals and Annual Reassessments
[2] SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet)

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	Package Leaflet is updated accordingly. Changes have also been made to the contact details of Italy, the Netherlands, Norway and Sweden in the Package Leaflet.				has been included in sections 4.4 and 4.8 of the SPC, which should improve awareness and treatment and consequently outcome of this serious condition.
II/0056	Change(s) to the manufacturing process for the finished product	19/07/2007	24/07/2007		
II/0054	Change(s) to the test method(s) and/or specifications for the finished product	22/03/2007	29/03/2007		
II/0053	Update of Summary of Product Characteristics and Package Leaflet Further to pre-clinical follow up measures in the neonatal and juvenile rat concerning ribavirin, sections 4.4 and 5.3 of the SPC are updated to warrant the attention of prescribers on the need to clearly assess the benefit-risk of the combined use of ribavirin and interferon alfa-2b in young children in period of growth. Changes have also been made in the package leaflet to the contact details of Denmark, Latvia and Lithuania. In addition the MAH completed the list of local representatives in the PL to include the two new EU Member States (Bulgaria and Romania).	16/11/2006	09/01/2007	SPC, PL	Results of preclinical oral toxicity study of ribavirin in the neonatal and juvenile rat showed a dose-related decrease in the overall growth, which concerned body weight, crown-rump length and bone length. No histopathological effects on bone were observed. No ribavirin effects were observed regarding neurobehavioral or reproductive development. In view of the results of the preclinical study on bone growth, a warning was warranted in order to highlight to prescribers the need to clearly assess the benefit-risk of the combined use of ribavirin and interferon alpha 2b in young children in period of growth. Sections 4.4 and 5.3 of the SPC are updated accordingly.
II/0051	Update of Summary of Product Characteristics, Labelling and Package Leaflet Update of section 4.8 of the SPC with the addition of the adverse reaction pure red cell aplasia. The MAH also introduces outstanding quality comments to section 6 of the SPC. The package leaflet and labelling has been updated accordingly. The MAH	27/07/2006	01/09/2006	SPC, Labelling, PL	This variation is submitted further to the CHMP conclusions dated 7th April on ribavirin FUM 25, in which a cumulative update of pure red cell aplasia (PRCA) was requested to determine the number of reported cases and further characterise this effect. Pure red cell aplasia is a condition where the body stops or reduces the production of red blood cells. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy. A number of cases reported in the safety review are in favour of a potential link between ribavirin and/or interferon therapy and the development of pure red cell aplasia due to a suggestive chronology. The number of cases of pure red cell

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	also takes the opportunity to update the contact details of the local representatives for Lithuania and Iceland in the package leaflet.				aplasia, although remaining limited, increased since the last safety review on this issue (FUM 25) dated 7th April 2005. As a result of the cumulative safety review, the CHMP agreed to the addition of the adverse reaction pure red cell aplasia in section 4.8 of the SPC and section 4 of the package leaflet of Viraferon.
II/0050	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.4 of the SPC of Viraferon further to the adoption of a class labelling for psychiatric disorders by the CHMP meeting on 23rd March 2006. The Package Leaflet has been updated to reflect the SPC changes.	28/06/2006	19/07/2006	SPC, PL	Following a safety review on suicide and attempted suicide Section 4.4 of the SPCs of a number of the interferon alfa-2b and ribavirin containing medicinal products, respectively were updated to include a warning on the duration of psychiatric disorders. This update took place in September 2005. On assessment of a subsequent pharmacovigilance follow up measure for ribavirin the CHMP requested a class labelling to put more emphasis on psychiatric disorders in the SPC and Package Leaflet of the interferon-alfa and ribavarin containing products. Due to differences in the indications it was not possible to propose a class labelling "text" for all these products. Therefore the existing paragraphs pertaining to psychiatric disorders in the SPC and Package Leaflet of Viraferon have been moved to the beginning of the corresponding sections and placed in a warning box in order to draw attention to these serious adverse effects.
II/0049	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.6 of the SPC with regard to recommendations on pregnancy and lactation. This change is further to the adoption of a class labelling by the CHMP on 26 January 2006 for the interferons and ribavirin on pregnancy and lactation. Corresponding revisions to the Package Leaflet are made.	27/04/2006	19/05/2006	SPC, PL	The need to harmonise the SPCs of the ribavirin and alfa interferon containing medicinal products has been highlighted on previous occasions as existing discrepancies regarding the recommendations for pregnancy and lactation might be confusing for prescribers and patients. The CHMP concluded that contraceptive measures should be used during treatment and for 4 months after treatment discontinuation in female patients and their partners and during treatment and for 7 months after treatment discontinuation in male patients and their female partners. Section 4.6 of the SPC of Viraferon has therefore been updated to add the seven month duration of contraction for male patients and their female partners when alfa-interferon is used in combination with ribavarin. Regarding lactation the CHMP agreed that given the importance of the treatment to the mother, prescribers should not be given a choice between the discontinuation of treatment or breastfeeding. Rather a warning should be included in Section 4.6 that breastfeeding should be discontinued prior to treatment.

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II/0048	Update of Summary of Product Characteristics, Labelling and Package Leaflet Update of Section 4.4 of the Viraferon SPC, further to the assessment of PSUR 7 and of Pharmacovigilance follow up measures, to alert the prescribers on the fact that patients treated with ribavirin and interferon combination therapy and Zidovudine could be at higher risk of developing anaemia. The Package Leaflet has been updated accordingly. The annexes have also been updated in line with the latest QRD template (version 7).	23/03/2006	27/04/2006	SPC, Labelling, PL	Further to the assessment of PSUR 7 for IntronA/Viraferon (period covered 8 March 2004 to 9 September 2004) a report has drawn attention to a potential increase of anaemia in patients coinfected with HIV and HCV who received concomitant treatment with interferon or pegylated interferon and ribavirin with Zidovudine (AZT). As anaemia seemed is an important limiting factor for the success of combination therapy in patients coinfected with HIV and HCV, the CHMP requested that the MAH review safety data with regard to the necessity to include a warning in the SPC and Package Leaflet. In light of the safety review provided by the company the CHMP concluded that the hypothesis of an interference between haemolysis due to ribavirin and the myelosuppresive effect of AZT with reduction of erythropoiesis as suggested in literature should be taken into consideration. This has been reflected as a warning in the SPC of Rebetol, IntronA/Viraferon, and PegIntron/ViraferonPeg.
II/0047	Update of Summary of Product Characteristics Update of the information in section 5.1 of Viraferon SPC with results of the long-term follow-up protocol to assess patients after completing 24 weeks of follow-up in a clinical trial for the treatment of chronic hepatitis C with Rebetol and Intron A.	23/02/2006	29/03/2006	SPC	This was a 5-year, long-term follow-up study of naïve or relapse subjects who completed the 24-week follow-up period in 1 of 6, placebo controlled treatment protocols comparing IntronA (non pegylated interferon alfa-2b)/Rebetol (ribavirin) combination therapy (for 24 or 48 weeks), with Intron A monotherapy (for 24 or 48 weeks) in naïve or relapse subjects. Long-term follow-up began at the Follow-Up Week 24 visit in the treatment protocol, ie, 6 months post-treatment. The results of the study confirm the durability of the virologic response up to 5 years. The likelihood of maintaining virologic response over 5 years in subjects who initially achieved a sustained response is 97% with a 95% Confidence Interval of [95%, 99%]. The limitations of the study (limited percentage of non responders that enter the long term study and high number of discontinuation), preclude any conclusion across initial treatment groups. Further, if the long-term clearance of the virus could be considered as a clinical 'cure' from chronic HCV, this does not preclude the occurrence of hepatic events related to progression of liver disease. This change in section 5.1 of the SPC applies to Rebetol and also to Intron A and Viraferon, both non pegylated Interferon alfa-2b.
II/0044	Update of or change(s) to the pharmaceutical documentation	23/02/2006	28/02/2006		

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II/0041	Update of Summary of Product Characteristics, Labelling and Package Leaflet	15/09/2005	27/10/2005	SPC, Labelling, PL	Summary / scientific discussion: The MAH applied for a type II variation, upon request by the CHMP, to update section 4.4 of the Summary of Product Characteristics with reference to dental and periodontal disorders and to expand the wording on psychiatric and CNS disorders. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to introduce in the Summary of Product Characteristics, Labelling and Package Leaflet the minor CHMP quality comments resulting from the recent renewal procedure and to update the "how to self-inject" instructions in the Package Leaflet of the multidose pen presentations. Section 4.4 of the SPC now states: 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 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.

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					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.
II/0040	Update of or change(s) to the pharmaceutical documentation	15/09/2005	23/09/2005		
R/0038	Renewal of the marketing authorisation	17/02/2005	23/05/2005	SPC, Labelling, PL	The CHMP was of the opinion that the quality, safety and efficacy of Viraferon continues to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of this medicinal product remains favourable.
II/0037	Change(s) to the manufacturing process for the finished product	20/01/2005	31/01/2005		
II/0032	Extension of Indication	21/10/2004	25/01/2005	SPC, PL	Chidren and adolescents with Chronic Hepatitis C: 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. Interferon alfa-2b 3 MIU/m2 is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or 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).

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					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/m2 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. Summary of Clinical Efficacy: Virological response in previously untreated paediatric patients Viraferon 3 MIU/m2 3 times a week +ribavirin 15 mg/kg/day Overall Response1 (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 Summary of Clinical Safety: 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

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					decrease of 13 %) percentile were observed during treatment. 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). 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. Thyroid Monitoring: Approximately 12 % of children treated with interferon alfa-2b and ribavirin developed increase in TSH during interferon alfa-2b treatment. 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. There are no data on long-term effects on growth and development and on sexual maturation.

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II/0034	Update of or change(s) to the pharmaceutical documentation	16/09/2004	28/10/2004	SPC, PL	The MAH applied for an update of the Plasma Master File (Viraferon powder formulation contains Human Serum Albumin as an excipient). In the context of this update, the MAH took the opportunity to amend the SPC and PL to comply with the "Note for Guidance on the warning on transmissable agents in SPCs and PLs for plasma-derived products (CPMP/BPWG/BWP/561/03)".
II/0036	Update of Summary of Product Characteristics, Labelling and Package Leaflet	29/07/2004	13/09/2004	SPC, Labelling, PL	The MAH applied to modify the safety information in the SPC of Intron A with the following: -Addition of cerebrovascular ischaemia and cerebrovascular haemorrhage in section 4.8 as requested by the CHMP following the assessment of a Follow-Up Measure concerning cerebral haemorrhage. -Addition of encephalopathy in section 4.4 and 4.8, hearing loss in section 4.8 and modification of the section regarding cardiac disorders in section 4.8 as requested by CHMP. -Addition of myositis, colitis and injection site necrosis in section 4.8 and modifications of the warning on graft rejection in section 4.4 as a harmonisation with peginterferon alfa. During this procedure the CHMP recommended to replace the existing contraindication in patients with existence of or history of severe psychiatric conditions by a warning in section 4.4. The PL has been updated accordingly. The MAH took this opportunity to include editorial changes and update the wording of the storage conditions in the SPC, PL and labelling in accordance with the latest templates. Additional minor changes were made to the SPC and PL, mainly sections 3 and 6.6, regarding the need for a colourless solution.
II/0035	Change(s) to the test method(s) and/or specifications for the active substance	29/07/2004	02/08/2004		

MINOR CHANGES[3]

No	Scope	Product Information affected[2]	Date[4]
IA/0060	08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	Annex II, PL	14/03/2008
IB/0046	36_a_Change in shape or dimensions of the container/closure - sterile ph. forms/biologicals		23/11/2005
IB/0045	36_a_Change in shape or dimensions of the container/closure - sterile ph. forms/biologicals		23/11/2005
IA/0043	28_Change in any part of primary packaging material not in contact with finished product		31/08/2005
IB/0042	20_c_Change in test procedure for an excipient - other changes		13/09/2005
IA/0039	09_Deletion of manufacturing site		08/12/2004
I/0033	Extension of shelf-life or retest period of the active substance		06/11/2003

[3] Minor changes e.g. Type I variations and Notifications
[4] Date of entry into force of the change