Avonex

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
II/0193	Update of sections 4,1 4.2, 4.8 and 5.1 of the SmPC in order to update safety information for the paediatric population based on the final results of the Tecfidera Paediatric study (109MS306) (CONNECT - part 1), submitted as part of the PAM procedure P46/089, availability of data from published literature	15/12/2022		SmPC and PL	For more information, please refer to the Summary of Product Characteristics.

[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).

	and postmarketing data form Biogen global safety database; the Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0192	Update of section 4.4 of the SmPC in order to add a new warning regarding the risk of injection site necrosis based on post marketing experience. The Package Leaflet sections 2 and 4 are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/09/2022		SmPC and PL	Section 4.4 of the SmPC was updated to add a warning to minimise of the risk of injection site necrosis. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10725 /202105	Periodic Safety Update EU Single assessment - interferon beta-1a (intramuscular use)	13/01/2022	n/a		PRAC Recommendation - maintenance
IB/0191	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	21/10/2021	n/a		
IB/0189/G	This was an application for a group of variations. B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS	12/08/2021	n/a		

	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised				

IA/0188	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)	24/03/2021	n/a		
IAIN/0187/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	11/02/2021	17/02/2022	Annex II and PL	
N/0186	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/12/2020	17/02/2022	Labelling and PL	
IA/0185	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	03/09/2020	n/a		
N/0184	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/08/2020	17/02/2022	PL	

II/0182/G	This was an application for a group of variations. To update sections 4.3 and 4.6 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 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 of the SmPC. The Package leaflet has been updated accordingly. This submission fulfils MEA 87.2 and 84. 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	19/09/2019	22/06/2020	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 A large amount of data (more than 1000 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 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 Avonex 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. Avonex can be used during breast-feeding. The PL has been updated accordingly.
IB/0183	C.I.7.a - Deletion of - a pharmaceutical form	06/06/2019	22/06/2020	SmPC, Labelling and PL	
IA/0181/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material	19/12/2018	n/a		
PSUSA/9198/ 201805	Periodic Safety Update EU Single assessment - interferon beta-1a	29/11/2018	n/a		PRAC Recommendation - maintenance
IB/0180	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	22/10/2018	n/a		

	manufacturer				
T/0178	Transfer of Marketing Authorisation	03/07/2018	02/08/2018	SmPC, Labelling and PL	
IB/0177	B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	10/01/2018	n/a		
IA/0176/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	04/09/2017	n/a		
IB/0174	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/05/2017	26/04/2018	SmPC, Annex II, Labelling and PL	
IA/0175	A.7 - Administrative change - Deletion of manufacturing sites	05/05/2017	n/a		
IB/0173	A.7 - Administrative change - Deletion of manufacturing sites	27/04/2017	n/a		
II/0170/G	This was an application for a group of variations. IA: B.II.d.1.a - To tighten release and stability specification limits for protein concentration from 54.0 - 69.0 µg/mL to 56.0 - 68.0 µg/mL of the	15/09/2016	n/a		

	finished product IA: B.II.d.1.a - To tighten release specification for deamidation from ≤ 55% to ≤ 46% of the finished product IA: B.II.d.1.a - To tighten release specification for biantennary sialylation from ≥ 90% to ≥ 92% of the finished product II: B.II.d.1.e To change release and stability specifications for potency from 10-17 MU/mL to 9-15 MU/mL for release and 10-17 MU/mL to 8-16 MU/mL for stability of the finished product II: B.II.d.1.f To remove biantennary sialylation from the stability specification of the finished product B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product				

IB/0172	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	18/08/2016	n/a		
WS/0927	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	14/07/2016	n/a		
IB/0168	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	01/07/2016	n/a		
N/0171	Update of the package leaflet with revised contact details of the local representatives for Romania and Norway. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/06/2016	26/04/2018	PL	
IB/0169	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting	30/06/2016	n/a		

	material/intermediate				
IAIN/0167	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	14/06/2016	n/a		
IA/0165	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	04/04/2016	n/a		
IA/0164	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	04/04/2016	n/a		
N/0163	Update of the Package Leaflet with revised contact details of the local representatives for Estonia and Latvia and removal of the word '(see right)' in Section 7 of the package leaflet for all the languages as it is not appropriate for some countries. In addition, the MAH took the opportunity to make minor linguistic amendments , formatting changes and alignments of texts to ensure consistency in the Package Leaflets for: DA, EL, ES, FI, IS, LT, LV, NL, CS, DE, IT, NO, PT, and SL. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/02/2016	16/06/2016	PL	
IA/0162	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	21/12/2015	n/a		

IA/0161	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	21/12/2015	n/a		
IA/0160/G	This was an application for a group of variations. B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former	21/12/2015	n/a		

	non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material				
PSUSA/9198/ 201505	Periodic Safety Update EU Single assessment - interferon beta-1a	03/12/2015	n/a		PRAC Recommendation - maintenance
IA/0159	A.7 - Administrative change - Deletion of manufacturing sites	12/11/2015	n/a		
IB/0158	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	29/10/2015	n/a		
WS/0805	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of SmPC section 4.8 and PL section 4 in order to include class text for interferon-beta products regarding pulmonary arterial hypertension (PAH). This change has been agreed by PRAC and endorsed by CHMP on 23 April 2015. C.I.z - Changes (Safety/Efficacy) of Human and	29/10/2015	16/06/2016	SmPC and PL	

	Veterinary Medicinal Products - Other variation				
WS/0806	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of SmPC, Labelling and Package Leaflet in line with EMA recommendation and QRD template. In addition, MAH took the opportunity to implement linguistic and editorial corrections. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/09/2015	16/06/2016	SmPC, Labelling and PL	
IG/0615	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	11/09/2015	n/a		
WS/0750	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	06/08/2015	n/a		
IA/0155	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	05/08/2015	n/a		

	manufacturer of a novel excipient				
IAIN/0152	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	26/06/2015	16/06/2016	Annex II and PL	
IG/0558/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	12/05/2015	n/a		
IA/0149	A.7 - Administrative change - Deletion of manufacturing sites	29/04/2015	n/a		
IAIN/0148	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	02/02/2015	n/a		

IB/0147/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.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 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 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 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	22/12/2014	n/a		
IA/0146	A.7 - Administrative change - Deletion of manufacturing sites	10/12/2014	n/a		
N/0145	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/10/2014	16/06/2016	PL	
II/0143	Update of the SmPC Sections 4.4 and 4.8 to include class labelling wording on thrombotic	24/07/2014	26/08/2014	SmPC, Annex II, Labelling	The MAH conducted a cumulative search for cases of thrombotic microangiopathy. Further to the PRAC review of

	microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS). The Package leaflet has been updated accordingly. Furthermore, minor editorial changes have been introduced throughout the PI. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation			and PL	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.
IA/0144	A.7 - Administrative change - Deletion of manufacturing sites	06/06/2014	n/a		
IB/0142	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	09/05/2014	26/08/2014	SmPC	
II/0141	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. Furthermore, the Product Information (PI) was brought in line with the latest QRD template version 9.0. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/04/2014	26/08/2014	SmPC, Annex II, Labelling 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/0140/G	This was an application for a group of variations.	23/01/2014	n/a		

	Major changes to the manufacturing process of the active substance. Introduction of a new site for QC testing for the active substance. B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method 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 B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol				

	B.I.e.2 - Introduction of a post approval change management protocol related to the AS B.II.h.1.a - Update to the Adventitious Agents Safety Evaluation information - Studies related to manufacturing steps investigated for the first time for one or more advantitious agents B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
IB/0138/G	This was an application for a group of variations. B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.II.d.2.d - Change in test procedure for the finished	09/09/2013	n/a		

	product - Other changes to a test procedure (including replacement or addition) B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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 B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction				
IA/0139	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	19/08/2013	n/a		
N/0137	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/08/2013	26/08/2014	PL	

II/0136	Additional site for manufacturing and QC testing of finished product. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.	25/07/2013	n/a		
IA/0135	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)	22/11/2012	n/a		
N/0133	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/10/2012	26/08/2014	PL	
IA/0132	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)	24/08/2012	n/a		
IB/0130/G	This was an application for a group of variations. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	10/08/2012	n/a		

II/0125	Update of section 5.2 of the SmPC in order to delete information on the comparison of intramuscular vs subcutaneous bioavailability in accordance with the SmPC guideline. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/06/2012	20/07/2012	SmPC	The MAH submitted data from a clinical pharmacokinetic study evaluating bioequivalence of Avonex administered subcutaneously versus intramuscularly in healthy volunteers. The CHMP considered that the data did not significantly contribute to the knowledge of the pharmacokinetic profile of Avonex and were not of relevance to the prescriber and thus did not accept them as basis for updating the Product Information. In the context of evaluating relevance of the information in section 5.2 to the prescriber in general, the existing text concerning bioavailability after subcutaneous administration was deleted, as the product is not authorised for subcutaneous use.
II/0128/G	This was an application for a group of variations. Change to the assay for the determination of biological activity for active substance and finished product B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/ immunological/immunochemical test method or a method using a biological reagent	21/06/2012	n/a		
IA/0129	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the	12/06/2012	n/a		

	dossier) - Replacement or addition of a supplier				
IB/0127	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	11/04/2012	n/a		
IB/0126	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	15/02/2012	n/a		
IB/0121	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	10/01/2012	n/a		
IB/0124	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	05/01/2012	n/a		
IB/0123	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	05/01/2012	n/a		
N/0122	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/12/2011	20/07/2012	PL	
IB/0120	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	10/11/2011	n/a		
II/0115	Update of sections 4.2 and 4.8 of the SPC and	22/09/2011	24/10/2011	SmPC and PL	The product information for Avonex has been updated with

	sections 3, 4 and 7 of the Package Leaflet with details of a titration schedule to limit the occurrence of flu-like symptoms at the initiation of therapy, based on data from a controlled study in healthy volunteers and a retrospective analysis of a study in patients. In addition, the list of local representatives in the PL has been updated, and minor editorial and formatting amendments have been made across the product information. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				details of a titration schedule to limit the occurrence of flu-like symptoms at the initiation of therapy. The titration schedule is based on data from a controlled study in 234 healthy volunteers and a retrospective analysis of a study in 47 patients with multiple sclerosis (MS). The clinical data from the study in healthy volunteers show that titration of Avonex to full dose in ¼-dose increments over 3 weeks produces a statistically significant reduction in the incidence and severity of flu-like symptoms over 8 weeks compared with the no dose titration regimen. The results of the retrospective analysis of a study in MS patients seem to confirm the efficacy of titration in reducing flu-like symptoms associated with Avonex and support the extension of the findings in healthy volunteers to the target population.
II/0118	-To introduce a post-approval change management protocol related to the manufacturing process of the AS. B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the AS	20/10/2011	20/10/2011		
IA/0119	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	28/09/2011	n/a		
IA/0117	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	18/08/2011	n/a		

IB/0116	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	01/08/2011	n/a		
IB/0112/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation 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	15/06/2011	n/a		
IB/0113	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	31/05/2011	n/a		
II/0110/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging	14/04/2011	27/05/2011	SmPC, Labelling and PL	

IA/0114	A.7 - Administrative change - Deletion of manufacturing sites	19/05/2011	n/a	Annex II and PL	
IA/0111	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)	11/01/2011	n/a		
II/0109/G	This was an application for a group of variations. B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance b) Tightening of specification limits IA IB9 f) Change outside the approved specifications limits range for the active substance II B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State a) Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance e) Other changes to a test procedure (including	24/06/2010	30/06/2010		

	replacement or addition) for the active substance or a starting material/intermediate 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 B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.III.2.a.1 - Change of specification('s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS				
II/0108	Based on the submission of the article 45 of the Paediatric Regulation 1901/2006, as amended, the CHMP recommended an update of the Product Information to reflect results from one completed paediatric study for Avonex (Pakdaman et al 2006), that was a trial treating 16 Multiple Sclerosis (MS) patients under the age of 16, with 15 micrograms IM Avonex once per week. In line with the CHMP conclusions, the MAH amended the Product Information in section 5.1 and further updated	21/01/2010	15/03/2010	SmPC	

	sections 4.2 and 4.8 in relation to paediatric information to be in accordance with the SPC guideline. The following was introduced in relevant sections of the SPC: - The safety and efficacy of Avonex in adolescents aged 12 to 16 years have not yet been established. Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made. - The safety and efficacy of Avonex in children below 12 years of age have not yet been established. No data are available. - Limited published data suggest that the safety profile in adolescents from 12 to 16 years of age receiving AVONEX 30 micrograms IM once per week is similar to that seen in adults. - Limited data of the efficacy/safety of AVONEX 15micrograms IM once per week (n=8) as compared to no treatment (n=8) with follow up for 4 years showed results in line to those seen in adults,although the EDSS scores increased in the treated group over the 4 year follow-up thus indicating disease progression. No direct comparison with the dose currently recommended in adults is available. Update of Summary of Product Characteristics				

II/0107	Changes to the manufacturing process for the finished product Change(s) to the manufacturing process for the finished product	24/09/2009	30/09/2009		
IA/0106	IA_05_Change in the name and/or address of a manufacturer of the finished product	01/07/2009	n/a		
II/0105	The MAH applied for changes to the specifications of the finished product. Change(s) to the test method(s) and/or specifications for the finished product	18/12/2008	05/01/2009		
II/0103	Update of section 4.2 of the SPC and sections 3 and 7 of the PL to introduce recommendations for a titration period at the beginning of Avonex solution for injection treatment, and a device to enable delivery of approximately half the dose of Avonex during the titration phase. The MAH also took this opportunity to update the contact details of the local representatives in the PL for all presentations. Update of Summary of Product Characteristics and Package Leaflet	20/11/2008	17/12/2008	SmPC and PL	The new dose recommendation allowing for the use of half the dose of Avonex at the beginning of treatment before reaching and maintaining the full dose (30 micrograms) was essentially based on literature data, as no new clinical data were submitted. Published data available do not provide direct comparison on the incidence of flu-like symptoms between patients receiving Avonex 30 mcg and those receiving titrated doses of other interferon beta at the beginning of treatment. However, the review of safety data from previously conducted trials with Avonex and other interferons beta show a clear trend towards the reduction in the incidence of flu-like symptoms when dose titration is applied. Beside, titration is common practice with interferon beta containing medicinal products indicated in the treatment of multiple sclerosis.

IA/0104	IA_37_a_Change in the specification of the finished product - tightening of specification limits	24/07/2008	n/a		
IB/0100	IB_30_b_Change in supplier of packaging components - replacement/addition	08/07/2008	n/a		
IA/0102	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	02/07/2008	n/a		
IA/0101	IA_01_Change in the name and/or address of the marketing authorisation holder	27/06/2008	n/a	SmPC, Labelling and PL	
II/0098	Change to the Manufacturing process of the Finished Product Change(s) to the manufacturing process for the finished product	24/04/2008	20/06/2008	SmPC and PL	
IB/0099	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	30/04/2008	n/a	SmPC	
II/0097	Change in the Manufacturing Process of the active substance. Change(s) to the manufacturing process for the active substance	24/04/2008	28/04/2008		
II/0096	Update of SPC sections 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.	24/01/2008	03/03/2008	SmPC, Labelling and PL	The current indication of Avonex in the "relapsing multiple sclerosis (MS) characterised by at least two recurrent attacks of neurological dysfunction (relapses) over the preceeding three year period" reflects the inclusion criteria

	Update of Summary of Product Characteristics, Labelling and Package Leaflet				used in the clinical studies which formed the basis for approval of Avonex, in line with the then applicable Poser diagnostic criteria of definite MS. Therefore, the indication in relapsing MS was revised to align it with the current medical practice, while keeping it restricted to patients with diagnosed relapsing MS. The indication wording also clarifies that in clinical trials where Avonex has been administered, the disease was characterised by two or more acute exacerbations in the previous three years. The indication in patients with a single demyelinating event and an active inflammatory process remained unchanged.
IA/0095	IA_05_Change in the name and/or address of a manufacturer of the finished product	06/11/2007	n/a		
N/0094	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2007	n/a	Labelling	
II/0091	Change(s) to the test method(s) and/or specifications for the finished product	19/07/2007	01/08/2007		
N/0092	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/07/2007	n/a	PL	
IA/0093	IA_47_a_Deletion of a pharmaceutical form	18/06/2007	n/a	SmPC, Labelling and PL	
II/0087	Change(s) to the test method(s) and/or specifications for the finished product	26/04/2007	03/05/2007		
N/0088	Minor change in labelling or package leaflet not	25/04/2007	n/a	PL	

	connected with the SPC (Art. 61.3 Notification)				
IA/0090	IA_09_Deletion of manufacturing site IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	25/04/2007	n/a		
IA/0089	IA_09_Deletion of manufacturing site IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	25/04/2007	n/a		
II/0086	Update of or change(s) to the pharmaceutical documentation Change(s) to the manufacturing process for the active substance	22/02/2007	27/02/2007		
II/0085	Update of or change(s) to the pharmaceutical documentation	22/02/2007	27/02/2007		
II/0084	Change(s) to the manufacturing process for the active substance	22/02/2007	27/02/2007		
R/0081	Renewal of the marketing authorisation.	14/12/2006	21/02/2007	SmPC, Annex II, Labelling 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 Avonex continues to be favourable. The CHMP recommended the renewal of the Marketing Authorisation for Avonex with unlimited validity.
II/0082	The MAH submitted this variation to implement revised wording to section 4.2 of the SPC and	14/12/2006	31/01/2007	SmPC and PL	The MAH submitted a review of published literature regarding the use of Avonex in paediatric patients aged 12

	sections 2 and 3 of the Package Leaflet regarding the use of Avonex in paediatrics, as recommended by the CHMP. Update of Summary of Product Characteristics and Package Leaflet				to 18, as well as an assessment of the available post marketing database for children. No specific studies or data collection have been conducted so far by the MAH in the paediatric multiple sclerosis population. A few dozens of patients, mainly around 12 years old, have been treated and followed by their physicians. The treating physicians used recommended adult doses and observed a decrease of relapse rate with the treatment. Supporting MRI is not available. It is not possible to discriminate between the possible efficacy in decreasing the relapse rate and regression to the mean and other factors influencing the observed effect. Therefore, efficacy cannot be considered specifically demonstrated in children. From a safety point of view, there are no signals of specific safety issues in paediatric patients although available data are scarce. The CHMP recommended that the available information is reflected in the product information.
IB/0083	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	20/12/2006	20/12/2006	SmPC, Labelling and PL	
II/0078	Change(s) to the manufacturing process for the finished product	21/09/2006	20/10/2006	SmPC, Labelling and PL	
II/0077	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.

IA/0080	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	30/08/2006	n/a	Annex II	
N/0079	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/08/2006	n/a	Labelling and PL	
II/0076	Change(s) to the manufacturing process for the active substance	28/06/2006	03/07/2006		
II/0074	Change(s) to the manufacturing process for the active substance	28/06/2006	03/07/2006		
N/0075	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/03/2006	n/a	PL	
S/0066	Annual re-assessment.	26/01/2006	22/03/2006	Annex II	
N/0073	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/03/2006	n/a		
II/0070	Change(s) to the manufacturing process for the finished product	26/01/2006	02/02/2006		
IB/0072	IA_28_Change in any part of primary packaging material not in contact with finished product IB_30_b_Change in supplier of packaging components - replacement/addition	02/02/2006	n/a		
II/0068	Change(s) to the manufacturing process for the active substance	14/12/2005	21/12/2005		

IB/0069	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	13/12/2005	n/a		
N/0067	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/10/2005	n/a	PL	
II/0065	Change(s) to the manufacturing process for the active substance	15/09/2005	26/09/2005		
II/0063	Change(s) to the manufacturing process for the active substance	15/09/2005	26/09/2005		
II/0061	Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	31/08/2005	SmPC and PL	Following the assessment of the 13th PSUR, the MAH applied to update sections 4.4 "Special warnings and special precautions for use" and 4.8 "Undesirable effects" of the SPC. In section 4.4, the sentence "In some patients a recurrence of elevated serum levels of hepatic enzymes has occurred upon Avonex rechallenge.", was considered misleading since it might be interpreted that only elevated hepatic enzymes recur upon rechallenge, and no other laboratory tests (e.g. platelet counts, white blood cells counts). In section 4.8, the following ADRs were included: "angioneurotic oedema", "injection site bleeding" and a description of the most common hypersensitivity reactions reported ("angioedema", "dyspnoea", "urticaria", "rash" and "pruritic rash"). The Package Leaflet has been updated accordingly.
II/0059	Update of Summary of Product Characteristics, Labelling and Package Leaflet	27/07/2005	31/08/2005	SmPC, Annex II, Labelling	The MAH applied for an administrative type II variation to update the SPC, Labelling and Package Leaflet of Avonex in line with the latest SPC guideline, QRD templates and

				and PL	standard terms. The MAH also took the opportunity to ensure consistency between the product information of the different strengths.
II/0062	Change(s) to shelf-life or storage conditions	28/07/2005	10/08/2005		
II/0060	Change(s) to the manufacturing process for the finished product	23/06/2005	29/06/2005		
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/06/2005	n/a	PL	
II/0058	Change(s) to the manufacturing process for the active substance	26/05/2005	02/06/2005		
T/0056	Transfer of Marketing Authorisation	14/01/2005	14/02/2005	SmPC, Labelling and PL	The MAH applied for the transfer of the Marketing Authorisation of Avonex from Biogen Idec France to Biogen Idec Ltd.
IA/0057	IA_05_Change in the name and/or address of a manufacturer of the finished product	27/01/2005	n/a		
IA/0055	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	29/11/2004	n/a		
II/0053	Change(s) to the test method(s) and/or specifications for the finished product Change(s) to container	18/11/2004	23/11/2004		
IA/0054	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	10/11/2004	n/a	Annex II	

S/0052	Annual re-assessment.	21/10/2004	21/10/2004		The CHMP, having reviewed the evidence of compliance with the specific obligations submitted and having re-assessed the benefit/risk profile of the medicinal product, recommended that the marketing authorisation should remain under exceptional circumstances. The Specific Obligation still pending was the submission of the analysis of the secondary variables (MSFC and MRI) of the CHAMPION study by December 2005 at the latest.
II/0045	Update of Summary of Product Characteristics and Package Leaflet	29/07/2004	27/09/2004	SmPC and PL	Following the sixth annual reassessment, the CHMP considered that the MAH should update the SPC and PL in order to reflect the current safety knowledge about Avonex and to reorganise it according to the current SPC guideline. The main changes approved in section 4.8 (adverse reactions) were the following: The section 4.8 was reorganised according to the current SPC guideline and its content updated in order to reflect the current safety knowledge. Frequencies in the first sub section (experience from studies) were recalculated and, as recommended by the CHMP, open label studies were used for frequencies of ADRs not detected in clinical trials. The MAH has reviewed the time of occurrence of hypertonia during treatment in studies C94-801, C94-805, C94-812 and phase III Study NS26321. At the request of the CHMP, the information given in the section 4.8 of the SPC was modified in order to mention that hypertonia could occur at any time in the course of therapy. Following assessment of previous PSURs, "rash vesicular", "aggravation of psoriasis", "sweating" and "injection site necrosis" have been added in the table of adverse reactions

					identified through spontaneous reporting in section 4.8 of the revised SPC. Injection site reactions have been further detailed as follows: "Injection site reaction, including pain, inflammation and very rare cases of abscess or cellulitis that may require surgical intervention have been reported" The special warnings in the section 4.4 were modified as follows: Warning on depression: The results from study 801 provided information on the frequency of symptoms of depression when patients treated with Avonex were followed over a long period (up to 5.5 years). This study shows a frequency probably higher than expected. The specific warning in section 4.4 was modified in order to reflect that depression has been reported in association with Avonex use and that it may occur at any time during treatment. Warning on hepati
II/0050	Change(s) to the test method(s) and/or specifications for the finished product	16/09/2004	21/09/2004		
II/0049	Change(s) to container	29/07/2004	02/08/2004		
N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/06/2004	n/a	PL	
II/0047	Change(s) to the test method(s) and/or specifications for the finished product	03/06/2004	07/06/2004		

IA/0046	IA_01_Change in the name and/or address of the marketing authorisation holder IA_05_Change in the name and/or address of a manufacturer of the finished product	13/02/2004	n/a	SmPC, Annex II, Labelling and PL	
II/0039	Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	30/01/2004	SmPC, Labelling and PL	AVONEX has been investigated in progressive multiple sclerosis and the available evidence did not support the use of Avonex in this indication. The MAH therefore proposed to delete in section 4.1 (Indications) of the SPC the following sentences: - [AVONEX] "has not yet been investigated in patients with progressive multiple sclerosis, and " - "Not all patients respond to treatment with AVONEX. No clinical criteria that would predict the response to treatment has been identified." Section 5.1 of the SPC states that "Avonex should be discontinued in patients who develop progressive multiple sclerosis."
II/0044	Change(s) to the test method(s) and/or specifications for the active substance	17/12/2003	15/01/2004		
I/0043	25_Change in test procedures of the medicinal product	17/12/2003	15/01/2004		
I/0041	15_Minor changes in manufacture of the medicinal product	17/12/2003	15/01/2004		
S/0038	Annual re-assessment.	25/09/2003	12/01/2004	SmPC, Annex II and PL	Since the last annual reassessment, the final report of the open label study (C94-801) in patients with MS receiving 30 mg of AVONEX im to determine safety, antigenicity and

					the effect of neutralising antibody (NAB) on pharmacodynamics had been submitted on 30 January 2003. Regarding the immunogenicity of Avonex (antigenicity and effect of neutralising antibodies), the data provided was considered in line with previous reports, although the development of neutralising antibodies was slightly lower than stated in the SPC. No changes in the SPC were considered needed with regard to the data on the appearance of neutralising antibodies as a result of the evaluation of final report of study 801. The CHMP concluded that this specific obligation was considered fulfilled. The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product in the approved indications, recommended that the marketing authorisation should remain under exceptional circumstances since the long-term follow-up of the patients entered study C94-805 (CHAMPS), a 5-year MRI report from this add-on study (CHAMPION), had still to be submitted as a Specific Clinical Obligation. During this annual reassessment and following the assessment of the safety data submitted in the C94-801 study and in the 9th and 10th PSURs, the CHMP considered that the MAH should update the SPC and PL and reorganise it according to the current SPC guideline. It was considered that the MAH should continue to closely

					monitor and review a number of identified safety signals in the next PSURs.
I/0040	31_Change in container shape	08/10/2003	15/10/2003		
I/0037	23_Change in storage conditions	06/08/2003	08/10/2003	SmPC and PL	
II/0036	Update of Summary of Product Characteristics and Package Leaflet	25/04/2003	30/07/2003	SmPC, Labelling and PL	The terms "auto immune hepatitis" and "pancytopenia" were added under section 4.8 of the SPC following the assessment of the seventh PSUR. The PL has been revised accordingly. Minor revisions of the instructions for use have also been included. In addition, the correct name of the MAH (Biogen SAS) was included in the product information.
X/0031	X-3-iv_Change or addition of a new pharmaceutical form	20/02/2003	24/06/2003	SmPC, Annex II, Labelling and PL	The MAH applied for a new pharmaceutical form (solution for injection) of the already approved medicinal product AVONEX 30 mcg (powder for solution for injection). The new pharmaceutical form, solution for injection, has a different formulation (i.e. acetate versus phosphate buffers and no presence of human serum albumin (HSA). The main advantage of the new presentation of AVONEX in a pre-filled syringe is the elimination of the reconstitution step, facilitating the administration of the product.
II/0035	Quality changes	20/02/2003	03/03/2003		
S/0034	Annual re-assessment.	21/09/2002	10/01/2003	SmPC, Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted and having re-assessed the benefit/risk profile of the medicinal product, recommended that the marketing authorisation should remain under exceptional circumstances. The specific Obligations still pending were the submission of the final study report providing safety and antigenicity data Study

					(C94-801) and the Long-term follow-up of the patients entered study C94-805 (CHAMPS): a 5-year MRI report from this add-on study (CHAMPION).
I/0032	12_Minor change of manufacturing process of the active substance	25/07/2002	31/07/2002		
N/0033	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/07/2002	06/08/2002	PL	
R/0030	Renewal of the marketing authorisation.	17/01/2002	07/05/2002	SmPC, Annex II, Labelling and PL	
II/0022	Extension of Indication	16/01/2002	07/05/2002	SmPC and PL	
S/0029	Annual re-assessment.	15/11/2001	08/03/2002		
II/0020	New presentation(s)	21/09/2001	24/01/2002	SmPC, Labelling and PL	
II/0027	Update of Summary of Product Characteristics	26/07/2001	03/12/2001	SmPC	
II/0026	Update of or change(s) to the pharmaceutical documentation	27/06/2001	03/07/2001		
II/0024	Update of Summary of Product Characteristics and Package Leaflet	01/03/2001	08/06/2001	SmPC and PL	
II/0025	Change(s) to the test method(s) and/or specifications for the active substance	01/03/2001	13/03/2001		

S/0021	Annual re-assessment.	21/09/2000	28/12/2000	Annex II	
I/0023	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	17/08/2000	17/08/2000		
I/0019	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	20/06/2000	27/07/2000	PL	
II/0018	Quality changes	13/04/2000	04/05/2000		
S/0015	Annual re-assessment.	21/10/1999	21/02/2000	Annex II	
II/0016	Update of Summary of Product Characteristics and Package Leaflet	18/11/1999	21/02/2000	SmPC and PL	
I/0017	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	14/01/2000	n/a		
II/0013	Update of Summary of Product Characteristics and Package Leaflet	25/02/1999	18/06/1999	SmPC and PL	
S/0014	Annual re-assessment.	22/10/1998	03/02/1999	Annex II	
I/0012	20a_Extension of shelf-life or retest period of the active substance	06/11/1998	n/a		
I/0011	17_Change in specification of the medicinal product	06/11/1998	n/a		
I/0010	14_Change in specifications of active substance	06/11/1998	n/a		
I/0009	01_Change in the name of a manufacturer of the	15/07/1998	06/11/1998	Annex II,	

	medicinal product			Labelling and PL	
II/0008	Update of Summary of Product Characteristics and Package Leaflet	24/06/1998	23/10/1998	SmPC and PL	
II/0006	Update of Summary of Product Characteristics and Package Leaflet	22/04/1998	17/08/1998	SmPC and PL	
II/0005	Quality changes	18/11/1997	n/a		
I/0007	11_Change in or addition of manufacturer(s) of active substance	18/11/1997	n/a		
I/0004	17_Change in specification of the medicinal product	18/11/1997	n/a		
I/0003	14_Change in specifications of active substance	18/11/1997	n/a		
I/0001	20_Extension of shelf-life as foreseen at time of authorisation	13/06/1997	27/08/1997	SmPC and PL	
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/06/1997	27/08/1997	Labelling	