EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Extavia

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
PSUSA/1759/ 202407	Periodic Safety Update EU Single assessment - interferon beta-1b	13/03/2025	n/a		PRAC Recommendation - maintenance
IA/0120/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of	14/06/2024	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
IAIN/0119	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	10/06/2024	n/a		
IAIN/0118	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	03/03/2023	n/a		
II/0116/G	This was an application for a group of variations. Update of sections 4.4 and 4.8 of the SmPC in order to expand the language regarding the risk of injection site infection; the Package Leaflet is updated accordingly. Update of section 4.8 of the SmPC to merge the existing two tables for ADRs that occurred during clinical trials and those reported post-marketing, requested by PRAC following the assessment of PSUSA procedure (PSUSA/00001759/202107); the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI not related to safety.	08/12/2022	29/11/2023	SmPC and PL	Sections 4.4 and 4.8 of the SmPC are updated to add clarity on the warnings related with hypersensitivity reactions and injection site reactions. Section 4.8 of the SmPC is updated to provide a single table of Adverse Drug Reactions based on reports from clinical trials and identified during post-marketing surveillance. For more information, please refer to the Summary of Product Characteristics.

	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				
IAIN/0117	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	05/09/2022	n/a		
IAIN/0115	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	08/08/2022	n/a		
IG/1521	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	23/06/2022	n/a		
IAIN/0114/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes	22/06/2022	n/a		

	do not affect the properties of the FP				
IA/0112/G	This was an application for a group of variations. 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.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure 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	22/04/2022	n/a		
PSUSA/1759/202107	Periodic Safety Update EU Single assessment - interferon beta-1b	10/03/2022	n/a		PRAC Recommendation - maintenance
IB/0111/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	07/01/2022	n/a		
N/0109	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2021	29/11/2023	PL	
IAIN/0108	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier	24/08/2021	n/a		

	of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
IAIN/0107	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	06/04/2021	n/a		
IAIN/0106	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	25/03/2021	n/a		
IB/0105	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	19/03/2021	n/a		
IA/0104	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	18/11/2020	n/a		
II/0102	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	12/11/2020	n/a		
II/0103	Type II variation to update SmPC Section 4.8 with the addition of Haemolytic anaemia (HA) as an adverse drug reaction of 'unknown' frequency' based on cumulative review of available data including case reports from post-marketing surveillance and scientific literature.	29/10/2020	03/11/2021	SmPC and PL	The MAH provided a rationale to support the proposed labelling update in order to amend an existing warning on Thrombotic Microangiopathy to update with the inclusion of haemolytic anaemia (HA) as adverse drug reaction (ADR) with frequency unknown, achieved by a systematic review of information from clinical studies, post-marketing data

	Section 4.4 of the SmPC and corresponding sections in the PL are updated with a precautionary statement, considering the importance of drug discontinuation for patients with Thrombotic Microangiopathy TMA/HA, to reflect the most recent post marketing experience. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				and scientific literature.
IAIN/0101	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	02/07/2020	n/a		
IAIN/0100/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	25/02/2020	n/a		
II/0096/G	This was an application for a group of variations.	19/09/2019	30/09/2020	SmPC and PL	The SmPC section 4.3 has been updated to remove the contraindication 'initiation of treatment in pregnancy'

	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 and to update the Product information to the QRD template version 10.1. The Package leaflet has been updated accordingly. This submission fulfils MEA 024.2 and 21. The RMP has been updated (ver 4.6) 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				The SmPC section 4.6 has been updated as follows: Pregnancy A large amount of data (more than 1,000 pregnancy outcomes) from interferon beta registries, national registries and post marketing experience indicates no increased risk of major congenital anomalies, after pre-conception exposure or 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 was likely interrupted when the pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimesters 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 by means of the currently available data, but the data suggest no increased risk so far. If clinically needed, the use of Extavia may be considered during pregnancy. Breast-feeding Limited information available on the transfer of interferon beta-1b into breast milk, together with the chemical / physiological characteristics of interferon beta, suggests that levels of interferon beta-1b excreted in human milk are negligible. No harmful effects on the breast-fed newborn/infant are anticipated. Extavia can be used during breast-feeding. Fertility No investigations on fertility have been conducted (see

					section 5.3). The PL has been updated accordingly.
II/0099/G	This was an application for a group of variations. 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 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	12/09/2019	n/a		
IAIN/0098	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	28/05/2019	n/a		
PSUSA/1759/ 201807	Periodic Safety Update EU Single assessment - interferon beta-1b	14/03/2019	n/a		PRAC Recommendation - maintenance
IAIN/0097	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	18/12/2018	n/a		
IAIN/0093	B.V.a.1.d - PMF - Inclusion of a new, updated or	16/10/2018	n/a		

	amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
IA/0094/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	02/10/2018	n/a		
IA/0092	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/06/2018	06/06/2019	SmPC, Annex II, Labelling and PL	
IAIN/0091	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	02/05/2018	n/a		
T/0090	Transfer of Marketing Authorisation	20/03/2018	12/04/2018	SmPC, Labelling and PL	
IB/0089/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.g.5.c - Implementation of changes foreseen in	22/03/2018	n/a		

	an approved change management protocol - For a biological/immunological medicinal product				
IA/0088	A.7 - Administrative change - Deletion of manufacturing sites	11/12/2017	n/a		
IB/0087	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	14/11/2017	n/a		
II/0084	Submission of a Post Approval Change Management Protocol (PACMP) for the introduction of a new fill and finish area (designated DPM 6) in addition to the currently licensed fill and finish areas DPM 2, DPM 3 and DPM 5 at the manufacturing site Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	14/09/2017	n/a		
IAIN/0086	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	25/08/2017	n/a		
IAIN/0085	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	28/04/2017	n/a		

IA/0083	A.7 - Administrative change - Deletion of manufacturing sites	12/12/2016	n/a		
IB/0082/G	This was an application for a group of variations. 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.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	24/11/2016	n/a		
IA/0081	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	11/11/2016	n/a		
IAIN/0080	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	14/06/2016	n/a		
PSUSA/1759/ 201507	Periodic Safety Update EU Single assessment - interferon beta-1b	17/03/2016	n/a		PRAC Recommendation - maintenance
IAIN/0079/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of	14/12/2015	02/09/2016	SmPC, Labelling and	

	manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes			PL	
II/0076/G	This was an application for a group of variations. Update of section 4.8 of the SmPC in order to update the safety information regarding Drug-induced lupus erythematosus with a frequency not known after analysis of a MAH internal signal. The MAH also implemented an update of section 4.8 of the SmPC as a consequence of the final PRAC recommendation on a signal for Pulmonary arterial hypertension added with a not known frequency. The Package Leaflet is updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/09/2015	02/09/2016	SmPC and PL	

IAIN/0077	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	18/08/2015	n/a		
II/0072/G	This was an application for a group of variations. A.1: To update the address of the MAH (Novartis Europharm Limited) from Wimblehurst Road Horsham, West Sussex, RH12 5AB, UK to Frimley Business Park, Camberley, GU16 7SR, UK. The Package Leaflet is updated accordingly. The Labelling is updated accordingly. C.I.4: To update sections 4.4 and 6.6 of the SmPC with a statement informing that the Extavia pre-filled syringe contains a derivative of natural rubber latex and that the safe use of Extavia PFS in latex-sensitive individuals has not been studied. The Package Leaflet is updated accordingly. The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet. A.1 - Administrative change - Change in the name and/or address of the MAH C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/07/2015	08/09/2015	SmPC, Labelling and PL	The removable tip cap of the Extavia pre-filled syringe contains a derivative of natural rubber latex. Although no natural rubber latex is detected in the cap, the safe use of Extavia pre-filled syringe in latex-sensitive individuals has not been studied and there is therefore a potential risk for hypersensitivity reactions which cannot be completely ruled out.

IAIN/0075	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	09/06/2015	n/a		
IA/0074/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	20/05/2015	08/09/2015	SmPC, Labelling and PL	
IB/0073/G	This was an application for a group of variations. B.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product B.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting	21/04/2015	n/a		

	material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				
IB/0071	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	15/04/2015	n/a		
IA/0070/G	This was an application for a group of variations. 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.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.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	26/11/2014	n/a		
IG/0484/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites	12/11/2014	n/a		

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
IA/0068	A.7 - Administrative change - Deletion of manufacturing sites	25/09/2014	08/09/2015	Annex II	
II/0065/G	This was an application for a group of variations. change to a test procedure of the active substance and finished product B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of 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 - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol	25/09/2014	n/a		
II/0064	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.	24/07/2014	04/09/2014	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

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				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/0443	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)	20/08/2014	n/a		
IAIN/0066	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	29/07/2014	n/a		
IAIN/0063	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	25/04/2014	n/a		
II/0061	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.	25/04/2014	04/09/2014	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-b 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

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				periodically assess renal function were of relevance to the prescriber and should be added to the SmPC.
IA/0062	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)	20/12/2013	n/a		
IAIN/0060/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	29/10/2013	n/a		
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/09/2013	18/12/2013	PL	
N/0058	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/08/2013	18/12/2013	PL	
II/0054/G	This was an application for a group of variations. To harmonise the specifications and analytical test methods applied for quality control of the drug product and its intermediates	25/07/2013	n/a		

	B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter 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.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 B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				

	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
II/0053/G	This was an application for a group of variations. To harmonise specifications and analytical test methods applied for quality control of the drug substance 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.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting	25/07/2013	n/a		

	material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
IB/0057/G	This was an application for a group of variations. B.V.a.1.b - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - First-time inclusion of a new PMF NOT affecting the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	08/05/2013	n/a		
IAIN/0055/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.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished	05/04/2013	18/12/2013	SmPC, Labelling and PL	

	product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
IAIN/0056/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	04/04/2013	n/a		
IAIN/0052	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/02/2013	n/a		
R/0051	Renewal of the marketing authorisation.	18/10/2012	20/12/2012	SmPC, Annex II, Labelling	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance,

				and PL	the CHMP was of the opinion that the quality, safety and efficacy of Extavia remains adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Extavia continues to be favourable. The CHMP recommended the renewal of the Marketing Authorisation with unlimited validity.
II/0050/G	This was an application for a group of variations. Replacement of the diluent pre-filled syringe and consequential variations to the batch size, in-process controls, and specifications applied during the manufacture of the finished product B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products 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.b.4.z - Change in the batch size (including batch size ranges) 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 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 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	13/12/2012	13/12/2012	SmPC, Annex II, Labelling and PL	Addition of a new diluent pre-filled syringe (luer lock) and consequential variations to the batch size, in-process controls, and specifications applied during the manufacture of the finished product

	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 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 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 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 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 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.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.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.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				

IB/0049	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	14/06/2012	n/a		
IAIN/0047/G	This was an application for a group of variations. B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	25/05/2012	20/12/2012	Annex II and PL	
II/0036	Update of section 4.8 of the SmPC in order to add the following adverse reactions identified during post-marketing surveillance: weight increased, menorrhagia, arthralgia, dizziness, vasodilatation, diarrhoea and the following terms which are described in section 4.4: capillary leak syndrome, hepatic injury and hepatic failure. Table 2 in section 4.8 (i.e. adverse drug reaction listing based on reports from post marketing surveillance) was amended such that reaction frequencies are based on pooled clinical trial data. Update of section 4.4 of the SmPC to align the text with the reference product Betaferon. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	19/04/2012	25/05/2012	SmPC and PL	In order to adapt Extavia Product Information to the current Corporate Core Data Sheet, the MAH proposed to update section 4.8 of the SmPC with adding adverse reactions based on the post-marketing reporting. The CHMP considered the MAH´s assessment of causality for arthralgia, diarrhoea, dizziness, menorrhagia, vasodilatation and weight increased and concluded that adding these reactions into section 4.8 of the SmPC was justified, since these events were considered as "possibly related". The CHMP was also of the view that "weight decreased" can be moved from section "Investigation" to section "Metabolism and nutrition disorder" and that the following terms: capillary leak syndrome, hepatic injury and hepatic failure, already captured in section 4.4, can also be listed in section 4.8 of the SmPC. Following a request from the CHMP, adverse reaction frequencies in table 2 were updated based on incidence rates of the pooled clinical trial data, when feasible.

	clinical, clinical or pharmacovigilance data				
IA/0048/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	14/05/2012	n/a		
IB/0045	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	08/05/2012	n/a		
IAIN/0046/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	24/04/2012	n/a		

IA/0044	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	23/03/2012	n/a		
IAIN/0043	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	14/03/2012	n/a		
IG/0148/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD 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	22/02/2012	n/a		
II/0035	To introduce a post approval change management protocol for the FP. B.II.g.2 - Design Space - Introduction of a post approval change management protocol related to the finished product	19/01/2012	19/01/2012		

II/0033/G	This was an application for a group of variations. To introduce several changes in the manufacturing process of the active substance. To change the specification parameters and/or limits of reagents used in the manufacture of the active substance. To widen the specification parameters/limits of a reagent used in the manufacture of the active substance. To delete a test procedure for starting material used in the manufacture of the active substance. To introduce several changes to test procedures for starting materials. 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.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.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP B.I.b.2.b - Change in test procedure for AS or	19/01/2012	19/01/2012		

	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.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
II/0032	To introduce changes in the manufacturing process of the finished product B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	17/11/2011	17/11/2011		
IA/0039/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) 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)	26/09/2011	n/a		
IB/0037	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	15/08/2011	n/a		

IG/0088/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD 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	11/07/2011	n/a		
IA/0031/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	18/04/2011	n/a		
II/0028/G	This was an application for a group of variations. B.II.b.3.c. Change in the manufacturing process of the finished product. The product is a biological/immunological medicinal product and the	20/01/2011	03/02/2011		

	change requires an assessment of comparability. B.II.d.2.d. Change in test procedure for the finished product Conditions to be fulfilled. Other changes to a test procedure (including replacement or addition). B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
II/0027/G	This was an application for a group of variations. B.I.a.2.c. Changes in the manufacturing process of the active substance. The change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol. B.I.b.2.e. Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance. Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate. B.I.a.2.c - Changes in the manufacturing process of	20/01/2011	31/01/2011		

	the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol 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				
IG/0032/G	This was an application for a group of variations. To update the Detailed Description of the Pharmacovigilance System (DDPS) to version 9.0, to include: - a change in the deputy of the Qualified Person for Pharmacovigilance (QPPV); - a change in the major contractual arrangements. - administrative changes not impacting the operation of the pharmacovigilance system. Annex II.B has also been updated with the latest wording as per October 2010 CHMP procedural announcement. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	21/12/2010	n/a	Annex II	

	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				
IA/0030/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release A.7 - Administrative change - Deletion of manufacturing sites	08/09/2010	n/a		
IA/0029	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	28/07/2010	n/a		
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/06/2010	n/a	PL	
IA/0025	To amend the marketing authorisation dossier for Extavia with an approved 2nd step PMF re-certification procedure regarding human Serum Albumin excipient. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	07/04/2010	n/a		

II/0024	Update of the Detailed Description of the Pharmacovigilance system (DDPS). Changes to QPPV Update of DDPS (Pharmacovigilance)	18/02/2010	30/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (core version 8.0 and product specific version 4.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements.
IA/0023	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	24/11/2009	24/11/2009	SmPC, Labelling and PL	
IA/0022	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	24/11/2009	24/11/2009	SmPC, Labelling and PL	
IA/0021	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	05/11/2009	n/a	Annex II	
IA/0020	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	20/07/2009	n/a		
IA/0019	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	16/06/2009	n/a		
2PMF/0018	Inclusion of the updated or amended Plasma Master File (Grifols EMEA/H/PMF/000002/04) in the marketing authorisation dossier	06/04/2009	n/a		
II/0013	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Update of DDPS (Pharmacovigilance)	19/02/2009	25/03/2009	Annex II	With this variation the MAH submitted an updated DDPS. The CHMP concluded that the submitted DDPS contained all required elements. The CHMP also greed on the amendments to be introduced to the Product Information (Annex II) to include an updated wording of the section

					"other conditions" comprising the version numbers of the current DDPS and Risk Management Plan, and a clarification on the PSUR reporting cycle.
II/0008	Update of section 6.6 of the SPC, and section "Self-injection procedure" of the PL. Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	25/03/2009	SmPC and PL	Based on the information provided by the marketing authorisation holder, the CHMP endorsed the inclusion of a wording in the SPC and PL regarding the possibility of using a vial adapter for reconstitution as an alternative to a needle, and recommended the deletion of the existing recommendation for using a specific size needle (21 gauge) for reconstitution.
II/0007	Update of the testing requirements at various steps of the manufacturing process. Update of or change(s) to the pharmaceutical documentation	19/02/2009	26/02/2009		
IA/0017	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	10/02/2009	n/a		
IA/0016	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	26/01/2009	n/a		
IA/0015	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	26/01/2009	n/a		
IA/0014	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	26/01/2009	n/a		
IA/0012	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	14/01/2009	14/01/2009	SmPC, Labelling and	

				PL	
IA/0011	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	16/12/2008	n/a		
IA/0010	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	16/12/2008	n/a		
IA/0009	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	16/12/2008	n/a		
II/0003	The MAH applied to replace the current site for batch control/testing with a new site. Update of or change(s) to the pharmaceutical documentation	20/11/2008	27/11/2008		
IA/0005	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	21/11/2008	n/a	Annex II	
IA/0004	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	22/10/2008	n/a		
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/10/2008	n/a	PL	
IA/0001	IA_47_c_Deletion of a pack size(s)	10/06/2008	n/a	SmPC, Labelling and PL	