Rebif

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
IA/0156/G	This was an application for a group of variations. B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test A.7 - Administrative change - Deletion of	30/05/2023		Annex II	

[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).

	manufacturing sites				
IAIN/0155	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	25/01/2023		PL	
IA/0154	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	20/04/2022	n/a		
IA/0153	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	17/02/2022	n/a		
PSUSA/10726 /202105	Periodic Safety Update EU Single assessment - interferon beta-1a (subcutaneous use)	13/01/2022	n/a		PRAC Recommendation - maintenance
IA/0152	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	10/09/2021	n/a		
IB/0150	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	04/05/2021	n/a		
IB/0149	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	18/12/2020	n/a		
IB/0148	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/12/2020	13/12/2021	SmPC and PL	

IAIN/0147	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	27/08/2020	n/a		
IAIN/0146	B.IV.1.b - Change of a measuring or administration device - Deletion of a device	21/08/2020	15/10/2020	SmPC and PL	
IA/0145	A.7 - Administrative change - Deletion of manufacturing sites	15/07/2020	n/a		
II/0144	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	13/02/2020	n/a		
IB/0143	C.I.3.a - 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 - Implementation of wording agreed by the competent authority	08/01/2020	15/10/2020	SmPC and PL	
II/0137/G	This was an application for a group of variations. To update sections 4.3, 4.6 and 5.3 of the SmPC in order to remove the contraindication on the initiation of treatment in pregnancy and to update the recommendations on use in pregnancy and	19/09/2019	15/10/2020	SmPC and PL	The SmPC section 4.3 has been updated to remove the contraindication 'initiation of treatment in pregnancy'. The SmPC section 4.6 has been updated as follows: Pregnancy

	breastfeeding following the completion of the European IFN Beta Pregnancy Registry (8th Annual and final report) and the Final CSR of the register-based study in the Nordic countries (EUPAS13054). The MAH took the opportunity to add information about traceability in section 4.4 and to update the Product information to the QRD template version 10.1. The Package leaflet has been updated accordingly. This submission fulfils MEA 43.2 and 39. The RMP has been updated (ver 10.2) to include changes to the safety specification related to Pregnancy missing information status, in light of the new safety information received, as well as updates to other key sections of the RMP, adapting to the requirements of the GVP Module 5 revision 2 guidelines. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				A large amount of data (more than 1,000 pregnancy outcomes) from registries and post-marketing experience indicates no increased risk of major congenital anomalies after pre-conception exposure to interferon beta or such exposure during the first trimester of pregnancy. However, the duration of exposure during the first trimester is uncertain, because data were collected when interferon beta use was contraindicated during pregnancy, and treatment likely interrupted when the pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester is very limited. Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far. If clinically needed, the use of Rebif may be considered during pregnancy. Breast-feeding Limited information available on the transfer of interferon beta-1a into breast milk, together with the chemical/physiological characteristics of interferon beta, suggests that levels of interferon beta-1a excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated. Rebif can be used during breast-feeding.

					The SmPC section 5.3 has been updated as follows: A study on embryo/foetal toxicity in monkeys showed no evidence of reproductive disturbances. An increased risk of abortions has been reported in animal studies of other alpha and beta interferons. No information is available on the effects of the interferon beta 1a on male fertility. The PL has been updated accordingly.
II/0141	B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	25/07/2019	n/a		
IA/0142	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	09/07/2019	n/a		
IA/0140	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	23/05/2019	n/a		
IA/0139	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	08/05/2019	n/a		
IA/0138/G	This was an application for a group of variations. B.II.e.2.a - Change in the specification parameters	08/05/2019	n/a		

	and/or limits of the immediate packaging of the finished product - Tightening of specification limits B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure				
PSUSA/9198/ 201805	Periodic Safety Update EU Single assessment - interferon beta-1a	29/11/2018	n/a		PRAC Recommendation - maintenance
T/0135	Transfer of Marketing Authorisation	22/06/2018	13/07/2018	SmPC, Labelling and PL	
IB/0134/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	02/03/2018	n/a		
IB/0133/G	This was an application for a group of variations. B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished	19/12/2017	13/07/2018	SmPC, Labelling and PL	

	product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes				
IB/0132	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/12/2017	n/a		
IAIN/0131	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	14/11/2017	n/a		
II/0129	Submission of an updated RMP version 9.0 in order to upgrade the important potential risk "Immunogenicity/safety risk associated with the formation of neutralizing antibodies" to an important identified risk and rename it to "Immunogenicity/formation of neutralizing antibodies (NAbs) (reduced efficacy)". 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	06/07/2017	n/a		
N/0130	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/06/2017	13/07/2018	Labelling and PL	
IB/0127	B.I.a.2.z - Changes in the manufacturing process of	21/02/2017	n/a		

	the AS - Other variation				
IA/0126	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	30/11/2016	n/a		
IA/0125	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	11/11/2016	n/a		
IA/0124	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	27/10/2016	n/a		
II/0122	B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	15/09/2016	n/a		
IB/0121/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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	19/05/2016	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
PSUSA/9198/ 201505	Periodic Safety Update EU Single assessment - interferon beta-1a	03/12/2015	n/a		PRAC Recommendation - maintenance
IB/0120	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/10/2015	n/a		
II/0116	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/09/2015	n/a		
IB/0119	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	10/09/2015	n/a		
IB/0115	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/07/2015	22/07/2016	SmPC and PL	
IG/0500	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	17/11/2014	n/a		
IB/0112	B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	10/11/2014	n/a		

IA/0114/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 dossier) - Replacement or addition of a supplier	07/11/2014	n/a		
IB/0111	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	02/10/2014	n/a		
IB/0109	B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a safety or quality issue	30/09/2014	n/a		
II/0106	Update of the SmPC Sections 4.4 and 4.8 to include class labelling wording on thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS). The Package leaflet has been updated accordingly. In addition the RMP was updated to version 7.0. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/07/2014	26/08/2014	SmPC and PL	The MAH conducted a cumulative search for cases of thrombotic microangiopathy. Further to the PRAC review of these data, the CHMP concurred with the PRAC´s view that there might be a causal relationship between the class of interferons and thrombotic microangiopathy, and that the PI should be updated accordingly. Furthermore, the CHMP concurred that a warning about the risk of thrombotic microangiopathy, including recommendations for monitoring of early symptoms, prompt treatment and discontinuation of interferon beta products when the reaction occurs, should be added to the Product

					Information.
IG/0461	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	22/07/2014	n/a		
IA/0107	A.7 - Administrative change - Deletion of manufacturing sites	04/07/2014	n/a		
II/0105	Update of section 5.1 of the Summary of Product Characteristics (SmPC) in order to include information about biological response markers and section 5.2 in order to update the information about the pharmacokinetic properties. Furthermore, the PI was brought in line with the latest QRD template version 9.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	26/08/2014	SmPC and PL	Further to their review of results from the Study EMR200136-027 evaluating pharmacokinetics, pharmacodynamics, safety and tolerability of Rebif in healthy volunteers, the CHMP concluded that information about markers of biological response should be added to section 5.1 of the SmPC and section 5.2 of the SmPC should be updated to reflect on newly available data on absorption, distribution and elimination.
II/0104	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) in order to add safety information with regards to nephrotic syndrome and glomerulosclerosis. The Package Leaflet was updated in accordance. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/04/2014	26/08/2014	SmPC and PL	The MAH conducted a cumulative search for cases of glomerulosclerosis and nephrotic syndrome. Further to their review of these data, the CHMP was of the opinion that there might be a causal relationship between interferon beta 1-a and glomerulosclerosis and nephrotic syndrome, and that the PI should be updated accordingly. Furthermore, the CHMP concluded that a warning about the risk of nephrotic syndrome (including examples of underlying conditions) and a recommendation to periodically assess renal function were of relevance to the

					prescriber and should be added to the SmPC.
II/0103	Update of sections 4.2 and 4.8 of the SmPC in order to add safety information relevant to the paediatric population. The Package Leaflet was updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2013	28/02/2014	SmPC and PL	Please refer to the scientific discussion Rebif H-000136-II-103-AR.
N/0102	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/10/2013	28/02/2014	PL	
IA/0101	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	21/08/2013	n/a		
IB/0100/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 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	07/08/2013	n/a		

	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
IB/0098	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits	23/07/2013	n/a		
IAIN/0099	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	16/07/2013	n/a		
IB/0097	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits	21/06/2013	n/a		
IB/0096	B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	18/06/2013	n/a		
II/0094/G	This was an application for a group of variations. To replace the a QC analytical method for drug substance and drug product and to amend corresponding specifications 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	30/05/2013	n/a		

	biological reagent for a biological AS B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation				
IAIN/0095	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	26/02/2013	n/a		
II/0093	Update of section 4.8 of the SmPC in order to add "pancytopenia" and "increased sweating" as adverse reactions, following a previous PSUR assessment. In addition, frequency categories of adverse reactions in section 4.8 of the SmPC were re-calculated based on the SmPC guideline. The Package Leaflet was updated accordingly. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8.3 and to introduce minor editorial changes. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	21/02/2013	28/02/2014	SmPC, Annex II, Labelling and PL	Following conclusions of a previous PSUR assessment, the MAH complied with the request of the CHMP to update the Product Information by adding the adverse reactions "pancytopenia" and "increased sweating". With respect to pancytopenia, the CHMP considered the available literature data concerning the effects of interferon on blood cells and the available clinical data from clinical trials and post-marketing setting. The CHMP considered that no serious cases of pancytopenia were observed in clinical trial and no reports concerning pancytopenia were identified in literature, but cases of pancytopenia were reported in the post-marketing setting. Taken together with the known effect of IFN on blood cells, the possibility of decrease in several bone marrow cell-lines and a number of cases of positive de-challenge and even a couple of cases with positive re-challenge, the evidence available was considered supportive of at least a possible causality. Thus, the CHMP concluded on the need to update section 4.8 of

					the SmPC by including pancytopenia as an adverse reaction. The level of evidence available with the previous PSUR was sufficient to support adding increased sweating to the PI without a need for additional data. The CHMP endorsed the MAH´s frequency estimations of both pancytopenia and excessive sweating and considered that these substantiated the frequency category "rare" for pancytopenia and "uncommon" for excessive sweating. The CHMP also acknowledged that the MAH followed the SmPC guideline and estimated frequencies for all adverse reactions previously categorised as frequency "not known". The CHMP endorsed the MAH´s proposals for the new frequency categories and agreed on the update of section 4.8 of the SmPC.
IG/0224	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/10/2012	n/a		
II/0091	Update of section 4.8 of the SmPC in order to add the following adverse reactions identified during the post-marketing surveillance: autoimmune hepatitis and drug-induced lupus erythematosus. The Package Leaflet was updated in accordance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	27/06/2012	SmPC and PL	This update of Product Information followed a cumulative review of cases of autoimmune hepatitis and systemic lupus erythematosus in multiple sclerosis patients exposed to interferon-beta-1a. It was based on the company´s internal safety database, pooled clinical trial database, the FDA adverse event reporting system (AERS) database, as well as on a literature review. The CHMP considered that the level of evidence available through safety reporting allowed establishing a causal relationship with autoimmune hepatitis and drug-induced lupus erythematosus and that it indicated increased risk of occurrence of these reactions in multiple sclerosis patients treated with Rebif.

II/0088/G	This was an application for a group of variations. Extension of indication: Update of sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and sections 1 and 3 of the Package Leaflet to include information on a new indication, i.e. treatment of patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. These updates affect the PI of the 44 mcg presentations (pre-filled syringe, pre-filled pen and cartridges) and the PI of the initiation pack presentations (pre-filled syringe, pre-filled pen and cartridges). In addition, minor editorial changes were implemented across the SmPC and the Package leaflet and the DDPS version number was removed from Annex II. Furthermore, Annex II was updated to introduce the standard text regarding the risk management system. The MAH also took the opportunity to update the list of local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	17/11/2011	20/01/2012	SmPC, Annex II, Labelling and PL	Please refer to the scientific discussion Rebif H-136-II-88G-AR
IAIN/0089	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	18/11/2011	n/a		

IB/0087	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	08/08/2011	n/a	SmPC, Annex II, Labelling and PL	
IG/0076/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	01/07/2011	n/a		
N/0086	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/05/2011	n/a	Labelling and PL	
II/0085/G	This was an application for a group of variations. -To change the active substance and finished product specifications. - To change the shelf-life of the active substance. B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	17/02/2011	25/02/2011		

	B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range				
IB/0084/G	This was an application for a group of variations. B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	09/09/2010	09/09/2010	SmPC, Labelling and PL	
II/0081	Update of the Summary of Product Characteristics (Section 4.8) and Package Leaflet (Section 4). Update of Summary of Product Characteristics and Package Leaflet	24/06/2010	06/08/2010	SmPC and PL	The product information was updated to include "hepatic failure" in section 4.8 of the SmPC and to add information on symptoms of severe liver problems in Section 4 of the Package Leaflet. The update was based on a CHMP requirement following assessment of the PSURs 19 and 20 and was further supported by a summary of available safety data presented by the MAH. In addition, the MAH took the opportunity to review the SOC order within the table in section 4.8 of the SmPC to be compliant with the order defined in the SmPC guideline and to replace "hair loss" by "alopecia", as "alopecia" is the preferred term (PT) and includes "hair loss".

II/0082	Additional manufacturer of active substance. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	22/04/2010	02/06/2010	Annex II	
II/0080	Introduction of a pre-filled pen as a new presentation in addition to the currently approved pre-filled syringe and cartridge. New presentation(s)	22/04/2010	02/06/2010	SmPC, Labelling and PL	The proposed Rebif pre-filled pen is manufactured by inserting the currently approved syringes (8.8, 22 and 44 micrograms) into a single use auto-injector, called pre-filled pen. There are no changes in the drug substance or drug product (formulation, strength and primary container) of the currently approved Rebif pre-filled syringe. The only change is the additional step in the manufacturing process to assemble the pre-filled syringe into the pre-filled pen. The pre-filled pen is for single use i.e. injection of one dose of Rebif. There are no changes in the therapeutic indication, posology, administration route and treatment duration.
II/0079	Update of the Detailed Description of the Pharmacovigilance system (DDPS). Update of DDPS (Pharmacovigilance)	22/04/2010	02/06/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (version 9.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements. Consequently, Annex II has been updated with the new version number of the agreed DDPS.
N/0083	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/03/2010	n/a	Labelling and PL	

II/0078	Removal of a test from drug substance quality control release specifications and tests Change(s) to the test method(s) and/or specifications for the active substance	21/01/2010	02/02/2010		
II/0077	Introduction of a new cell banking system for interferon beta-1a Change(s) to the manufacturing process for the active substance	21/01/2010	02/02/2010		
II/0074	Revision of the storage conditions Change(s) to shelf-life or storage conditions	24/09/2009	23/10/2009	SmPC, Labelling and PL	
N/0076	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/09/2009	n/a	PL	
N/0073	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/07/2009	n/a	Labelling	
IA/0075	IA_01_Change in the name and/or address of the marketing authorisation holder	24/07/2009	n/a	SmPC, Labelling and PL	
II/0072	Change in the storage conditions Update of or change(s) to the pharmaceutical documentation	29/05/2009	01/07/2009	SmPC, Labelling and PL	

II/0070	Update of section 4.8 of the SPC and section 4 of the PL, in line with the CHMP conclusions on the PSUR (covering the period from 04.05.07 to 03.05.08), the company core safety information and QRD guidelines. Update of Summary of Product Characteristics and Package Leaflet	19/03/2009	22/04/2009	SmPC and PL	The MAH conducted cumulative reviews of the safety information available regarding the risk of multiple sclerosis pseudo-relapses, retinal vascular disorder, thrombotic thrombocytopenic purpura and haemolytic uremic syndrome, in patients treated with Rebif. This resulted in the inclusion of these syndromes and disorders as possible adverse drug reactions associated with Rebif treatment. The frequency for such adverse drug reactions could not be established based on the information available.
IA/0071	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	10/03/2009	n/a	Annex II and PL	
II/0069	Change in the manufacturing process of the active substance. Change(s) to the manufacturing process for the active substance	22/01/2009	28/01/2009		
II/0067	The MAH applied to implement a new test method and revised drug substance and drug product specifications. Change(s) to the test method(s) and/or specifications for the finished product	22/01/2009	28/01/2009		
X/0064	The applicant has applied for three additional presentations of Rebif: 8.8 mcg/0.1ml, 22 mcg/0.25ml (in a cartridge	20/11/2008	16/01/2009	SmPC, Labelling and PL	The Marketing Authorisation Holder applied for the introduction of three additional presentations of Rebif: 8.8 mcg/0.1ml, 22 mcg/0.25ml (in a cartridge containing

	containing 1,5ml, corresponding to 6 doses of 8.8 mcg/0.1ml and 22 mcg/0.25 ml, respectively) 44 mcg/ml (in a cartridge containing 1.5ml, corresponding to 3 doses of 22 mcg/0.5 ml) and 88 mcg/ml (in a cartridge containing 1.5ml, corresponding to 3 doses of 44 mcg/0.5 ml). Annex I_2.(d) Change or addition of a new pharmaceutical form				1,5ml, corresponding to 6 doses of 8.8 mcg/0.1ml and 22 mcg/0.25 ml, respectively) 44 mcg/ml (in a cartridge containing 1.5ml, corresponding to 3 doses of 22 mcg/0.5 ml) and 88 mcg/ml (in a cartridge containing 1.5ml, corresponding to 3 doses of 44 mcg/0.5 ml). The presentations are solutions for injection in multidose pre-filled cartridges, which will allow the patient to administer the three weekly doses form the same cartridge. The excipients used in the manufacture of the approved and the proposed Rebif HSA-free formulations are identical. The manufacturing process of the proposed Rebif drug product in cartridges remains the same as the manufacturing process of the approved Rebif in pre-filled syringes. There are no changes in the currently approved clinical indication, route of administration, dosage regimen and treatment duration.
II/0065	Change(s) to the drug product specifications. Change(s) to the test method(s) and/or specifications for the finished product	23/10/2008	03/11/2008		
IA/0068	IA_05_Change in the name and/or address of a manufacturer of the finished product	20/10/2008	n/a	Annex II and PL	
IA/0063	IA_05_Change in the name and/or address of a manufacturer of the finished product	05/06/2008	n/a		

IA/0062	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	28/05/2008	n/a		
R/0061	Renewal of the marketing authorisation.	19/03/2008	20/05/2008	SmPC and PL	Based on their review of the available information and on the basis of a re-evaluation of the benefit/risk balance, the CHMP was of the opinion that the quality, safety and efficacy continue to be adequately and sufficiently demonstrated. Therefore, the benefit/risk profile of Rebif continues to be favourable. However, the review of safety data led to the inclusion of "dyspnoea" and "Stevens-Johnson syndrome" in section 4.8 of the SPC. The MAH will continue to submit yearly periodic safety update reports until otherwise specified by the CHMP. The CHMP recommended the renewal of the Marketing Authorisation for Rebif with unlimited validity.
II/0060	Update of section 4.8 of the Summary of Products Characteristics (SPC) to reflect the overall percentage of treated patients expected to experience injection site reactions. Update of Summary of Product Characteristics	15/11/2007	14/12/2007	SmPC	The 48-week results of study 25632 submitted for the approval of the HSA-free formulation of Rebif showed an incidence rate of injection site reactions following administration of 44 mcg subcutaneously, three times per week, of 29.6 % in 260 subjects. This represents a lower incidence rate than the 80 to 90% observed in the historical comparator studies or "Historical cohort," which comprised 727 subjects treated with the previous HSA-containing formulation of Rebif at 44 mcg subcutaneously three times per week in three controlled studies.
II/0054	Change in formulation	21/06/2007	10/08/2007	SmPC, Annex II, Labelling and PL	
II/0055	Change(s) to the manufacturing process for the active substance	21/06/2007	27/06/2007		

II/0059	Update of section 4.2 of the SPC to include information regarding the use of Rebif in paediatrics, as recommended by the CHMP. The Package Leaflet was amended accordingly. In addition the MAH took the opportunity to update the contact details for Spain, Portugal, France, Greece and Sweden and to add local representatives for the two new EU Member States Bulgaria and Romania. Annex II is amended according to the latest QRD template. Update of Summary of Product Characteristics and Package Leaflet	22/02/2007	28/04/2007	SmPC, Annex II and PL	No specific studies or data collection have been conducted so far by the MAH in the paediatric multiple sclerosis population. The CHMP has reviewed published data on the use of interferon beta in paediatric patients, mostly in the range of 12 to 16 years of age. In addition, the CHMP reviewed a recent publication provided by the MAH and reporting the results of a 6-year open-label, prospective single-centre study assessing the safety and tolerability of Rebif administered at different doses in 24 children or adolescent, including 8 children less than 10 years of age (Tenembaum SN, Segura MJ. Neurology 2006; 67:511-513). The information available on efficacy and safety of interferon beta in children is limited. Efficacy cannot be considered specifically demonstrated in children but there are no signals of specific safety issues in paediatric patients. Although the data are scarce, the CHMP recommended that the available information is reflected in the product information of all interferon beta.
II/0058	Change(s) to the manufacturing process for the active substance Change(s) to the manufacturing process for the finished product	16/11/2006	27/11/2006		
II/0057	This variation relates to the update of SPC sections 4.3, 4.4 and 4.6 in order to implement the interferon beta class review SPC wording on contraindications adopted by the CHMP in April 2006. The Package Leaflet has been amended accordingly. Update of Summary of Product Characteristics and	27/07/2006	01/09/2006	SmPC and PL	Further to the request of the CHMP, the CHMP Pharmacovigilance Working Party (PhVWP) performed a class review of all interferons beta authorised in the treatment of multiple sclerosis to provide recommendations on the need for and the nature of changes to the current contraindications in pregnancy, patients with a history of severe depressive disorders and/or suicidal ideation and

	Package Leaflet				patients with epilepsy not adequately controlled by treatment. Based on the data submitted by the MAH (clinical trial, post-marketing data and literature) and the PhVWP recommendations, the CHMP agreed on the following changes: - Removal of the absolute contraindication (section 4.3) in patients with epilepsy not adequately controlled with treatment and revision of section 4.4 of the SPC to indicate that interferon beta should be used with caution in patients with epilepsy, particularly if their epilepsy is not adequately controlled - Revision of the contraindication (section 4.3) in pregnancy to indicate that initiation of treatment in pregnancy is contraindicated but leave some room for clinical judgement as to whether a patient who becomes pregnant while taking interferon beta should continue or stop treatment. Consequential changes were made to section 4.6 of the SPC. - Revision of the contraindication (section 4.3) in patients with a history of severe depressive disorders and/or suicidal ideation, to indicate that treatment of patients with current severe depression and/or suicidal ideation is contraindicated. Consequential changes were made to section 4.4 of the SPC. The Package Leaflet was amended accordingly.

II/0056	The Marketing Authorisation Holder applied for an update of the Summary of Product Characteristics (sections 4.4, 4.8 and 4.9) based on literature and post-marketing data. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	01/09/2006	SmPC and PL	The safety information of the SPC was updated based on literature and post-marketing data provided by the MAH. The recommendations for the monitoring of haematological laboratory parameters were amended in section 4.4 to provide more information on the timing of blood cell counts. Section 4.8 was updated as follows: - Change of frequency of the adverse reactions neutropenia, lymphopenia, leucopenia, thrombocytopenia and anemia from 'Common' to 'Very common" - Addition of "injection site infections, including cellulitis" - Update of the endocrine disorders related information with the replacement of the wording "elevated T3 and T4, reduced TSH" by "most often presenting as hypothyroidism or hyperthyroidism" Section 4.9 was also updated further to the first report of overdose with Rebif. The Package Leaflet was updated in line with the SPC changes.
N/0053	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/05/2006	n/a	Labelling	
II/0052	This variation relates to the update of the wording of section 4.1 and 5.1 in order to align them with the current medical practice, taking into account the McDonald criteria for the diagnosis of multiple sclerosis. Update of Summary of Product Characteristics	27/04/2006	31/05/2006	SmPC	The current indication of Rebif in the "treatment of patients with multiple sclerosis and with 2 or more relapses within the last 2 years" reflects the inclusion criteria used in the clinical studies which formed the basis for approval of Rebif, in line with the then applicable Poser diagnostic criteria of definite multiple sclerosis. As it stands, this indication excludes the patients with a diagnosis of MS who have had a clinically isolated syndrome with lesion dissemination on subsequent MRI scans according to the more recent McDonald's criteria. Therefore, the indication

					was revised so it is expressed in a way as to align it with the current medical practice, while keeping it restricted to patients with diagnosed MS. The indication wording clarifies that in clinical trials where Rebif has been administered, the disease was characterised by two or more acute exacerbations in the previous two years. A cross-reference is made in section 4.1 to section 5.1 where the inclusion criteria used in the clinical trials supporting the original approval of Rebif (i.e. multiple sclerosis characterised by 2 or more acute exacerbations in the previous 2 years and with an EDSS of 0-5.0 at entry) have been specified.
X/0051	The Marketing Authorisation Holder applied to introduce a new strength product that will be provided in a Initiation pack, containing 6 syringes of the 8.8 micrograms and 22 micrograms presentation, respectively. Annex I_2.(c) Change or addition of a new strength/potency	15/09/2005	19/01/2006	SmPC, Annex II, Labelling and PL	Currently, the registered strengths of Rebif are 22 µg and 44 µg in 0.5 ml. The recommended posology of Rebif is 44 micrograms given three times weekly by subcutaneous injection. The currently approved SPC also indicates that: "When first starting treatment with Rebif, in order to allow tachyphylaxis to develop thus reducing adverse reactions, it is recommended that 8.8 micrograms (0.1 ml of the 44 micrograms strength or 0.2 ml of the 22 micrograms strength) be administered during the initial 2 weeks of therapy, 22 micrograms (0.25 ml of the 44 micrograms strength or the total of the 22 micrograms strength) be administered in weeks 3 and 4, and the total of the 44 micrograms strength be administered from the fifth week onwards." An additional strength (Rebif 8.8 µg/0.2 ml) will allow the patient to follow the recommended initial dose titration without the need to discard part of the syringe content.

					The new strength product will be provided in a "Initiation pack", containing 6 syringes of the 8.8 µg and 22 µg presentation, respectively. Each pre-filled syringe (1ml) is designed to deliver 0.2 ml (for 8.8 µg) or 0.5 ml (for 22 µg) of a sterile, clear aqueous solution. The interferon-ß-1a 8.8 µg finished product batches have been manufactured using the same compounding, manufacturing process, equipment and quality control procedures as for the currently marketed Interferon-ß-1a finished product (22 and 44 µg) and are differing only in the syringe fill volume (0.2 ml instead of 0.5 ml per syringe).
N/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/11/2004	n/a	PL	
II/0047	Change(s) to the manufacturing process for the active substance	23/06/2004	20/07/2004	Annex II	
II/0049	Update of Summary of Product Characteristics and Package Leaflet	17/12/2003	23/02/2004	SmPC and PL	
I/0046	15a_Change in IPCs applied during the manufacture of the product	01/12/2003	n/a		
I/0045	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	01/12/2003	n/a		
II/0044	Change(s) to the test method(s) and/or specifications for the active substance	22/10/2003	30/10/2003		
I/0048	15a_Change in IPCs applied during the manufacture of the product	20/10/2003	22/10/2003		

I/0043	31_Change in container shape	20/08/2003	18/09/2003		
II/0038	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	25/06/2003	SmPC and PL	
R/0040	Renewal of the marketing authorisation.	19/03/2003	04/06/2003	SmPC, Labelling and PL	
II/0042	Change(s) to the test method(s) and/or specifications for the active substance	22/05/2003	27/05/2003		
N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/01/2003	04/03/2003	PL	
X/0022	X-1-vi_Repl. of biological substance with one of a diff. molecular structure; modification of vector	17/10/2002	16/01/2003	Annex II	
I/0037	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	11/12/2002	13/12/2002		
I/0036	12_Minor change of manufacturing process of the active substance	22/08/2002	10/09/2002		
I/0035	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	22/08/2002	10/09/2002		
II/0033	Change(s) to the test method(s) and/or specifications for the finished product	25/07/2002	31/07/2002		

I/0034	24_Change in test procedure of active substance 25_Change in test procedures of the medicinal product	25/07/2002	31/07/2002		
II/0030	Update of Summary of Product Characteristics and Package Leaflet	21/02/2002	17/05/2002	SmPC and PL	
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/03/2002	02/04/2002	Labelling	
I/0031	16_Change in the batch size of finished product	01/02/2002	11/02/2002		
II/0029	Change(s) to the manufacturing process for the active substance	15/11/2001	28/11/2001		
II/0017	Change(s) to the test method(s) and/or specifications for the active substance	21/09/2000	20/11/2001		
II/0011	Update of Summary of Product Characteristics and Package Leaflet	26/07/2001	20/11/2001	SmPC and PL	
I/0028	20a_Extension of shelf-life or retest period of the active substance	21/09/2001	n/a		
I/0026	03_Change in the name and/or address of the marketing authorisation holder	26/07/2001	18/09/2001	SmPC, Labelling and PL	
I/0027	01_Change following modification(s) of the manufacturing authorisation(s)	17/08/2001	07/09/2001		

N/0024	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/08/2001	03/10/2001	Labelling	
I/0025	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	09/08/2001	n/a		
I/0021	23_Change in storage conditions	11/06/2001	19/07/2001	SmPC and PL	
I/0015	11_Change in or addition of manufacturer(s) of active substance	14/12/2000	20/03/2001	Annex II	
I/0020	26_Changes to comply with supplements to pharmacopoeias	28/02/2001	11/03/2001		
II/0013	Update of Summary of Product Characteristics and Package Leaflet	19/10/2000	22/01/2001	SmPC and PL	
I/0019	01_Change following modification(s) of the manufacturing authorisation(s)	14/12/2000	20/12/2000		
S/0014	Annual re-assessment.	26/07/2000	08/12/2000	Annex II	
I/0016	12_Minor change of manufacturing process of the active substance	21/09/2000	n/a		
I/0018	17_Change in specification of the medicinal product 31_Change in container shape	01/09/2000	n/a		
I/0012	11b_Change in supplier of an intermediate compound used in manufacture of the active	16/03/2000	n/a		

	substance				
I/0010	01_Change following modification(s) of the manufacturing authorisation(s)	12/11/1999	20/01/2000	Annex II and PL	
I/0008	20_Extension of shelf-life as foreseen at time of authorisation	05/10/1999	14/12/1999	SmPC, Labelling and PL	
S/0003	Annual re-assessment.	23/06/1999	03/12/1999	Annex II	
II/0009	Quality changes	18/11/1999	02/12/1999		
N/0007	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/10/1999	14/12/1999	PL	
I/0006	12_Minor change of manufacturing process of the active substance	22/09/1999	05/10/1999		
I/0005	13_Batch size of active substance	28/07/1999	n/a		
X/0001	X-3-iii_Addition of new strength	16/12/1998	29/03/1999	SmPC, Annex II, Labelling and PL	
II/0002	Update of Summary of Product Characteristics and Package Leaflet	22/10/1998	01/02/1999	SmPC and PL	