IntronA

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
IB/0122	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/06/2021		SmPC, Annex II, Labelling and PL	
N/0121	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/12/2019	15/10/2020	Labelling and PL	

[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).

IB/0120	C.I.7.a - Deletion of - a pharmaceutical form	22/10/2019	15/10/2020	SmPC, Labelling and PL	
IB/0119	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	13/06/2019	n/a		
IG/1088	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	05/04/2019	n/a		
N/0117	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/01/2019	15/10/2020	Labelling	
T/0116	Transfer of Marketing Authorisation	17/07/2018	28/09/2018	SmPC, Labelling and PL	
IB/0115/G	This was an application for a group of variations. 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 B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	18/05/2018	n/a		

IG/0884	A.7 - Administrative change - Deletion of manufacturing sites	21/12/2017	n/a		
PSUSA/1758/ 201609	Periodic Safety Update EU Single assessment - interferon alpha-2b	22/06/2017	28/09/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1758/201609.
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 Package Leaflet are updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to bring the PI in line with the latest QRD	22/06/2017	28/09/2017	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.

	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				
II/0110	Update of section 4.8 of the SmPC in order to add pericarditis with the frequency uncommon based on continuous monitoring of the safety profile; the Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/06/2017	28/09/2017	SmPC and PL	
IA/0111	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	28/04/2017	n/a		
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	06/02/2017	22/05/2017	Annex II	

	(excluding manufacturer for batch release)				
IB/0106/G	This was an application for a group of variations. 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.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes 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.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within	15/12/2015	22/05/2017	SmPC, Labelling and PL	

	the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
IAIN/0105	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	09/10/2015	22/05/2017	SmPC, Labelling and PL	
IG/0570	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/06/2015	22/05/2017	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 for patients with cirrhosis and update in section 4.8 of the SmPC with pulmonary 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.	25/06/2015	22/05/2017	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.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0102/G	This was an application for a group of variations. 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	19/02/2015	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		

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	05/03/2014	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.
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		
IA/0094/G	This was an application for a group of variations. B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the	03/09/2013	n/a		

	dossier) - Replacement or addition of a supplier 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)				
IA/0093/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 A.7 - Administrative change - Deletion of manufacturing sites	26/07/2013	n/a		
N/0092	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/07/2013	05/03/2014	PL	Inclusion of additional local representative of the MAH for the new member state Croatia. In addition minor corrections to the FR and PT were included to align the annexes.
II/0090	Update of sections 4.1, 4.4 and 4.8 of the SmPC based on long-term follow-up data on the reversibility of growth inhibition, which was assessed in follow-up measure FU2 041.3 (parental height collection in study P01906). Additionally, the MAH revised the illustrations in the "How to self-inject IntronA" section of the PL for the 30 and 60 million IU pens (Diagram N) for improved clarity to the patient. In addition, the MAH took the opportunity to update the list of local representatives for Czech Republic, Greece, Malta, Netherlands, Portugal and Slovakia in the Package Leaflet. The PI was also	21/03/2013	05/03/2014	SmPC, Annex II, Labelling and PL	To address a CHMP request to investigate the reversibility of growth inhibition observed in children treated with interferon alfa-2b plus ribavirin, the MAH has collected the heights of paediatric patients who had experienced possible growth retardation following treatment and of their biological parents 10-12 years after the end of therapy. While the majority (12/14) of the patients for whom data was available had current heights considered to be within the normal range (5th to 95th percentile), there was still an impact of treatment on the height achieved 10 to 12 years after the end of therapy, with 12 out of 14 patients still showing a height deficit >15 percentiles as compared to

	brought in line with the latest QRD template version 8.3. 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				baseline. Based on these data, the statement that "the reversibility of growth inhibition is uncertain" in sections 4.1, 4.4 and 4.8, which was based on a long-term follow-up of five years, was replaced by a clear message that growth inhibition "results in reduced final adult height in some patients".
IG/0225	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/02/2013	n/a		
IB/0089	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		
T/0083	Transfer of Marketing Authorisation	28/09/2011	24/10/2011	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	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

	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				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 PL is updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	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 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	16/06/2011	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/0082	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/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	17/02/2011	17/02/2011		

	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				
N/0081	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2010	n/a	PL	
IB/0080/G	This was an application for a group of variations. 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 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	20/08/2010	n/a	SmPC and PL	To add an introduction statement to the current indication related to CHC in the SmPC section 4.1. To update the SmPC and PL to remove Raynaud's disease from the list of undesirable effects. Furhermore the MAH took this oportunity to update the contact details of the local representatives in Sweden and Finland.
II/0078	To change in the manufacturing process of the active 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	24/06/2010	06/07/2010		

	product and is not related to a protocol				
IB/0079	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	21/06/2010	n/a	SmPC and PL	
II/0077	Update of Summary of Product Characteristics	18/02/2010	26/03/2010	SmPC	
R/0073	Renewal of the marketing authorisation.	17/12/2009	15/03/2010	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of IntronA continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation for IntronA with unlimited validity.
II/0076	Changes in the integrity filter testing. Change(s) to the test method(s) and/or specifications for the active substance	18/02/2010	03/03/2010		
II/0074	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/0075	To change the shelf life from 18 months to 15 month for the multi dose pen presentations. Change(s) to shelf-life or storage conditions	22/10/2009	19/11/2009	SmPC	
II/0065	Update of Summary of Product Characteristics with the results of the long term follow-up study (P01906) conducted in Paediatric patients. The Package Leaflet is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	12/11/2009	SmPC and PL	Study P01906 was a 5 year follow up study to assess the durability of virologic response and clinical progression of liver disease in paediatric subjects ages 3-16 previously treated with interferon alfa-2b in combination with ribavirin. The long term data are indicative of substantial decrease in height percentile growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children despite being off treatment for more than 5 years. When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition. The reversibility of growth inhibition is uncertain.
II/0072	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	07/05/2009		
II/0070	Change in the integrity testing of the product filter during sterilisation filtration step of the manufacturing process for IntronA multidose pen Update of or change(s) to the pharmaceutical documentation	19/02/2009	09/03/2009		

II/0069	Update of section 4.8 "Undesirable Effects" of the SPC with a statement on pancytopenia and the addition of the adverse reaction "homicidal ideation" further to a cumulative review. The package leaflet is updated accordingly. The address of the Czech local representative is updated in the package leaflet. Update of Summary of Product Characteristics and Package Leaflet	22/01/2009	06/03/2009	SmPC and PL	A total of 139 cases of pancytopenia were identified further to a cumulative search conducted by the MAH up to 29 February 2008. A statement concerning pancytopenia has as such been reflected in the product information. Furthermore the MAH carried out a cumulative search for cases of homicidal ideation up to 11 July 2008. The search identified 334 case reports. This adverse reaction has been reflected in the product information.
IB/0071	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	09/02/2009	n/a	SmPC	
II/0066	Update of section 4.8 of the SPC to include the adverse reaction peripheral neuropathy, bacterial infection and sepsis further to a review of available safety data. Section 4.4 and 4.8 were updated regarding psychiatric adverse reactions in line with other interferons. The package leaflet is updated accordingly. The contact details of the local representatives are updated in the package leaflet for the following countries: Austria, Bulgaria, Finland, France and Poland. Update of Summary of Product Characteristics and Package Leaflet	20/11/2008	09/01/2009	SmPC and PL	A cumulative search of the safety database of the Marketing Authorisation Holder up until the 29 February 2008 identified 314 cases of bacterial infection (including sepsis) and 284 cases of peripheral neuropathy. The SPC now reflects "peripheral neuropathy" and "bacterial infection" under the frequency categories "uncommon" and sepsis under the frequency category "rare". To be in line with the SPC of other inferferon containing products the adverse reactions bipolar disorder and mania have also been added to the SPC.
II/0068	Change in the Interferon alfa-2b fermentation process Change(s) to the manufacturing process for the	18/12/2008	05/01/2009		

	active substance				
II/0067	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	02/12/2008		
II/0063	Update of section 5.1 "Pharmacodynamic Properties" of the Summary of Product Characteristics (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 IntronA. The details of the Romanian local representative are updated in the Package leaflet. Update of Summary of Product Characteristics and Package Leaflet	19/03/2008	22/04/2008	SmPC and PL	In the context of the 5 year renewal of IntronA 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.
IA/0064	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	14/03/2008	n/a	Annex II and PL	
II/0062	Update of or change(s) to the pharmaceutical documentation	21/02/2008	26/02/2008		

II/0061	Update of section 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 SPC guideline further to a request from the CHMP. The PL is updated accordingly. Changes have also been made to the contact details of Sweden in the PL. Update of Summary of Product Characteristics and Package Leaflet	13/12/2007	28/01/2008	SmPC and 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 has been included in section 4.4 and 4.8 of the SPC, which should improve awareness and treatment and consequently outcome of this serious condition.
II/0060	Change(s) to the manufacturing process for the finished product	19/07/2007	24/07/2007		
II/0059	Update of section 4.4 of the SPC with a warning pertaining to the risk of cutaneous vasculitis when IntronA is co-administered with hydroxyurea in oncology indications based on a review of relevant safety data. Update of Summary of Product Characteristics	24/05/2007	09/07/2007	SmPC	A review on cutaneous vasculitic toxicities in patients receiving IntronA and hydroxyurea (also known as hydroxycarbamide) therapy was carried out. Overall a literature search and review of the Global Pharmacovigilance Database of the Marketing Authorisation Holder did not identify a signal of an increased risk of cutaneous vasculitis when interferon and hydroxyurea are co-administered; however the results of the pharmacoepidemiology analysis with calculations of Proportional Reporting Ratio did identify a possible signal of this phenomenon. A possible higher severity of cutaneous vasculitis with interferon/hydroxyurea combinations was also noted in some cases (potentially leading to amputations or requiring aggressive immunosuppressive therapy). Based on this review the CHMP agreed that a

					warning should be included in the SPC of IntronA.
II/0058	Change(s) to the test method(s) and/or specifications for the finished product	22/03/2007	29/03/2007		
II/0057	Further to pre-clinical follow up measures in the neonatal and juvenile rat concerning ribavirin, sections 4.4 and 5.3 of the SPC of IntronA 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). Update of Summary of Product Characteristics and Package Leaflet	16/11/2006	09/01/2007	SmPC and 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/0055	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 also takes the opportunity to update the contact details of the local representatives for Lithuania and Iceland in the package leaflet. Update of Summary of Product Characteristics, Labelling and Package Leaflet	27/07/2006	01/09/2006	SmPC, Labelling and PL	This variation is submitted further to the CHMP conclusions dated 7th April 2005 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 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 IntronA.
II/0054	Update of section 4.4 of the SPC further to the adoption of a class labelling for psychiatric disorders by the CHMP on 23rd March 2006. The Package Leaflet has been updated to reflect the SPC changes Update of Summary of Product Characteristics and Package Leaflet	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 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 IntronA 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/0053	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	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

	and ribavirin on pregnancy and lactation. Corresponding revisions to the Package Leaflet are made. Update of Summary of Product Characteristics and Package Leaflet				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 IntronA 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.
II/0052	Update of Section 4.4 of the IntronA SPC, further to the assessment of the 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 is updated accordingly. The annexes have also beeen updated in line with the latest QRD template (version 7). Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/03/2006	27/04/2006	SmPC, Annex II, Labelling and 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 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/0051	Update of the information in section 5.1 of IntronA 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 IntronA. Update of Summary of Product Characteristics	23/02/2006	29/03/2006	SmPC	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 2-b) / 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/0048	Update of or change(s) to the pharmaceutical documentation	23/02/2006	28/02/2006		
IB/0050	IB_36_a_Change in shape or dimensions of the	23/11/2005	n/a		

	container/closure - sterile ph. forms/biologicals				
IB/0049	IB_36_a_Change in shape or dimensions of the container/closure - sterile ph. forms/biologicals	23/11/2005	n/a		
II/0045	The MAH applies for a type II variation, upon request by the CHMP, to update section 4.4 of the SPC with reference to dental and periodontal disorders and to expand the wording on psychiatric and CNS disorders also in section 4.4. The PL has been updated accordingly. In addition, the MAH is taking the opportunity to introduce in the SPC, Labelling and PL the minor CHMP quality comments resulting from the recent renewal procedure and to update the "how to self-inject" instructions in the PL of the multidose pen presentations. Update of Summary of Product Characteristics, Labelling and Package Leaflet	15/09/2005	27/10/2005	SmPC, Labelling 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 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 IntronA therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Among children and adolescents treated with IntronA 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 IntronA be discontinued, and the patient followed, with psychiatric intervention as appropria
II/0044	Update of or change(s) to the pharmaceutical documentation	15/09/2005	23/09/2005		
IB/0046	IB_20_c_Change in test procedure for an excipient - other changes	13/09/2005	n/a		
IA/0047	IA_28_Change in any part of primary packaging material not in contact with finished product	31/08/2005	n/a		
R/0041	Renewal of the marketing authorisation.	17/02/2005	23/05/2005	SmPC, Annex II, Labelling and PL	The CHMP was of the opinion that the quality, safety and efficacy of IntronA continues to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of this medicinal product remains favourable.
II/0040	Change(s) to the manufacturing process for the	20/01/2005	31/01/2005		

	finished product				
II/0034	Extension of Indication	21/10/2004	25/01/2005	SmPC and PL	Chidren and adolescents with Chronic Hepatitis C: IntronA 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). 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 IntronA 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 t
IA/0043	IA_05_Change in the name and/or address of a manufacturer of the finished product	08/12/2004	n/a		
IA/0042	IA_09_Deletion of manufacturing site	08/12/2004	n/a		
II/0036	Update of or change(s) to the pharmaceutical documentation	16/09/2004	28/10/2004	SmPC and PL	The MAH applied for an update of the Plasma Master File. 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/0039	Update of Summary of Product Characteristics, Labelling and Package Leaflet	29/07/2004	13/09/2004	SmPC, Labelling and PL	The MAH applied to modify the safety information in the SPC of Intron A with the following: -Addition of 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 myosisits, 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/0038	Change(s) to the test method(s) and/or specifications for the active substance	29/07/2004	02/08/2004		
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/05/2004	n/a	PL	
I/0035	20a_Extension of shelf-life or retest period of the active substance	06/11/2003	13/11/2003		
II/0032	Update of or change(s) to the pharmaceutical documentation Update of Summary of Product Characteristics and Package Leaflet	25/04/2003	28/07/2003	SmPC and PL	

I/0033	12_Minor change of manufacturing process of the active substance	26/06/2003	14/07/2003		
II/0031	Quality changes	19/03/2003	31/03/2003		
II/0026	Update of Summary of Product Characteristics and Package Leaflet	19/09/2002	05/12/2002	SmPC and PL	
I/0030	04_Replacement of an excipient with a comparable excipient	22/11/2002	03/12/2002		
I/0029	15_Minor changes in manufacture of the medicinal product	17/10/2002	28/10/2002		
I/0027	21_Change in shelf-life after first opening 30_Change in pack size for a medicinal product	28/08/2002	10/10/2002	SmPC, Labelling and PL	
I/0028	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	10/09/2002	24/09/2002		
I/0025	25_Change in test procedures of the medicinal product	13/08/2002	17/09/2002		
II/0024	Change(s) to the test method(s) and/or specifications for the active substance	25/07/2002	30/07/2002		
II/0021	Update of Summary of Product Characteristics and Package Leaflet	17/01/2002	19/04/2002	SmPC and PL	
I/0023	14_Change in specifications of active substance	26/03/2002	08/04/2002		

II/0019	Update of Summary of Product Characteristics and Package Leaflet	18/10/2001	02/04/2002	SmPC and PL	
I/0022	20a_Extension of shelf-life or retest period of the active substance	28/02/2002	06/03/2002		
II/0017	Update of or change(s) to the pharmaceutical documentation	20/09/2001	12/10/2001		
I/0018	16_Change in the batch size of finished product	29/03/2001	21/05/2001		
I/0016	24_Change in test procedure of active substance	04/01/2001	21/05/2001		
I/0014	24_Change in test procedure of active substance	19/12/2000	21/05/2001		
I/0013	14_Change in specifications of active substance	19/12/2000	21/05/2001		
I/0012	14_Change in specifications of active substance	19/10/2000	21/05/2001		
I/0011	14_Change in specifications of active substance	19/10/2000	21/05/2001		
I/0010	14_Change in specifications of active substance	19/12/2000	21/05/2001		
I/0009	14_Change in specifications of active substance	19/12/2000	21/05/2001		
I/0015	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	15/11/2000	15/11/2000		
II/0002	Update of Summary of Product Characteristics and Package Leaflet	13/04/2000	28/08/2000	PL	

I/0008	15_Minor changes in manufacture of the medicinal product	27/07/2000	28/08/2000		
I/0007	16_Change in the batch size of finished product	27/07/2000	28/08/2000		
I/0006	25_Change in test procedures of the medicinal product	23/06/2000	28/08/2000		
I/0005	30_Change in pack size for a medicinal product	14/04/2000	21/08/2000		
II/0004	Change(s) to the manufacturing process for the active substance	27/07/2000	01/08/2000		
I/0003	12_Minor change of manufacturing process of the active substance	25/05/2000	n/a		
I/0001	02_Change in the name of the medicinal product (either invented name of common name)	10/03/2000	17/05/2000	SmPC, Labelling and PL	