EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PegIntron

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification [1] issued on	Commission Decision issued [2] / amended on	Product Information affected [3]	Summary
T/0135	Transfer of Marketing Authorisation	17/07/2018	28/09/2018	SmPC, Labelling and PL	
WS/1384/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.d.1.a.4 - Stability of AS - Change in the re-test	07/06/2018	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol				
IG/0884	A.7 - Administrative change - Deletion of manufacturing sites	21/12/2017	n/a		
WS/1216	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	14/09/2017	n/a		
IG/0834	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	29/08/2017	n/a		
WS/1105	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on HCV/HBV co-infection and to add hepatitis B reactivation in HCV/HBV co-infected patients as an ADR, respectively, based on post marketing adverse experience. The Labelling and	22/06/2017	19/02/2018	SmPC, Annex II, Labelling and PL	Cases of hepatitis B re-activation (some with severe consequences) have been reported in patients co-infected with hepatitis B and C viruses treated with interferon. The frequency of such re-activation appears to be low. All patients should be screened for hepatitis B before starting treatment with interferon for hepatitis C; patients co-infected with hepatitis B and C must then be monitored and managed according to current clinical guidelines.

	Package Leaflet are updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to bring the PI in line with the latest QRD template version 10 including the implementation of the use of combined SmPCs and PLs for PegIntron and ViraferonPeg and the use of combined SmPCs for Intron A in multidose pen. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/2327/ 201607	Periodic Safety Update EU Single assessment - peginterferon alpha-2b	09/03/2017	n/a		PRAC Recommendation - maintenance
IG/0763/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	06/02/2017	19/02/2018	Annex II	
IG/0761	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	11/01/2017	n/a		

WS/0735	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.5 of the SmPC in order to include new information on the potential interactions of peginterferon alfa-2b with drugs metabolized by CYP1A2, CYP3A4, CYP2C9 and CYP2D6. In addition, the Worksharing applicant took the opportunity to make minor editorial changes to sections 4.8 and 5.1 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/07/2015	26/06/2016	SmPC	The potential interaction of peginterferon alfa 2b (PegIntron) on substrates of metabolic enzymes was evaluated in 3 multiple-dose clinical pharmacology studies. In these studies, the effects of multiple dose regimens of peginterferon alfa 2b (PegIntron) were investigated in Hepatitis C subjects (1.5 mcg/week) or healthy subjects (1 mcg/week or 3 mcg/week). A clinically significant pharmacokinetic interaction was not observed between peginterferon alfa 2b (PegIntron) and tolbutamide, midazolam or dapsone; therefore, no dosing adjustment is necessary when peginterferon alfa 2b (PegIntron) is administered with medicines metabolized by CYP2C9, CYP3A4 and N acetyltransferase. Concomitant administration of peginterferon alfa 2b (PegIntron) with caffeine or desipramine modestly increased the exposure of caffeine and desipramine. When patients are administered PegIntron with medications metabolized by CYP1A2 or CYP2D6, the extent of the decrease in cytochrome P 450 activity is unlikely to have a clinical impact, except with medicines which have a narrow therapeutic margin.
IG/0570	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/06/2015	26/06/2016	SmPC and PL	
WS/0611	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the Summary of Product Characteristics (SmPC) with updated information on homicidal ideation and in patients with cirrhosis and update in section 4.8 of the SmPC with pulmonary	25/06/2015	26/06/2016	SmPC and PL	The product SmPC has been revised with updated information on homicidal ideation and patients with cirrhosis in section 4.4 of the Summary of Product Characteristics (SmPC), and in section 4.8 of the SmPC pulmonary fibrosis has been added as post marketing adverse experience. The Package Leaflet and EU RMP have been revised accordingly.

	fibrosis added as post-marketing adverse experience. The Package Leaflet has been revised accordingly. In addition, minor linguistic revisions and update of local representatives for Luxemburg and Portugal have also been amended. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/0737/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	21/05/2015	n/a		
WS/0716	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	23/04/2015	n/a		
IG/0483	A.7 - Administrative change - Deletion of manufacturing sites	13/02/2015	n/a		

WS/0662	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	22/01/2015	n/a		
IG/0507	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	16/12/2014	n/a		
PSUV/0117	Periodic Safety Update	20/03/2014	22/05/2014	SmPC and PL	Please refer to: H-280-PSUV-117"Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation."
WS/0527/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. additional manufacturing and testing site for diluent B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological	25/04/2014	n/a		

	medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information				
WS/0429	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC with the adverse event of serous retinal detachment, based on a safety review requested in the 9th PSUR for IntronA. Furthermore, the PI is being brought in line with the latest QRD template version 9.0, and some minor linguistic corrections are included. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	21/11/2013	22/05/2014	SmPC, Annex II and PL	An overview of postmarketing surveillance for IFN and PEG-IFN involved a cumulative review of 54 adverse event reports with IFN and 57 adverse event reports with PEG-IFN of retinal detachment. A number of these reports are confounded with independent risk factors for the development of retinal detachment. Furthermore, retinal detachment is more common with increasing age, and many of the reports occurred in individuals over the age of 49 which is the peak age at which retinal detachment occurrs. Nevertheless, there were reports with no clear confounders and with ages below the peak incidence of retinal detachment. Therefore the term of “serous retinal detachment” has been included into the established ocular sections of sections 4.4 and 4.8 of the SmPC.
WS/0414	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Work-sharing procedure for ViraferonPeg and	21/11/2013	22/05/2014	SmPC and PL	To address the CHMP concern regarding the reversibility of growth inhibition observed in children treated with (pegylated) interferon, the MAH performed a long-term follow-up of study P02538 in children treated with peginterferon alfa-2b/ribavirin bitherapy.

	PegIntron to update of sections 4.1, 4.4, 4.8 and 5.1 of the SmPC with long-term follow-up safety and efficacy data on the durability of virologic response and growth amongst paediatric patients from study P02538, submitted in accordance with Article 46 of Regulation (EC) 1901/2006. Section 4 of the PL is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				The final results of this long-term follow-up confirm that height (linear growth) can be seriously affected by combination therapy with pegylated interferon/ribavirin, in particular in paediatric patients treated for 48 weeks or longer. Growth inhibition was observed that may be irreversible in some patients. As reflected in the product information, initiation of therapy in children who have not reached their adult height should be restrictive and carefully considered on a case-by-case basis.
IG/0366	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	08/11/2013	n/a		
N/0114	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/10/2013	22/05/2014	PL	Inclusion of additional local representative of the MAH for the new member state Croatia.
IG/0303/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	01/04/2013	n/a		
WS/0303/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Registration of a new pre-filled pen delivery device,	25/04/2013	30/05/2013	SmPC, Labelling and PL	

	introduction of a new push on needle and deletion of some pack-sizes. B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)				
IG/0225	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/02/2013	n/a		
IB/0110/G	This was an application for a group of variations. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	09/01/2013	n/a		
IB/0109	B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	01/10/2012	n/a		

WS/0216	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication to reflect the triple combination use of peginterferon alfa 2b, ribavirin and boceprevir in the treatment of Hepatitis C. In the labelling of Rebetol the use of "Lot" and "Exp" has been aligned in all languages. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	16/02/2012	26/03/2012	SmPC, Labelling and PL	Please refer to the Assessment Report: H-XXX-WS-216-AR
T/0106	Transfer of Marketing Authorisation	24/02/2012	19/03/2012	SmPC, Labelling and PL	
IG/0140	To change the address of the Marketing Authorisation Holder Schering -Plough Europe from 73, rue de Stalle, B-1180 Bruxelles, Belgium to Clos du Lynx 5, B-1200, Brussels, Belgium. In addition, MAH takes the opportunity to make minor editorial changes in Annex IIIA for Rebetol and Annex I in the Czech translation for Pegintron and ViraferonPeg. A.1 - Administrative change - Change in the name and/or address of the MAH	11/01/2012	19/03/2012	SmPC, Labelling and PL	
IG/0095	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	12/09/2011	n/a		

WS/0124	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Further to request of the CHMP On 16 December 2010, as part of a class-labelling change, the Product Information of ribavirin and the interferon-containing products is updated to remove from SmPC section 4.6 the requirement of double contraceptive measures for a treated woman and male patients, and to revise SmPC section 5.2 to reflect the results of the pharmacokinetic study related to transfer in seminal fluid. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	21/07/2011	24/08/2011	SmPC and PL	A review of reported relevant prospective cases of maternal and paternal exposure to ribavirin has been carried out. Only a limited number of cases are available. However, a large number of data would be necessary to draw a definitive conclusion on the teratogenic potential of ribavirin. The malformative risk is possible in human, but it is not confirmed. For paternal exposure, the malformative risk is unlikely in humans. Taking into account the number of reference cases outnumbering 300 after paternal exposure with no increase of congenital anomaly risk, it is recommended to remove the requirement of double contraceptive measures for a treated woman and male patient. For female patients, the CHMP agreed that they should be instructed to use an effective contraceptive. For male patients, the CHMP recommended that either male patients or their female partners of childbearing age must be advised to use an effective contraceptive. Furthermore the results of the pharmacokinetic study related to the transfer of ribavirin in seminal fluid are included in the SmPC.
WS/0110	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.3 and 4.5 to update the product information in line with Sebivo to reflect a contraindication for the use of interferon in combination with Sebivo. The PI is updated accordingly.	19/05/2011	29/06/2011	SmPC and PL	The efficacy and the safety of telbivudine in combination with 180 µg pegylated interferon alfa-2a once weekly was investigated in the Phase IIIb CLDT600A2406. An increased risk of peripheral neuropathy was observed with this combination. As a consequence the SmPC and PL for telbuvidine and pegylated interferon alfa 2a have been updated, contraindicating the combination of telbuvidine and standard or pegylated interferon alfa products. Due to the similarity of the two interferon alfa 2a and interferon alfa 2b products an increased risk of peripheral neuropaty

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				associated with the combination of interferon alfa 2b products cannot be ruled out. As such the CHMP has recommended that the prescribing information of all the interferon alfa containing products be adapted accordingly.
WS/0080	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC further to the evaluation of FUM regarding recommendations in patients with psychiatric disorders and substance abuse/use. The addresses of the local representatives are updated for Poland, Germany, Belgium, the Netherlands, Luxembourg Slovenia, Slovakia, Czech, Italy, Norway, Denmark, Romania and Austria. A number of editorial changes are made to the annexes. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	14/04/2011	15/06/2011	SmPC and PL	Interferon alfa-induced psychiatric adverse reactions still represent one of the major difficulties for the management of HCV-infected patients. In order to get a better insight to this issue, and to improve the information available to prescribers in SmPC of interferon-alfa containing products, the CHMP requested the MAH to provide yearly literature review on the management of psychiatric disorders in HCV-infected patients. This first literature review indicated that, as for patients with psychiatric disorders, patients with substance abuse/use need to be carefully managed with the aim of improving the adherence to therapy and the treatment success. It was noted that this issue was currently not addressed in the SmPC of interferon-alfa/ribavirin containing products as well as data on the management of patients with alcohol abuse. Thus, the recommendations in the product information for this sensitive population of patients have been updated.
N/0096	Update of the local representatives contact details in Bulgaria, Estonia, Greece, Spain, Ireland, Cyprus, Latvia, Lithuania, Malta, the Netherlands, Austria, Sweden and the United Kingdom. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/06/2011	n/a	PL	
WS/0079	This was an application for a variation following a worksharing procedure according to Article 20 of	20/01/2011	28/02/2011	SmPC	In study P02569 the safety and efficacy of peginterferon alfa-2b was evaluated as maintenance therapy for the

	Commission Regulation (EC) No 1234/2008. In fulfilment of the request from CHMP (FUM 082 PegIntron and FUM 080 ViraferonPeg) to update section 4.4 of the SmPC to include CHMP proposed statement in relation to the P02569 results.Editorial changes have been included in the Swedish Product Information. This application was submitted for a group of variations consisting of Type IB variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				prevention of disease progression in adult subjects with compensated cirrhosis (Metavir F4) who failed to respond to previous therapy with any interferon-alfa plus ribavirin. There results showed that there was no overall benefit to long-term low dose peginterferon alfa-2b treatment. This has been reflected in section 4.4 of the SmPC.
WS/0090	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change to the control of the active substance B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS	17/02/2011	17/02/2011		

IG/0037	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	13/01/2011	n/a		
II/0095	Update of SmPC sections 4.4 and 4.8 information related to growth inhibition and psychiatric side-effects in children. The MAH is also taking the opportunity to revise in the PIL the paragraph dedicated to HCV patients also HIV co-infected, for the sake of clarity/patient friendliness. Results of a user testing are reflected in the package leaflet. A QRD-related change has been made in the Annex II and the address of the Finnish respresentative has been updated in section 6 of the PL. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	23/09/2010	28/10/2010	SmPC, Annex II and PL	In the scope of the Renewal, the CHMP highlighted that growth inhibition is an important issue to be monitored. Information on growth retardation is already provided in the SPC section 4.4 but was not present in 4.8. As a consequence growth rate decrease (height and/or weight decrease for age)" has been included in section 4.8 of the SmPC. Furthermore the CHMP highlighted that an important issue arisen from previous PSURs is psychiatric adverse reactions. In the SmPC, this issue is already addressed in sections 4.3 and 4.4. However, in section 4.8, information on these adverse events in children was missing and as such has been inlcuded. Although suicidal ideation and/or attempts were not reported in the clinical trial of paediatric patients treated with peginterferon alfa-2b/ribavirin (P02538), suicidal ideation or attempts were reported among paediatric patients participating in the standard interferon/ribavirin clinical trials (P00018/P00321). Based on these reports, these terms have been included in the IntronA and Rebetol SmPCs in Section 4.8. For harmonization of the potential paediatric events that may occur when a pegylated interferon/ribavirin therapy is used, the terms suicidal ideation and suicide attempts have been added to section 4.8 of the SmPC. In the scope of these updates of safety information the package leaflet has been updated accordingly.
II/0094	Change in the manufacturing process of the active	24/06/2010	06/07/2010		

	substance including the introduction of a processing hold time in the active substance purification process. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol				
R/0093	Renewal of the marketing authorisation.	18/02/2010	05/05/2010	SmPC, Annex II, Labelling and PL	
II/0091	Changes in some testing methods of the drug substance Change(s) to the test method(s) and/or specifications for the active substance	19/11/2009	08/12/2009		
II/0087	Extension of the therapeutic indication of combination therapy peginterferon alfa-2b and ribavirin to include treatment of the paediatric population based on the results of Study P02538 Extension of Indication	24/09/2009	11/11/2009	SmPC and PL	Please refer to the scientific discussion: PegIntron-H-280-II-87-AR
II/0085	Extension of indication of peginterferon alfa-2b in combination with ribavirin for the treatment of adult patients with chronic hepatitis C who are positive for serum HCV-RNA, including patients with compensated cirrhosis based on the results of the IDEAL study. Extension of Indication	24/09/2009	11/11/2009	SmPC and PL	Please refer to the scientific discussion: PegIntron-H-280-II-85-AR

IA/0092	Deletion of a manufacturing site for the finished product IA_09_Deletion of manufacturing site	03/11/2009	n/a		
II/0090	Update of section 4.8 "Undesirable Effects" of the SPC to include adverse reactions further to assessment of PSUR 12 (period covered 25 July 2007 to 24 July 2008). The package leaflet is updated accordingly. The contact details for the local representatives in Bulgaria, Czech Republic, France, The Netherlands and Poland are updated. Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	03/08/2009	SmPC and PL	A cumulative review was carried out of safety data from clinical trials and post marketing data for the adverse reactions ketoacidosis, suicide, and congestive heart failure. Based on this review the term suicide is included in the SPC with a frequency of "uncommon", and the terms diabetic ketoacidosis and congestive heart failure are included with a frequency of "rare".
II/0089	To include an alternative source for a raw material source used in the fermentation process for the production of Interferon alfa-2b Drug Substance. Change to the test procedure and/or specification of a raw material	23/04/2009	06/05/2009		
II/0088	Change in the Interferon alfa-2b fermentation process Change(s) to the manufacturing process of the active substance	18/12/2008	05/01/2009		
II/0082	Update of section 4.2 and 5.1 of the SPC with data on the retreatment patients with of prior treatment failure from the final report of study P02370.	23/10/2008	05/12/2008	SmPC	In the final study report of P02370, the sustained virologic response based on the complete data set is nearly identical to that based on the first cohort (22% vs 23% for the interim

	Update of Summary of Product Characteristics and Package Leaflet				results). Of note is a low rate of response in non responders to a bitherapy including pegylated interferon who were re-treated by the same bitherapy. Section 5.1 has been updated accordingly. A statement has been included in section 4.2 to inform prescribers of the lack of data for peginterferon alfa-2b with ribavirin to substantiate the re-treatment of non-responder Genotype 1 patients for more than 48 weeks. This statement takes into account treatment recommendations for other pegylated interferons.
II/0086	To change the preparation and amount of a digestion enzyme used in an identification test of Interferon Alfa-2b Drug Substance Update of or change(s) to the pharmaceutical documentation	20/11/2008	28/11/2008		
II/0083	Update of Section 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the Summary of Product Characteristics (SPC) further to CHMP Request made in the context of the evaluation of PSUR 11, covering the period 25.07.2006 -24.07.2007, to include the following adverse reaction: pericardial effusion, pericarditis, bipolar disorders and mania. Other adverse reactions are added to section 4.8 to harmonise the SPC with the Company Core Data Sheet, United States Package Insert, and International Package Insert. The package leaflet is updated accordingly. In addition the details of the local representatives are updated in the package leaflet for the following countries: Poland, Bulgaria, Finland and Austria.	25/09/2008	31/10/2008	SmPC and PL	Based on a cumulative review covering the period up until 31 December 2007 and data from the literature a causal relationship could not be excluded between pegylated interferon alfa 2b and the adverse reaction "pericarditis". Pericarditis is serious and may be fatal if diagnosis is delayed, therefore, in order to increase physicians awareness this adverse reaction has been included in section 4.8 of the SPC. A cumulative search was carried out for all reports of bipolar disorder up until 31 December 2007. The data from this review, together with abundant data from the literature, suggest that treatment with interferon alpha 2b may induce mania and bipolar disorders, especially in patients with predisposing factors such as previous psychiatric history, substance use disorders or family history of bipolar disorders.

	Update of Summary of Product Characteristics and Package Leaflet				As such section 4.4 and 4.8 of the SPC has been updated to inform doctors prescribing IFN treatment and doctors treating patients with bipolar disorders and mania of this risk.
IA/0084	IA_09_Deletion of manufacturing site	23/07/2008	n/a		
II/0080	Update of section 4.9 "Overdose" of the SPC further to a request of the CHMP made in the context of the assessment of PSUR 11. The MAH also takes the opportunity to make an amendment to section 9 "Date of the first authorisation/renewal of the authorisation" of the SPC for some strengths of PegIntron to correctly reflect the date of the initial marketing authorisation. Update of Summary of Product Characteristics	30/05/2008	10/07/2008	SmPC	A cumulative search for overdose cases that occurred in patients taking peginterferon alfa-2b up until 24 January 2008 was conducted. Of the 68 cases reporting an overdose of peginterferon alfa-2b there were three cases of note: one was with a potential overdose of 10.5 times the intended dose (about 500 mcg), one of 7.5 times the dose (1200 mcg) and one of 5 times the dose (600 mcg, taken over a 5-day period). There were an additional seven cases reported in patients taking between 300 and 575 mcg (2 to 4 times the intended dose), with a maximum of four times the intended dose administered Based on a review of these cases, the majority of reported events resulting from an overdose of up to 10.5 times the intended dose were generally events that are part of the known spectrum of pharmacologic effects of alfa interferons but perhaps were of greater severity than the adverse events reported for peginterferon alfa-2b during therapeutic use. The SPC has been updated to reflect this.
II/0077	Change(s) to the test method(s) and/or specifications for the active substance	30/05/2008	11/06/2008		
IA/0081	IA_08_b_01_Change in BR/IPC testing - repl./add. manuf. responsible for BR/IPC testing incl. BC/testing	21/05/2008	n/a	Annex II and PL	

II/0079	Update of sections 4.4 and 4.5 of the SPC with a warning regarding the concomitant use of ribavirin with zidovudine in HCV/HIV co-infected patients. The package leaflet is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	21/02/2008	14/04/2008	SmPC and PL	Data from the pivotal studies conducted in HIV/HCV coinfected patients as well as published data consistently show a higher risk of anaemia when ribavirin and zidovudine are co-administered. Anaemia is the primary cause for ribavirin dose reduction. Since ribavirin dose reduction may negatively impact Sustained Virologic Response, risk factors for anaemia such as concomitant use of zidovudine is a cause of concern on a safety but also efficacy point of view. As such the product information is revised to include a warning to prescribers that the concomitant use of ribavirin with zidovudine is not recommended and to highlight the associated risk of anaemia.
II/0078	Update of section 5.1 of the SPC with the results of a long-term follow-up study to assess the sustained virological response after the treatment of chronic hepatitis C. Update of Summary of Product Characteristics	21/02/2008	14/04/2008	SmPC	This was a multicenter, long-term follow-up study of subjects with chronic hepatitis C (HCV) who had been treated in a prior study with peginterferon alfa-2b (with or without ribavirin). This study aimed to assess the durability of virologic response and to assess HCV disease progression. Overall 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 99 % (95 % CI: 98-100 %). However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).
II/0076	Update of Summary of Product Characteristics and Package Leaflet	13/12/2007	28/01/2008	SmPC and PL	
II/0074	Update of section 4.5 of the SPC to delete information regarding the in vitro inhibition of the zidovudine and stavudine phosphorylation by ribavirin.	20/09/2007	30/10/2007	SmPC	The CHMP questioned the existing wording pertaining to the in vitro inhibition of the zidovudine and stavudine phosphorylation by ribavirin in section 4.5 of the SPC as some published data suggested that this in vitro interaction

	Update of Summary of Product Characteristics				had no clinical relevance. In two clinical studies in HCV-HIV coinfected patients co-administration of ribavirin with zidovudine or stavudine did not significantly affect the intracellular phosphorylation of these NRTIs in vivo. Furthermore there is evidence that ribavarin does not negatively interfere with antiviral efficacy in HIV infection. As this in vitro interaction has no clinical impact the CHMP agreed to delete the entire existing paragraph referring to this interaction from section 4.5 of the SPC.
II/0072	Following the assessment of PSUR 10, covering the period from 26 November 2005 to 24 July 2006, section 4.8 of the SPC is updated with the addition of "Anaphylactic reactions, including Anaphylactic shock" and "facial palsy" upon request of the CHMP. In addition the MAH was requested to update the section 4.8 in line with the SPC guideline and the MedRA terminology. Section 4 of the package leaflet is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	30/10/2007	SmPC and PL	During the assessment of PegIntron PSUR 10 covering the period 26 November 2005 to 24 July 2006, it was noted that cumulatively there were 22 reports of anaphylactic reactions, including 4 cases of anaphylactic shock and 86 of medically confirmed cases of facial palsy. Therefore the adverse reactions "facial palsy" and "anaphylactic reactions, including anaphylactic shock" have been included in section 4.8 of the SPC. In addition, the section 4.8 was reformatted with the SPC guideline and the MedRA terms.
II/0069	Extension of the therapeutic indication of peginterferon alfa 2b in combination with ribavirin to include treatment of adult patients who failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy or interferon monotherapy. The MAH also takes the opportunity to update the details of the local representative for Sweden in the package leaflet.	20/09/2007	30/10/2007	SmPC and PL	This will refer to the scientific discussion of this assessment report.

	Extension of Indication				
II/0073	Change(s) to the test method(s) and/or specifications for the active substance	20/09/2007	27/09/2007		
IB/0075	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	17/08/2007	n/a		
II/0068	Extension of Indication	26/04/2007	13/06/2007	SmPC and PL	
II/0070	Change(s) to shelf-life or storage conditions	22/02/2007	28/02/2007		
N/0071	The MAH completed the list of local representatives in the PL to include the two new EU Member States (Bulgaria and Romania) according to the latest EMEA/QRD template. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/01/2007	n/a	PL	
II/0067	Update of section 4.5 of Summary of Product Characteristics with the results of a study on the effect of Pegintron treatment on the pharmacokinetics of methadone and a related warning for patients monitoring. Update of Summary of Product Characteristics	21/09/2006	23/10/2006	SmPC	This variation concerns an up date of section 4.5 of the SPC following the results of a study to determine the effect of Pegintron treatment on the pharmacokinetics of methadone. This study was carried out because some individuals who have previously used injected narcotics and subsequently take methadone have been identified as being infected with hepatitis C. Therefore these patients may be candidates for therapy with PegIntron/ViraferonPeg. The results demonstrate a small (about 15% to 19%) increase in the AUC and Cmax of methadone at addition of Pegintron therapy. The clinical significance of this increase is not known, however the CHMP concluded that it appears relevant

					to include in the SPC a warning to monitor patients for signs and symptoms of increased sedative effect.
II/0066	Update of section 4.2 "Posology and method of administration" of the Summary of Product Characteristics with a mention related to careful monitoring for anaemia in patients with impaired renal function. Section 2 of the Package Leaflet is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	23/10/2006	SmPC and PL	Data exploring the relationship between estimated creatinine clearance and Hb decrease in the pivotal Pegintron/ribavirin combination trial show an increased risk of anaemia with reduced kidney function. The CHMP therefore agreed to include a mention in section 4.2 that when Pegintron is administered in combination with ribavirin, subjects with impaired renal function should be more carefully monitored with respect to the development of anaemia.
II/0064	Update of section 4.8 "Undesirable effects" of the SPC with the addition of the adverse reaction pure red cell aplasia. The package leaflet has been updated accordingly. The MAH also takes the opportunity to update the contact details of the local representatives for Lithuania in the package leaflet. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	01/09/2006	SmPC and PL	This variation is submitted further to the CHMP conclusions on ribavirin FUM 25 in which a cumulative review of pure red cell aplasia (PRCA) was requested to determine the number of reported cases and further characterize 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 aplasia, although remaining limited, increased since the last safety review on this issue (FUM 25 dated 7th April 2005). As a result of this 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 PegIntron.
II/0063	Update of section 4.4 of the SPC of PegIntron further to the adoption of a class labelling for psychiatric	28/06/2006	19/07/2006	SmPC and PL	Following a safety review on suicide and attempted suicide Section 4.4 of the SPCs of a number of the interferon alfa-2b

	disorders by the CHMP on 23 March 2006. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				products and ribavarin were updated to include a warning on the duration of psychiatric disorders. This update took place in September 2006. 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 of these products it was not possible to propose a class labelling "text" for all these products. Rather the existing paragraphs pertaining to psychiatric disorders in the SPCs and Package Leaflets have been moved to the beginning of the corresponding sections and placed in a warning box in order to draw attention to these serious effects.
IB/0062	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	24/05/2006	n/a		
II/0061	Update of sections 4.6 of the SPC with regard to recommendations on pregnancy and lactation and section 4.2 and 4.3 to harmonise with the Interferons regarding presentation of information, further to the adoption by the CHMP on 26th January 2006 of a class labelling for the Interferons and ribavirin on pregnancy and lactation. Corresponding revisions to the Package Leaflet are made. Update of Summary of Product Characteristics and Package Leaflet	27/04/2006	19/05/2006	SmPC and 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 during treatment and for 7 months after treatment discontinuation in male patients and their female partners. Section 4.6 "Pregnancy and Lactation" of the SPC of Pegintron has therefore been up dated to add the seven month duration of contraception after treatment termination for male patients and their female partners when alfa-Interferon is used in combination with

					Ribavarin. Regarding lactation a minor change to the existing wording in section 4.6 "Pregnancy and Lactation" has been made to reflect the fact that although lactation is not recommended, it is not subject to a contraindication when alfa-Interferon is used without Ribavarin. The presentation of information in Section 4.2 and 4.3 have been harmonised as regards the contraindication for Pegintron when used in combination with Ribavarin. This change does not affect the content of the SPC, rather the presentation.
II/0059	Update of Summary of Product Characteristics and Package Leaflet	23/03/2006	27/04/2006	SmPC and PL	
II/0060	Quality changes	23/03/2006	27/03/2006		
II/0056	Update of Summary of Product Characteristics and Package Leaflet	15/09/2005	15/11/2005	SmPC and PL	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, section 4.4 to expand the wording on psychiatric and CNS disorders and sections 4.3 and 4.6 to delete the contraindication for the use of Pegintron/ViraferonPeg during pregnancy and lactation. The Package Leaflet has been updated accordingly. Section 4.4 of the SPC states: Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. 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 PegIntron be discontinued, and the patient followed, with psychiatric intervention as appropriate. Patients with existence of, or history of severe psychiatric conditions: If treatment with peginterferon alfa-2b is judged necessary in 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. Dental and periodontal disorders: Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could ha
II/0053	Update of Summary of Product Characteristics and Package Leaflet	15/09/2005	15/11/2005	SmPC and PL	The MAH applied to update sections 4.2, 4.3 and 5.2 of the SPC concerning information regarding patients with renal impairment. The Package Leaflet has been updated accordingly. Following multiple dosing of PegIntron (1.0 microgram/kg subcutaneously administered every week for four weeks) the

					clearance of PegIntron is reduced by a mean of 17 % in patients with moderate renal impairment (creatinine clearance 30-49 ml/minute) and by a mean of 44 % in patients with severe renal impairment (creatinine clearance 15-29 ml/minute) compared to subjects with normal renal function. Based on single dose data, clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving hemodialysis. The dose of PegIntron for monotherapy should be reduced in patients with moderate or severe renal impairment. Patients with creatinine clearance <50 ml/minute must not be treated with PegIntron in combination with ribavirin. Because of marked inter-subject variability in interferon pharmacokinetics, it is recommended that patients with severe renal impairment be closely monitored during treatment with PegIntron. The SPC recommendations on use in patients with renal impairment are as follows: Monotherapy: PegIntron should be used with caution in patients with moderate to severe renal impairment. In patients with moderate renal dysfunction (creatinine clearance 30-50 ml/minute), the starting dose of PegIntron should be reduced by 25 %. Patients with severe renal dysfunction (creatinine clearance 15-29 ml/minute) should have the starting dose of PegIntron reduced by 50 %. Data are not available for the use of PegIntron in patients with creatinine clearance < 15 ml/minute. Patients with severe renal impairment, including those on hemodialysis, should be closely monitored. If renal function decreases during

					treatment, PegIntron therapy should be discontinued. Combination therapy: Patients with creatinine clearance < 50 ml/minute must
II/0055	Update of or change(s) to the pharmaceutical documentation	15/09/2005	23/09/2005		
II/0054	Update of Summary of Product Characteristics	28/07/2005	08/09/2005	SmPC	Please refer to the Scientific discussion: "Pegintron-H-280-II-54".
IB/0057	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	05/09/2005	n/a		
IA/0058	IA_28_Change in any part of primary packaging material not in contact with finished product	31/08/2005	n/a		
R/0051	Renewal of the marketing authorisation.	16/03/2005	25/05/2005	SmPC, Annex II, Labelling and PL	
II/0050	Update of Summary of Product Characteristics	17/02/2005	22/03/2005	SmPC	The MAH applied for a type II variation to update Section 4.5 of the SPC further to the submission of the final report on the study "effects of multiple-dose PegIntron (SCH 54031 peginterferon alfa-2b) on the activity of drug metabolizing enzymes in volunteers with chronic Hepatitis C". This study showed that patients receiving once weekly PegIntron (1.5 µg/kg) for 4 weeks demonstrated an increase in activity of CYP2D6 and CYP2C8/9. No change in activity of CYP1A2, CYP3A4, or N-acetyltransferase was observed. Caution should be used when administering peginterferon

					alfa-2b with medications metabolised by CYP2D6 and CYP2C8/9, especially those with a narrow therapeutic window, such as warfarin and phenytoin (CYP2C9) and flecainide (CYP2D6). These findings may partly relate to improved metabolic capacity due to reduced hepatic inflammation in patients undergoing treatment with PegIntron. Caution is therefore advised when PegIntron treatment is initiated for chronic hepatitis in patients treated with medication with a narrow therapeutic window and sensitive to mild metabolic impairment of the liver.
II/0049	Change(s) to the manufacturing process for the active substance	17/02/2005	21/02/2005		
IA/0052	IA_09_Deletion of manufacturing site	20/01/2005	[illegible]a		
II/0048	Update of Summary of Product Characteristics and Package Leaflet	16/09/2004	20/10/2004	SmPC, Annex II, Labelling and PL	The MAH applied to modify the safety information in the SPC of Pegintron 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 a statement regarding cardiac disorders in section 4.8 (harmonisation with IntronA); - Addition of a statement regarding CNS disorders and addition of hypersensitivity terms in section 4.4; - Addition of "encephalopathy" in sections 4.4 and 4.8 and addition of "interstitial lung disease" in section 4.8 as requested by CHMP. During this procedure the CHMP recommended to replace the

					existing contra-indication in patients with existence of or history of severe psychiatric conditions by a warning in section 4.4. Further, the MAH took the opportunity to include minor changes to section 6.6 regarding the need for a colourless solution. The PI has been updated accordingly.
II/0042	Change(s) to the manufacturing process for the finished product	16/09/2004	22/09/2004		
II/0045	Update of Summary of Product Characteristics and Package Leaflet	23/06/2004	23/08/2004	SmPC, Labelling and PL	Please refer to the Scientific discussion: "Pegintron-H-280-II-45".
II/0047	Change(s) to the test method(s) and/or specifications for the active substance	29/07/2004	02/08/2004		
N/0046	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/05/2004	n/a	PL	
II/0044	Change(s) to shelf-life or storage conditions	21/01/2004	16/03/2004	SmPC	The MAH applied to extend the shelf-life of the finished product (pre-filled pen presentations) from 24 to 36 months.
II/0041	Change(s) to the manufacturing process for the finished product	26/02/2004	05/03/2004		
II/0043	Change(s) to the test method(s) and/or specifications for the finished product	21/01/2004	10/02/2004		
II/0038	Update of Summary of Product Characteristics and Package Leaflet. Change to Section 4.4 and 4.8 of the	20/11/2003	05/02/2004	SmPC and PL	Changes to Sections 4.4 and 4.8 were made following the 5th PegIntron PSUR.

	SPCCorresponding changes were made to the Package Information Leaflet. The applicant took the opportunity to make very minor linguistic corrections to the SPC and PL in certain languages. Update of Summary of Product Characteristics and Package Leaflet				The use of interferon alpha in patient undergoing solid organ transplantation is controversial and has been debated over the years as Chronic Hepatitis C (CHC) regularly recurs after liver transplantation and concomitant CHC is common in patients undergoing renal transplantation. Based on case series, there seems to be an increased risk for rejection in patients with kidney grafts, but, surprisingly, no such tendencies have been reported (or actually refuted) in patients with liver grafts. Following reports of several cases of liver transplant rejection in the PSUR, the following warning was added to Section 4.4 of the SPC: "Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for treatment of hepatitis C in liver or other organ transplant recipients have not been studied. 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. Based on an analysis of safety data, the adverse reactions: rhabdomyolysis/myositis, renal insufficiency and renal failure were added as rare reactions. Ulcerative and ischaemic colitis and aplastic anaemia were added as very rare reactions.
I/0040	20a_Extension of shelf-life or retest period of the active substance	06/11/2003	13/11/2003		
IB/0039	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	31/10/2003	n/a	SmPC	

II/0036	Update of Summary of Product Characteristics and Package Leaflet. Change to Section 4.2 SPC (Posology and method of administration) to include dosing tables. The applicant took the opportunity to update Annex IIIA according to the last EMEA/QRD templates, and to correct errors, make linguistic corrections and change a telephone number in Annex IIIB. Update of Summary of Product Characteristics and Package Leaflet	24/07/2003	24/10/2003	SmPC, Labelling and PL	Dosing tables were added to section 4.2 of the SPC to provide advice on the recommended strength and volume of PegIntron to be injected based on the patient's body weight. Retrospective analysis of clinical data showed that the response to treatment was correlated with body weight in that lighter patients had a better response than heavier patients. As a result of this, the clinical trials of PegIntron/ViraferonPeg used dosages based on body weight. Results from the PegIntron/ViraferonPeg monotherapy study confirmed that when dosing is based on body weight, body weight is no longer a predictive factor for response. Therefore being able to titrate the dose according to the individual patient's weight is important for efficacy. The currently authorised formulations of PegIntron include 5 vial and pen strengths: 50, 80, 100, 120 and 150 µg/0.5 ml. Although the physician is advised on the appropriate dose per kg, no guidance is given on what strength to prescribe or the amount the patient needs to inject to obtain the required dosage. There is an additional complication in that the dosing recommendations for PegIntron when used in combination with Rebetol are 1.5 µg/kg/week whilst in monotherapy the dose is either 0.5 or 1.0 µg/kg/week. If a reduced dose is necessary because of adverse events, the current recommendations are to reduce the PegIntron dose by half but again no recommendations as to how this is to be achieved are given. The tables which have been added to section 4.2 of the SPC provide information on suggested strengths and volume for

					injection when PegIntron is used in combination therapy at a dose of 1.5 µg/kg and also for the 1.0 µg/kg and 0.5 µg/kg PegIntron dose when used as monotherapy. The tables for combination therapy also provide guidance on Rebetol posology. Achievement of target doseWith full dose combination therapy, using the tables provided, the amount to be injected is either 0.4ml or 0.5ml which enables the delivered
II/0035	Update of Summary of Product Characteristics and Package Leaflet. Change to Section 4.1 and 4.4 of the SPC regarding the need for histology before treatment commencement. Update of Summary of Product Characteristics	26/06/2003	02/10/2003	SmPC	The CPMP requested that the term "histologically proven" be removed from the indication of all the centrally authorised alfa interferons and an appropriate warning added to section 4.4 of the SPC. In the French Consensus Conference on Hepatitis C it is stated that biopsy may not be necessary if a decision to treat has been made on other grounds and the primary objective is viral eradication. This is also largely in line with other National Guidelines. The viral eradication rate is sufficiently high for patients with genotype 2/3 that treatment is indicated in many cases even if the histology turns out to be benign. Therefore histology is not always needed. In the French Consensus Conference on Hepatitis C it is stated that biopsy may not be necessary if a decision to treat has been made on other grounds and the primary objective is viral eradication. This is also largely in line with other National Guidelines. The viral eradication rate is sufficiently high for patients with genotype 2/3 that treatment is indicated in many cases even if the histology turns out to be benign. Therefore histology is not always needed.

II/0037	Change(s) to the test method(s) and/or specifications for the active substance	25/09/2003	30/09/2003		
I/0034	12_Minor change of manufacturing process of the active substance	26/06/2003	14/07/2003		
N/0033	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/04/2003	14/05/2003	PL	
II/0032	Change(s) to the test method(s) and/or specifications for the finished product	19/03/2003	02/04/2003		
II/0028	Update of Summary of Product Characteristics and Package Leaflet. Changes to sections 4.2, 4.4, 4.6, 4.8 and 5.1 of the SPC along with changes to the list of local representatives and minor template changes. Corresponding changes were made to the Package Information Leaflet. Update of Summary of Product Characteristics and Package Leaflet	18/12/2002	17/03/2003	SmPC and PL	This variation refers to changes to sections 4.2, 4.4. 4.6. 4.8 and 5.1 of the SPC. Changes were made to section 4.2 and section 5.1 to include information on the predictability of sustained virological response with recommendations for treatment duration. During a concurrent scientific advice procedure, the MAH presented data that a reliable decision regarding treatment discontinuation can be made at 3 months. Patients who fail to achieve virological response after 12 weeks treatment are highly unlikely to become sustained virological responders (negative predictive value 100% for combination therapy, 98% for monotherapy). For patients with genotype 1 who are responders at week 12, combination therapy should be continued for another 9 months. All patients with genotype 2 or 3 achieved virological response following 12 weeks of combination therapy. These patients should be treated for a total of 6 months with the decision to extend therapy to one year

					based on prognostic factors such as age, sex and bridging fibrosis. For patients on PegIntron monotherapy, responders at 12 weeks should have treatment continued for at least a further 3 months with the decision to extend therapy to one year of treatment based on the above prognostic factors.Sections 4.4 and 4.8 of the SPC were updated with regard to ophthalmological disorders. The current SPC already contained a warning in section 4.4 regarding ophthalmic symptoms and the need for eye examination. Section 4.4 was strengthened to advise that all patients should have a baseline eye examination and that periodic eye examinations were recommended, particularly in patients with disorders associated with retinopathy. Discontinuation of PegIntron should be considered in patients who developed new or worsening ophthalmological disorders. In section 4.8 the terms: retinopathies, retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic
I/0031	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	09/12/2002	13/12/2002		
N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 notification)	18/10/2002	26/11/2002	PL	
I/0027	17_Change in specification of the medicinal product	25/09/2002	08/10/2002		

I/0026	15_Minor changes in manufacture of the medicinal product	19/09/2002	27/09/2002		
I/0029	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	10/09/2002	24/09/2002		
II/0023	Change(s) to the test method(s) and/or specifications for the active substance	25/07/2002	30/07/2002		
I/0022	20_Extension of shelf-life as foreseen at time of authorisation	07/06/2002	19/07/2002	SmPC	
II/0020	Change(s) to the test method(s) and/or specifications for the finished product	30/05/2002	24/06/2002		
II/0019	Change(s) to the manufacturing process for the finished product	30/05/2002	24/06/2002		
I/0021	12_Minor change of manufacturing process of the active substance	30/05/2002	24/06/2002		
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/06/2002	15/07/2002	PL	
N/0024	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/06/2002	11/07/2002	Labelling	
II/0015	Update of Summary of Product Characteristics and Package Leaflet	15/11/2001	07/05/2002	SmPC and PL	
I/0018	14_Change in specifications of active substance	26/03/2002	08/04/2002		

I/0017	20a_Extension of shelf-life or retest period of the active substance	28/02/2002	04/03/2002		
X/0014	X-3-iv_Change or addition of a new pharmaceutical form	20/09/2001	06/02/2002	SmPC, Annex II, Labelling and PL	
II/0013	Update of or change(s) to the pharmaceutical documentation	20/09/2001	15/10/2001		
I/0016	20a_Extension of shelf-life or retest period of the active substance	01/06/2001	n/a		
II/0001	Extension of Indication	13/12/2000	26/03/2001	SmPC and PL	
I/0012	24_Change in test procedure of active substance	04/01/2001	n/a		
I/0011	14_Change in specifications of active substance	19/12/2000	n/a		
I/0010	14_Change in specifications of active substance	19/12/2000	n/a		
I/0009	14_Change in specifications of active substance	19/12/2000	n/a		
I/0007	14_Change in specifications of active substance	19/12/2000	n/a		
I/0006	14_Change in specifications of active substance	19/12/2000	n/a		
I/0005	30_Change in pack size for a medicinal product	10/08/2000	16/11/2000	SmPC and Labelling	
I/0004	20_Extension of shelf-life as foreseen at time of authorisation	11/08/2000	16/11/2000	SmPC and Labelling	

I/0008	14_Change in specifications of active substance	19/10/2000	n/a		
II/0002	Change(s) to the manufacturing process for the active substance	28/08/2000	14/09/2000		
I/0003	12_Minor change of manufacturing process of the active substance	28/08/2000	n/a		