ViraferonPeg

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification [1] issued on	Commission Decision issued / amended on	Product Information affected [3]	Summary
T/0128	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	29/06/2016	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	25/06/2015	29/06/2016	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	29/06/2016	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		

					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 (peginterferon alfa-2b) (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 ViraferonPeg. Caution is therefore advised when ViraferonPeg 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/0048	Change(s) to the manufacturing process for the active substance	17/02/2005	21/02/2005		
IA/0051	IA_09_Deletion of manufacturing site	20/01/2005	n/a		
II/0047	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 ViraferonPeg 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 PL 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: "ViraferonPeg-H-329-II-45".
II/0046	Change(s) to the test method(s) and/or specifications for the active substance	29/07/2004	02/08/2004		
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	26/02/2004	05/03/2004		

	finished product				
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 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	20/11/2003	05/02/2004	SmPC and PL	Changes to Sections 4.4 and 4.8 were made following the 5th ViraferonPeg PSUR. 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 ViraferonPeg 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_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	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 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.

					A warning was added in section 4.4: "All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (ie patients with genotype 2 or 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment."
II/0037	Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	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	24/04/2003	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.	10/12/2002	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	07/07/2002	19/07/2002	SmPC	
II/0020	Change(s) to the test method(s) and/or specifications for the finished product	30/05/2002	26/06/2002		
II/0019	Change(s) to the manufacturing process for the finished product	30/05/2002	26/06/2002		
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	16/07/2002	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 Update of Summary of Product Characteristics and Package Leaflet	01/06/2001	n/a		
II/0001	Extension of Indication	14/12/2000	26/03/2001	SmPC and PL	
I/0012	24_Change in test procedure of active substance	04/01/2001	n/a		
I/0005	30_Change in pack size of 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	
II/0002	Change(s) to the manufacturing process for the active substance	28/08/2000	28/08/2000		
I/0003	12_Minor change of manufacturing process of the active substance	28/08/2000	n/a		