Rebetol

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
IAIN/0093/G	This was an application for a group of variations. 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)	24/11/2022		Annex II 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).

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	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release				
N/0092	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2021	07/06/2022	PL	
PSUSA/10007 /202007	Periodic Safety Update EU Single assessment - ribavirin (oral formulations)	25/03/2021	01/06/2021		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10007/202007.
IB/0091	C.I.3.z - 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 - Other variation	19/05/2021	07/06/2022	SmPC and PL	
IA/0089	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)	09/10/2020	n/a		
IB/0088	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/09/2020	01/06/2021	SmPC, Annex II, Labelling and PL	
N/0087	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/10/2019	11/02/2020	Labelling and PL	
II/0086	Submission of an updated RMP version 6.0 in order to revise safety concerns for ribavirin based on GVP module V (rev. 2) guidance. In addition, the MAH took the opportunity to revise the safety concerns of	03/10/2019	n/a		

	ribavirin in light of the current era of IFN free regimen, as requested in a previous PSUSA procedure (EMEA/H/C/PSUSA/00010007/201707). C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IA/0085	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	08/02/2019	11/02/2020	SmPC	
T/0083	Transfer of Marketing Authorisation	17/07/2018	28/09/2018	SmPC, Labelling and PL	
IA/0084	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	30/08/2018	n/a		
IA/0082	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	01/06/2018	n/a		
PSUSA/10007 /201707	Periodic Safety Update EU Single assessment - ribavirin (oral formulations)	08/03/2018	n/a		PRAC Recommendation - maintenance

IA/0080	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)	06/06/2017	n/a		
IAIN/0079	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	03/02/2017	19/02/2018	Annex II and PL	
IA/0078	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	16/11/2016	n/a		
IA/0077	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)	01/06/2016	n/a		
II/0074	Change of the indication of Rebetol to reflect that ribavirin is indicated in in the treatment of hepatitis C in combination with other medicinal products and remove reference to the peginterferon used (2a or 2b) in line with the PRAC recommendation in the PSUR assessment (EMEA/H/C/PSUSA/000100007/201307). As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.7, 4.8, 4.9 and 5.1 of the SmPC are updated. The package leaflet is updated accordingly. Furthermore, the PI is being overall brought in line with the latest QRD	24/09/2015	28/10/2015	SmPC, Annex II, Labelling and PL	Please refer to scientific discussion in the published EPAR.

	template version 9.1. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0076	Submission of final report for study MK-8908-060 assessing the utilization of ribavirin in paediatric patients with hepatitis C virus. A revised RMP has been submitted with this procedure. The requested variation proposed amendments to the Risk Management Plan (RMP) and no amendments to the SmPC/PIL. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/06/2015	n/a		
PSUSA/10007 /201407	Periodic Safety Update EU Single assessment - ribavirin (oral formulations)	12/02/2015	n/a		PRAC Recommendation - maintenance
IB/0073/G	This was an application for a group of variations. B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-	29/04/2014	n/a		

	sterile medicinal products A.7 - Administrative change - Deletion of manufacturing sites				
PSUSA/10007 /201307	Periodic Safety Update EU Single assessment - ribavirin (oral formulations)	20/02/2014	28/04/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10007/201307.
IA/0072	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)	04/12/2013	n/a		
II/0066/G	This was an application for a group of variations. 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, and study P01906, as requested in PSU066. Section 4 of the PL is updated accordingly. This type II variation is grouped with a type 1b variation to update section 5.2 of the SmPC with agreed wording on the bioequivalence between oral solution and capsule formulations, as requested in FU2 57.4. Furthermore, the PI is being brought in line with the latest QRD template version 9.0 and to include some minor editorial and linguistic revisions. C.I.3.a - Implementation of change(s) requested	21/11/2013	28/04/2014	SmPC, Annex II, Labelling and PL	To address the CHMP concern regarding the reversibility of growth inhibition observed in children treated with ribavirin in combination with (pegylated) interferon, the MAH performed a long-term follow-up of study P02538 in children treated with peginterferon alfa-2b/ribavirin bitherapy and study P01906 in children treated with interferon alfa-2b and ribavirin. The final results from the long-term follow-up of these studies 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 that may be irreversible was observed 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. In a single dose, crossover study of ribavirin in healthy adult subjects, the capsule and oral solution formulations were found to be bioequivalent. This information has been

	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.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				reflected in the product information.
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		
IAIN/0069/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or	24/10/2013	n/a		

	deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.II.d.1.h - Change in the specification parameters and/or limits of the finished product - Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur. for the finished product				
IA/0068/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	11/10/2013	n/a		
IA/0067/G	This was an application for a group of variations.	30/07/2013	n/a		

	A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
N/0065	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/07/2013	28/04/2014	PL	The MAH completed the list of local representatives (LR) in the PL to include the new EU member state Croatia. Furthermore the MAH updated the local representatives in CZ, MT, EL, PT and SK.
IG/0225	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/02/2013	n/a		
IA/0063/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	21/01/2013	n/a		
T/0062	Transfer of Marketing Authorisation	24/02/2012	04/04/2012	SmPC and PL	
WS/0216	This was an application for a variation following a worksharing procedure according to Article 20 of	16/02/2012	30/03/2012	SmPC, Labelling and	Please refer to the Assessment Report: H-XXX-WS-216-AR

	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			PL	
IB/0057/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished	20/01/2012	n/a		

	product - Tightening of in-process limits B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions				
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	04/04/2012	SmPC, Labelling and PL	
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,	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

	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				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/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	29/06/2011	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/0056	Update of the local representatives contact details in Bulgaria, Estonia, Greece, Spain, Ireland, Cyprus,	09/06/2011	n/a	PL	

	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)				
N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2010	n/a	PL	
IB/0054	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 update the SmPC section 4.8 and PL section 4 to remove the adverse event Raynaud's disease. Furthermore the details of local representatives in Sweden and Finland were updated.
IA/0053/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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)	13/07/2010	n/a		
II/0051	At the request of the CHMP further to the assessment of FUM 054 section 4.5 of the SmPC is updated with a statement on co-administration of abacavir and ribavirin. Additionally, corrections have been made to the SmPC, and PL. Changes have also been made to the annexes to comply with QRD guidance.	20/05/2010	05/07/2010	SmPC, Annex II and PL	Further to review of available date from literature and the safety data base of the Marketing Authorisation Holder it was not possible to conclude if a clinically relevant interaction between abacavir and ribavirin exists or not. A statement has however been included in the SmPC as a conservative measure, to alert the prescribers on the potential negative impact of abacavir on response rate to

	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				HCV therapy (reinforcing the need to ensure adequate ribavirin exposure in this difficult-to-treat population).
IB/0052	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	22/04/2010	n/a	SmPC, Annex II and PL	
II/0049	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, Labelling and PL	Please refer to the scientific discussion: Rebetol-H-246-II-49-AR
II/0048	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: Rebetol-H-246-II-48-AR
II/0045	Update of Summary of Product Characteristics with	24/09/2009	11/11/2009	SmPC and PL	Study P01906 was a 5 year follow up study to assess the

	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				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.
R/0050	Renewal of the marketing authorisation.	19/02/2009	23/04/2009	SmPC, Annex II, Labelling and PL	
II/0047	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. Update of Summary of Product Characteristics	23/10/2008	02/12/2008	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 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 then 48 weeks. This statement takes into account treatment recommendations for other pegylated interferons.
II/0046	Further to a request of the CHMP made in the context of the assessment of PSUR 12, covering the period 25.07.2006-24.07.2007, section 4.8	25/09/2008	31/10/2008	SmPC and PL	In the context of PSUR 12 (period covered 25.07.06 - 24.07.07) it was noted that section 4.8 of the Rebetol SPC listed all adverse reactions reported in clinical trials with

	"Undesirable effects" of the Summary of Product Characteristics (SPC) is updated to include adverse reactions reported in postmarketing with ribavirin in combination with interferon alfa 2b containing products. Section 4.8 is also updated in line with the latest SPC guideline. The package leaflet is updated accordingly. The addresses of Bulgarian, Austrian, Polish and Finnish local representatives have also been updated in the package leaflet. A number of editorial changes have been made to the SPC and PL. Update of Summary of Product Characteristics and Package Leaflet				the combination of Rebetol with pegylated interferon alfa 2b or interferon alfa 2b. Some cases reported in post-marketing with one of these combinations had also been added in this section (such as pure red cell aplasia, seizure or pancreatitis). However, a certain number of adverse reactions reported in post-marketing and generally attributed to interferon therapy but that had been reported in the context of hepatitis C therapy (thus, in combination with Rebetol) were unlisted in the Rebetol SPC. For the sake of consistency and clarity, section 4.8 of Rebetol SPC has therefore been entirely reviewed to include adverse events reported in post-marketing with Rebetol in combination with interferon-containing products.
II/0044	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	08/04/2008	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/0042	Update of section 5.1 "Pharmacodynamic properties" of the Summary of Product Characteristics with the results of a long-term follow-up study to assess the sustained virological response after the treatment of	21/02/2008	08/04/2008	SmPC and PL	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

	chronic hepatitis C. In addition, the Package Leaflet has been amended with the contact details for the local representative in Romania. Update of Summary of Product Characteristics and Package Leaflet				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).
IA/0043	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	17/12/2007	n/a		
II/0039	Update of section 4.5 of the SPC to delete information regarding the in vitro inhibition of the zidovudine and stavudine phosphorylation by ribavirin. Update of Summary of Product Characteristics	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 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/0035	Extension of the therapeutic indication of Rebetol in combination with peginterferon alfa 2b to include treatment of adult patients who failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy or interferon monotherapy.	20/09/2007	30/10/2007	SmPC and PL	Please refer to the Scientific Discussion "Rebetol-H-C-246-II-35" for further information.

	The MAH also takes the opportunity to update the details of the local representative for Sweden in the PL. Extension of Indication				
IB/0041	IB_33_Minor change in the manufacture of the finished product	26/10/2007	n/a		
IA/0040	IA_20_a_Change in test procedure for an excipient - minor change to approved test procedure	30/08/2007	n/a		
II/0037	Update of section 4.8 of the SPC to include the adverse reaction "seizure", as requested by the CHMP following the assessment of PSURs 10 and 11 (covering the period from 25 July 2005 to 24 July 2006). Section 4 of the PL has been updated accordingly and has been further completed in order to reflect all adverse events listed in the SPC. Update of Summary of Product Characteristics and Package Leaflet	24/05/2007	09/07/2007	SmPC and PL	During the period covered by PSURs 10 and 11 (25 July 2005 to 24 July 2006), 9 serious cases of seizures or convulsions were reported. Some of them occurred in patients without a history of convulsion. The role of ribavirin in these cases could not be excluded due to a suggestive temporal causality. Furthermore, "seizure" is already listed in the Company Core Data Sheet for Rebetol and is also mentioned in the SPCs of peginterferon alfa-2b and interferon alfa-2b. Therefore, the CHMP considered that this adverse event should be included in the Rebetol SPC as well as in the Package Leaflet.
II/0038	Change(s) to the test method(s) and/or specifications for the finished product . Change(s) to the test method(s) and/or specifications for the finished product	21/06/2007	28/06/2007		
II/0034	Extension of Indication	26/04/2007	01/06/2007	SmPC, Labelling and	Please refer to the Scientific Discussion "Rebetol-H-C-246-

				PL	II-34" for further information.
II/0036	Further to pre-clinical follow up measures in the neonatal and juvenile rat sections 4.4 and 5.3 of the SPC are updated to warrant the attention of prescribers on the need to clearly assess the benefit-risk of the combined use of ribavirin and interferon alfa-2b in young children in period of growth. 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	04/01/2007	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/0033	Update of the section 4.2 of the SPC with a mention related to the potential negative impact of dose reduction and to the careful monitoring for anaemia in patients with impaired renal function. Section 2 of the PL has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	27/10/2006	SmPC and PL	Data exploring the relationship between estimated creatinine clearance and haemoglobin decrease in the pivotal peginterferon alfa-2b/Rebetol combination trial shows an increased risk of anaemia with reduced kidney function. The CHMP consider that this should be reflected in section 4.2 of the SPC. Furthermore the CHMP agreed that prescribers should be made aware of the potential negative impact of ribavirin dose reduction or discontinuation on efficacy.
II/0032	Update of section 4.8 of the SPC of Rebetol to add the adverse reaction pure red cell aplasia. The package leaflet has been updated accordingly. In addition minor changes have been made to the package leaflet and Annex II to be in accordance with version 7 of the QRD templates. The MAH also take the opportunity to update the contact details of	27/07/2006	01/09/2006	SmPC, Annex II and PL	This variation is submitted further to the CHMP conclusions dated 7thApril 2005 on Rebetol 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

	the local representatives for Lithuania in the package leaflet. Update of Summary of Product Characteristics and Package Leaflet				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 Rebetol.
II/0031	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	25/07/2006	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 products and Rebetol 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 Rebetol 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 Rebetol 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/0029	Update of section 4.4 of Rebetol SPC in order to	23/03/2006	27/04/2006	SmPC, Annex	Further to the assessment of PSUR 7 for interferon alfa-2b

	alert the prescribers to the fact that patients treated with Rebetol and interferon combination therapy and Zidovudine could be at an increased risk of anaemia, further to the assessment of PSUR 7 of interferon alfa-2b (period covered 8 March 2004 to 9 September 2004) as well as Pharmacovigilance follow-up measure. Section 4.4 and 4.5 of the SPC has also been updated with a warning pertaining to coadministration of ribavirin and didanosine and the consequent risk of mitochondrial toxicity, upon CHMP request, further to the assessment of PSUR 8 (8 November 2003 to 7 November 2004) of Rebetol. The Package Leaflet has been up dated accordingly. Further, section 4.4 of the SPC has been updated with a warning pertaining to the coadminstration of stavudine and ribavirin and the consequent risk of mitochondrial toxicity, upon CHMP request, further to the assessment of PSUR 8 of Rebetol. The Package Leaflet has been up dated accordingly. In section 4.2 of the SPC a minor correction to the paragraph on duration of treatment is introduced in order to replace the term "posology" by "duration of treatment" and the annexes have been updated in line with the latest QRD template (version 7). Update of Summary of Product Characteristics, Labelling and Package Leaflet			II, Labelling and PL	(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 safety data with regard to the necessity to include a warning in the SPC and Package Leaflet were reviewed. In light of this safety review 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's of Rebetol, IntronA/ Viraferon, and PegIntron/ViraferonPeg. Following the assessment of PSUR 8 of Rebetol (8 November 2003 to 7 November 2004) concerns were raised regarding the risk of mitochondrial toxicity when ribavarin is co-administered with didanosine. Further to a safety review on lactic acidosis/mitochondrial toxicity, the SPC of Rebetol was updated in order to warn clinicians against coadministration of ribavirin and didanosine. During the evaluation of the data regarding didanosine and the risk of mitochondrial toxicity the CHMP also noted that there were arguments suggesting that coadministration of ribavirin with stavudine also increased the risk of mitochondrial toxicity and considered that the prescription of stavudine should be avoided as far as possible in HIV/HVC co-infected patients in order to reduce the risk of overlapping mitochondrial toxicity, all the more because

					other safer alternatives are available. In this field, the CHMP concluded that a specific warning with regard to this combination should be introduced to the SPC of Rebetol.
II/0027	Update of the information in section 5.1 of Rebetol 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-2b)/Rebetol (ribavirin) combination therapy (for 24 or 48 weeks), with Intron A monotherapy (for 24 or 48 weeks) in naïve or relapse subjects. Long-term follow-up began at the Follow-Up Week 24 visit in the treatment protocol, ie, 6 months post-treatment. The results of the study confirm the durability of the virologic response up to 5 years. The likelihood of maintaining virologic response over 5 years in subjects who initially achieved a sustained response is 97% with a 95% Confidence Interval of [95%, 99%]. The limitations of the study (limited percentage of non responders that enter the long term study and high number of discontinuation), preclude any conclusion across initial treatment groups. Further, if the long-term clearance of the virus could be considered as a clinical 'cure' from chronic HCV, this does not preclude the occurrence of hepatic events related to progression of liver disease. This change in section 5.1 of the SPC applies to Rebetol and also to Intron A and Viraferon, both non pegylated interferon alfa-2b.
IA/0030	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	13/02/2006	13/02/2006	SmPC, Labelling and PL	

IA/0028	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	12/01/2006	n/a	Annex II and PL	
II/0026	To update section 4.4 of the SPC with a wording on the possibility of dental and periodontal disorders together with a recommendation to promote optimal health and to include a wording on the psychiatric disorders as requested by CHMP in its conclusions (FUM 025) dated 7 April 2005 further to the review of the safety database of the Marketing Authorisation Holder (MAH). Corresponding revisions to point 2 of the PL are proposed. The address of the Polish representative is updated in point 6 of the PL. Update of Summary of Product Characteristics and Package Leaflet	15/09/2005	25/10/2005	SmPC and PL	A total of 392 cases of dental disorders were reported through 1st April 2004 in the Schering-Plough Safety Database. Most of the cases were reported as "tooth disorder" without other specification precluding to any physiopathological interpretation. Furthermore, in France, there was concern about a worrying reporting of 7 non-serious and 1 serious cases of receding and teeth brittle for which no obvious aetiology other than hepatitis combination therapy was considered. Therefore, the CHMP considers that the substantial number of cases of tooth loss reported, including cases with a possible relationship to HCV treatment, along with the fact that reporting of such events is rather unusual in pharmacovigilance support the need to include the risk for the significant dental complication (loss of teeth) in the SPC and the PL. A total of 2077 cases of suicide-related events were reported through 7st June 2004 in the Schering-Plough Safety Database. Analysis by time to event and age group showed that: 1) there is no obvious trend for a higher reporting rate of suicide-related AE in the youngest population when taken into account demographic and epidemiologic data; 2) interestingly, a predominance of suicide attempt and complete suicide were reported in the early follow-up period. The CHMP concluded that in accordance with literature and the available data from Schering-Plough database, the wording on psychiatric and CNS disorders in Section 4.4 of the SPC for Rebetol should

					be modified in order to alert prescribers on the fact that psychiatric disorders may occur at any time during therapy but also after stopping treatment and that patients should be closely monitored and carefully evaluated for the need for adequate therapeutic management
II/0025	To update section 4.2 and section 5.1 of the SPC with new data obtained in the genotype 1 low viral load final study report: "PegIntron (peginterferon alfa-2b) plus Rebetol (ribavirin) for treatment of chronic hepatitis C in previously untreated subjects infected with HCV 2 or 3 or 2/3 and subjects with HCV 1 with pre-treatment HCV-RNA " 2,000,000 copies/ml". The PL has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	30/08/2005	SmPC and PL	Single arm, open label, European multicenter study of 24 weeks of treatment with PEGINTRON (peg-interferon) plus REBETOL (Ribavirin) in the treatment of chronic hepatitis C in anti-hepatitis C naïve patients infected with HCV 2 or 3 or 2/3 and in anti-hepatitis C pretreated patients infected with HCV 1 and with a HCV-RNA < 2,000, 000 copies/ml was presented. In total, 235 subjects with genotype 1 and low viral load (< 600,000 IU/ml) received PegIntron, 1.5 microgram/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50%. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at Week 4 and Week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48). Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).
II/0024	To update the SPC, section 4.2 and 4.4 on the safety of ribavirin in HCV/HIV co-infected patients as a class labelling request further to the conclusions of the	21/04/2005	03/06/2005	SmPC	It has previously been reported that patients co-infected with HCV and HIV and who are taking NRTI treatment in association with ribavirin and interferon alfa-2b or

	January 2005 CHMP meeting. Additionally, the MAH proposes to correct a typo error in SPC section 4.2 regarding the duration for the predictability in genotype I. Update of Summary of Product Characteristics				peginterferon alfa-2b may be at increased risk of mitochondrial toxicity, lactic acidosis and hepatic decompensation. Proper statements to that effect have been added to SPC sections 4.2 and 4.4.
IA/0023	IA_09_Deletion of manufacturing site	03/02/2005	n/a		
X/0016	Annex I_2.(d) Change or addition of a new pharmaceutical form	21/10/2004	25/01/2005	SmPC, Labelling and PL	
II/0014	This variation relates to an extension of the therapeutic indication to include " Treatment of Chronic hepatitis C in children 3 years of age and older "amending SPC sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3. These changes have been reflected in the PL. Extension of Indication	20/10/2004	25/01/2005	SmPC and PL	
II/0022	Quality changes	18/11/2004	25/11/2004		
II/0018	Type II variation, in order to address the benefit of a 6-month duration of treatment in hepatitis C patients with genotype 2/3 infection. Update of Sections 4.2 and 5.1 of the SPC. Sections 4.2 and 5.1 were also updated to include information regarding patients predictability of sustained response. Update of Summary of Product Characteristics	23/06/2004	09/09/2004	SmPC	The MAH presented a single arm, open label, European multicenter study of 24 weeks of treatment with Pegintron (peg-interferon) plus Rebetol (Ribavirin) in the treatment of chronic hepatitis C in anti-hepatitis C naïve patients infected with HCV 2 or 3 or 2/3 and in anti-hepatitis C pretreated patients infected with HCV 1 and with a HCV-RNA < 200 000 copies/ml; historical control consisting in 48 weeks data from study.

					Overall, the open label study submitted with an historical comparison supports the proposed 24 weeks treatment duration of REBETOL in combination with pegylated interferons in patients with genotype 2 or 3 as follows: · Genotype 1: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks). · Genotypes 2 or 3: It is recommended that all patients be treated for 24 weeks. · Genotype 4: In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a posology for genotype 1.
R/0019	Renewal of the marketing authorisation.	22/04/2004	02/09/2004	SmPC, Annex II, Labelling and PL	
N/0021	The Marketing Authorisation Holder applied for an update of the list of local representatives, in order to include the contact details of the new Member States. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/05/2004	n/a	PL	
IB/0020	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	29/03/2004	n/a		
N/0017	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/11/2003	12/12/2003	PL	

II/0011	Update of Summary of Product Characteristics	26/06/2003	03/10/2003	SmPC	
II/0015	Change(s) to the test method(s) and/or specifications for the active substance	25/09/2003	29/09/2003		
I/0013	15_Minor changes in manufacture of the medicinal product	10/04/2003	15/04/2003		
I/0012	15a_Change in IPCs applied during the manufacture of the product	10/04/2003	15/04/2003		
II/0008	Update of Summary of Product Characteristics and Package Leaflet	15/11/2001	12/04/2002	SmPC and PL	
N/0010	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/10/2001	07/02/2002	PL	
II/0009	Quality changes	18/10/2001	22/10/2001		
II/0006	Update of or change(s) to the pharmaceutical documentation	25/04/2001	26/06/2001		
II/0005	Extension of Indication	14/12/2000	26/03/2001	SmPC and PL	
I/0007	12_Minor change of manufacturing process of the active substance	02/03/2001	n/a		
II/0003	Update of Summary of Product Characteristics and Package Leaflet	16/03/2000	24/07/2000	SmPC and PL	
I/0004	12_Minor change of manufacturing process of the	24/03/2000	11/05/2000		

	active substance				
I/0002	12_Minor change of manufacturing process of the active substance	07/07/1999	n/a		
I/0001	01_Change following modification(s) of the manufacturing authorisation(s)	07/07/1999	n/a		