# Betaferon

## 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 |
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| II/0143/G | This was an application for a group of variations.<br><br>Update of sections 4.4 and 4.8 of the SmPC based on pooled clinical trial data from six phase II-IV studies: NASPMS (Study No. 3112), Pivotal RRMS (Study No. 13103), EUSPMS (Study No.93079), BENEFIT (Study | 08/12/2022 | | 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<br>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 |

[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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| | No. 304747), BEYOND (Study No. 306440) and BEYOND pilot (Study No. 307000), post-marketing experience, scientific literature and FAERS database; the Package Leaflet is updated accordingly.<br><br>Update of section 4.8 of the SmPC in order to merge the existing two tables for ADRs, requested by the PRAC following the assessment of PSUSA procedure EMEA/H/C/PSUSA/00001759/202107), based on pooled data from four placebo controlled trials: NASPMS (Study No. 3112), Pivotal RRMS (Study No. 13103), EUSPMS (Study No. 93079), and BENEFIT (Study No. 304747); the Package Leaflet is updated accordingly.<br>In addition, the MAH took the opportunity to implement editorial changes and to update the list of local representatives in the Package Leaflet.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data<br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | surveillance<br>For more information, please refer to the Summary of Product Characteristics. |
| IAIN/0144 | 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 | 23/08/2022 | n/a | | |

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| IAIN/0142/G | This was an application for a group of variations.<br><br>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<br>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 | 07/06/2022 | n/a | | |
| IA/0141 | B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 07/04/2022 | n/a | | |
| IA/0140/G | This was an application for a group of variations.<br><br>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<br>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 | 21/03/2022 | n/a | | |
| PSUSA/1759/202107 | Periodic Safety Update EU Single assessment - interferon beta-1b | 10/03/2022 | n/a | | PRAC Recommendation - maintenance |

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| IB/0138 | B.I.z - Quality change - Active substance - Other variation | 20/12/2021 | n/a | | |
| N/0139 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 09/12/2021 | | PL | |
| IA/0137 | B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) | 17/11/2021 | n/a | | |
| IAIN/0135 | 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 | 13/08/2021 | n/a | | |
| IB/0133 | B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process | 10/03/2021 | n/a | | |
| IAIN/0134 | 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 | 01/03/2021 | n/a | | |
| IAIN/0132 | 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 | 08/12/2020 | n/a | | |

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| | do not affect the properties of the FP | | | | |
| IA/0131/G | This was an application for a group of variations.<br><br>B.II.f.1.e - Stability of FP - Change to an approved stability protocol<br>B.II.f.1.e - Stability of FP - Change to an approved stability protocol | 19/11/2020 | n/a | | |
| II/0129 | B.I.e.2 - Introduction of a post approval change management protocol related to the AS | 12/11/2020 | n/a | | |
| II/0130 | C.I.4 Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on Thrombotic Microangiopathy by adding information about Haemolytic anaemia and add (Haemolytic anaemia) to the list of adverse drug reactions (ADRs) with frequency unknown based on a systematic review of information from clinical studies, post-marketing data and scientific literature. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 29/10/2020 | 22/10/2021 | SmPC and PL | Section 4.4 (subsection Thrombotic microangiopathy (TMA)) has been updated (subsection TMA and Haemolytic anaemia [HA]) to inform that cases of HA not associated with TMA have been reported with interferon beta products. Cases may occur several weeks to several years after starting treatment with interferon beta and may be severe (Life-threatening and fatal cases have been reported).<br>Section 4.8 has been updated to inform that the most serious adverse drug reactions (ADRs) include TMA and HA which has been added to the list of ADRs with frequency unknown.<br>For more information, please refer to the Summary of Product Characteristics. |
| IAIN/0128 | 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) - | 22/06/2020 | n/a | | |

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| | Inclusion of an updated/amended PMF when changes do not affect the properties of the FP | | | | |
| IAIN/0127/G | This was an application for a group of variations.<br><br>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<br>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/0124/G | This was an application for a group of variations.<br><br>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.<br>The Package leaflet has been updated accordingly. | 19/09/2019 | 27/08/2020 | SmPC and PL | The SmPC section 4.3 has been updated to remove the contraindication 'initiation of treatment in pregnancy'<br>The SmPC section 4.6 has been updated as follows:<br>Pregnancy<br>A large amount of data (more than 1000 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 likely interrupted when pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester is very |

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| | This submission fulfils MEA 024.2 and 21.<br>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.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data<br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | limited.<br>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.<br>If clinically needed, the use of Betaferon may be considered during pregnancy.<br>Breast-feeding<br>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 breastfed newborn/infant are anticipated.<br>Betaferon can be used during breast-feeding.<br>Fertility<br>No investigations on fertility have been conducted (see section 5.3).<br><br>The PL has been updated accordingly. |
| II/0126/G | This was an application for a group of variations.<br><br>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<br>B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The | 12/09/2019 | n/a | | |

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| | change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product | | | | |
| IAIN/0125 | 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 | 10/05/2019 | n/a | | |
| PSUSA/1759/ 201807 | Periodic Safety Update EU Single assessment - interferon beta-1b | 14/03/2019 | n/a | | PRAC Recommendation - maintenance |
| IAIN/0122 | 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 | 03/08/2018 | n/a | | |
| IB/0121 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 26/06/2018 | 06/06/2019 | SmPC, Labelling and PL | |
| IAIN/0120 | 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 | | |
| IB/0119 | B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product | 23/03/2018 | n/a | | |

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| II/0118 | Submission of the final report from study BETAPAEDIC, listed as a category 3 study in the RMP. This was a non-interventional study evaluating safety and tolerability of Betaferon in paediatric patients with multiple sclerosis.<br>The RMP version 3.3 has also been submitted.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 11/01/2018 | n/a | | |
| II/0114 | 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.<br><br>B.II.g.2 - Introduction of a post approval change management protocol related to the finished product | 14/09/2017 | n/a | | |
| 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 | 25/08/2017 | n/a | | |
| IA/0116 | B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) | 28/07/2017 | 09/07/2018 | SmPC, Annex II, Labelling | |

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| IAIN/0115 | 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 | 25/04/2017 | n/a | | |
| T/0113 | Transfer of Marketing Authorisation | 08/03/2017 | 22/03/2017 | SmPC, Labelling and PL | |
| IAIN/0112 | A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release | 31/01/2017 | 22/03/2017 | Annex II and PL | |
| IA/0111 | A.7 - Administrative change - Deletion of manufacturing sites | 12/12/2016 | n/a | | |
| IB/0110/G | This was an application for a group of variations.<br><br>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits<br>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure<br>B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits | 23/11/2016 | n/a | | |

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| N/0109 | Update of the package leaflet with revised contact details of the local representative for Portugal.<br><br>Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 06/07/2016 | 08/09/2016 | PL | |
| IAIN/0108 | 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 |
| II/0105/G | This was an application for a group of variations.<br><br>C.I.4 - Update of sections 4.8 of the SmPC in order to add "drug-induced lupus erythematosus" (DILE) as ADR.<br>The Package Leaflet is updated accordingly.<br>In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of the Norwegian local representatives in the Package Leaflet and to correct some editorial bring the PI.<br>C.I.z - Update of section 4.8 of the SmPC to add "pulmonary arterial hypertension" (PAH) following PRAC recommendation.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 24/09/2015 | 08/09/2016 | SmPC and PL | This grouped procedure amends sections 4.8 of the SmPC in order to add "drug-induced lupus erythematosus" (DILE) as ADR and "pulmonary arterial hypertension" (PAH) following PRAC recommendation. The Package Leaflet is updated accordingly.<br>In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of the Norwegian local representatives in the Package Leaflet and to correct some editorial bring the PI. |

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| | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | |
| 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 | 18/08/2015 | n/a | | |
| IAIN/0104 | C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location | 17/06/2015 | n/a | | |
| IAIN/0103 | 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/0102 | A.7 - Administrative change - Deletion of manufacturing sites | 29/04/2015 | n/a | | |
| II/0100 | RMP update<br><br>C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH | 23/04/2015 | n/a | | |

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| | where significant assessment is required | | | | |
| IB/0101/G | This was an application for a group of variations.<br><br>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<br>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<br>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<br>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<br>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 | 21/04/2015 | n/a | | |
| IA/0099/G | This was an application for a group of variations. | 01/12/2014 | n/a | | |

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| | 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<br>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<br>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 | | | | |
| II/0096/G | This was an application for a group of variations.<br><br>change to a test procedure of the active substance and finished product<br><br>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<br>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 | | |

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| IA/0098 | A.7 - Administrative change - Deletion of manufacturing sites | 03/09/2014 | 15/10/2015 | Annex II | |
| II/0095 | 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.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 24/07/2014 | 26/08/2014 | SmPC and PL | The MAH conducted a cumulative search for cases of thrombotic microangiopathy. Further to the PRAC review of these data, the CHMP concurred with the PRAC´s view that there might be a causal relationship between the class of interferons and thrombotic microangiopathy, and that the PI should be updated accordingly. Furthermore, the CHMP concurred that a warning about the risk of thrombotic microangiopathy, including recommendations for monitoring of early symptoms, prompt treatment and discontinuation of interferon beta products when the reaction occurs, should be added to the Product Information. |
| IAIN/0097 | 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/0094 | 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 | 30/04/2014 | n/a | | |
| II/0091 | 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 | 25/04/2014 | 26/08/2014 | SmPC, Annex II, Labelling | 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 |

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| | glomerulosclerosis. The Package Leaflet was updated in accordance.<br>Furthermore, the Product Information (PI) was brought in line with the latest QRD template version 9.0.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | | | and PL | there might be a causal relationship between interferon beta 1-b and glomerulosclerosis and nephrotic syndrome, and that the PI should be updated accordingly.<br>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. |
| N/0093 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 27/03/2014 | 26/08/2014 | PL | |
| IA/0092 | 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/0090/G | This was an application for a group of variations.<br><br>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<br>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 | | |
| II/0087/G | This was an application for a group of variations. | 25/07/2013 | n/a | | |

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| | To harmonise the specifications and analytical test methods applied for quality control of the drug product and its intermediates<br><br>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<br>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<br>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<br>B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits<br>B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits<br>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<br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)<br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure | | | | |

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| | (including replacement or addition)<br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)<br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)<br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)<br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) | | | | |
| II/0086/G | This was an application for a group of variations.<br><br>To harmonise specifications and analytical test methods applied for quality control of the drug substance<br><br>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<br>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits<br>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting | 25/07/2013 | n/a | | |

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| | material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method<br>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) | | | | |
| IB/0089/G | This was an application for a group of variations.<br><br>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<br>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/0088/G | This was an application for a group of variations.<br><br>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<br>B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier | 12/04/2013 | n/a | | |

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| | of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP<br>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<br>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 | | | | |
| II/0078 | 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.<br>The Package Leaflet is updated in accordance.<br>In addition, the MAH took the opportunity to make an editorial modification in Labelling and to update the list of local representatives in the Package Leaflet. | 19/04/2012 | 25/05/2012 | SmPC, Labelling and PL | In order to adapt Betaferon 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 |

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| | C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | | | | data, when feasible. |
| IB/0084 | 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 | 26/04/2012 | n/a | | |
| IAIN/0085/G | This was an application for a group of variations.<br><br>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<br>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<br>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/0083 | 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 | | |

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| IAIN/0082 | 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 | | |
| II/0079 | To introduce a post approval change management protocol for the FP<br><br>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/0076/G | This was an application for a group of variations.<br><br>To introduce several changes in the manufacturing process of the active substance.<br>To change the specification parameters and/or limits of reagents used in the manufacture of the active substance.<br>To widen the specification parameters/limits of a reagent used in the manufacture of the active substance.<br>To delete a test procedure for starting material used in the manufacture of the active substance.<br>To introduce several changes to test procedures for starting materials.<br><br>B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting | 19/01/2012 | 19/01/2012 | | |

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| | 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<br>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)<br>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<br>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<br>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 | | | | |
| II/0075 | To introduce changes in the manufacturing process of the finished product<br><br>B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the | 17/11/2011 | 17/11/2011 | | |

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| | change requires an assessment of comparability | | | | |
| IA/0081/G | This was an application for a group of variations.<br><br>A.1 - Administrative change - Change in the name and/or address of the MAH<br>A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release<br>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) | 22/08/2011 | n/a | SmPC, Annex II, Labelling and PL | |
| IB/0080 | 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 | | |
| IA/0074 | 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 | 13/04/2011 | n/a | | |
| IA/0073 | 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 | 15/03/2011 | n/a | | |
| II/0068/G | This was an application for a group of variations. | 21/01/2011 | 04/02/2011 | | |

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| | 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.<br><br>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).<br><br>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<br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) | | | | |
| II/0067/G | This was an application for a group of variations.<br><br>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.<br><br>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 | 21/01/2011 | 04/02/2011 | | |

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| | substance. Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate.<br><br>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 medicinal product and is not related to a protocol<br>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 | | | | |
| IA/0072/G | This was an application for a group of variations.<br><br>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<br>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 | 03/01/2011 | 03/01/2011 | SmPC, Labelling and PL | |
| N/0071 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 08/12/2010 | n/a | PL | |
| IA/0070/G | This was an application for a group of variations.<br><br>A.5.b - Administrative change - Change in the name | 08/09/2010 | n/a | | |

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| | and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)<br>A.7 - Administrative change - Deletion of manufacturing sites | | | | |
| IA/0069 | 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 | | |
| IA/0066 | To amend the marketing authorisation dossier for Extavia with an approved 2nd step PMF re-certification procedure regarding human Serum Albumin excipient.<br><br>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/0064 | Update of sections 4.2, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics (SPC) to include information from the 5 year integrated analysis of the BENEFIT study, in accordance with follow-up measure 8. Editorial changes are also made across the SPC and the PL and details of the local representatives in the PL are updated. | 17/12/2009 | 25/01/2010 | SmPC and PL | The MAH submitted the final report of the 5-year integrated analysis of the BENEFIT study. The BENEFIT study was composed of two parts. First a 24 month two-armed, placebo-controlled randomised, double-blind part, then an open-label follow-up part scheduled to last until 5 years after the initial study start. The follow-up part was primarily designed to assess the impact of the relative timing of treatment onset on subsequent disease progression: |

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| | Update of Summary of Product Characteristics and Package Leaflet | | | | immediate (after the first clinical event) versus delayed (after development of clinically defined multiple sclerosis [CDMS], or 24 months after the first clinical event). Out of 437 patients that qualified for the follow-up part, a total of 418 patients entered the study.<br><br>The 5-year integrated analysis showed a sustained efficacy of Betaferon treatment in patients with Clinically Isolated Syndrome (CIS) based on a significant delay in the progression to CDMS, whereas the other primary endpoints related to disability and quality of life failed to support the benefit of immediate vs. delayed treatment. The development of neutralising activity in patients during the 5 year treatment was associated with a significant increase in newly active lesions and T2 lesion volume on magnetic resonance imaging. However, this did not seem to be associated with a reduction in clinical efficacy (with regard to time to CDMS, time to confirmed EDSS progression and relapse rate). The long-term safety data from this trial did not raise any specific concern. Based on the submitted data the CHMP approved amendments to sections 4.2, 4.4, 4.8 and 5.1 of the SPC. |
| IA/0065 | IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) | 09/11/2009 | n/a | Annex II | |
| 2PMF/0063 | Inclusion of the updated or amended Plasma Master File (Grifols EMEA/H/PMF/000002/04) in the marketing authorisation dossier | 03/04/2009 | n/a | | |
| II/0060 | Update on testing requirements for active substance and finished product. | 19/02/2009 | 04/03/2009 | | |

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| | Update of or change(s) to the pharmaceutical documentation | | | | |
| IA/0062 | IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size | 16/02/2009 | 16/02/2009 | SmPC, Labelling and PL | |
| IA/0061 | IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size | 10/02/2009 | 10/02/2009 | SmPC, Labelling and PL | |
| II/0055 | Change in pack size of the finished product .<br><br>New presentation(s) | 25/09/2008 | 29/10/2008 | SmPC, Labelling and PL | |
| II/0054 | Change(s) to the test method(s) of the finished product.<br><br>Change(s) to the test method(s) and/or specifications for the finished product | 25/09/2008 | 02/10/2008 | | |
| IB/0059 | IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size | 31/07/2008 | 31/07/2008 | SmPC, Labelling and PL | |
| MF/0057 | 2PMF (2nd step of PMF certification procedure) | 08/07/2008 | n/a | | |
| IA/0058 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site | 03/07/2008 | n/a | | |
| IA/0056 | IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) | 27/06/2008 | n/a | Annex II | |

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| | IA_05_Change in the name and/or address of a manufacturer of the finished product | | | | |
| MF/0053 | 2PMF (2nd step of PMF certification procedure) | 20/05/2008 | n/a | | |
| II/0048 | Update of sections 4.2, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics (SPC) to include the results of the integrated analysis of the 2 years placebo controlled, randomised BENEFIT study in patients with a single demyelinating event and the first year of the open label BENEFIT follow-up study, as requested by the CHMP (FUM 007). In addition, the MAH took the opportunity to update the full list of local representatives in Section 6 of the Package Leaflet (PL).<br><br>Update of Summary of Product Characteristics and Package Leaflet | 15/11/2007 | 18/12/2007 | SmPC and PL | The MAH updated sections 4.2, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics (SPC) to include the results of the integrated analysis of the 2 years placebo controlled, randomised BENEFIT study in patients with a single demyelinating event and the first year of the open label BENEFIT follow-up study. After 3 years, a pre-planned interim analysis showed that confirmed disability progression (measured by EDSS; confirmed increase in EDSS scale of greater than or equal 1.0 compared to baseline) occurred in 24% of the patients in the delayed treatment group compared to 16% in the immediate treatment group. There is no evidence for benefit in terms of confirmed disability progression in the majority of patients receiving 'immediate' treatment. Follow-up of patients is continuing in order to provide additional data. No benefit, attributable to Betaferon, in quality of life (as measured by FAMS - Functional Assessment of MS: Treatment Outcomes Index) was seen. |
| II/0045 | Quality changes | 15/11/2007 | 21/11/2007 | | |
| IA/0052 | IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)<br>IA_05_Change in the name and/or address of a manufacturer of the finished product | 26/10/2007 | n/a | Annex II | |

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| N/0049 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 05/10/2007 | n/a | PL | |
| IA/0047 | IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)<br>IA_05_Change in the name and/or address of a manufacturer of the finished product | 20/06/2007 | n/a | | |
| II/0041 | Update of section 4.2 of the SPC regarding the use of Betaferon in paediatrics, as recommended by the CHMP. The Package Leaflet was amended accordingly. In addition a minor mistake was corrected in section 5.1 of the SPC.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 22/02/2007 | 29/03/2007 | SmPC and PL | No specific studies or data collection have been conducted so far by the MAH in the paediatric multiple sclerosis population. The CHMP has reviewed published data on the use of interferon beta in paediatric patients, mostly in the range of 12 to 16 years of age. The information available on efficacy and safety of interferon beta in children is limited. Efficacy cannot be considered specifically demonstrated in children but there are no signals of specific safety issues in paediatric patients. Although the data are scarce, the CHMP recommended that the available information is reflected in the product information of all beta-interferons. |
| IA/0044 | IA_01_Change in the name and/or address of the marketing authorisation holder<br>IA_05_Change in the name and/or address of a manufacturer of the finished product | 28/03/2007 | n/a | SmPC, Annex II, Labelling and PL | |
| MF/0043 | 2PMF (2nd step of PMF certification procedure) | 22/03/2007 | n/a | | |
| N/0042 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 12/02/2007 | n/a | PL | |

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| II/0040 | Change(s) to the manufacturing process for the finished product<br>New presentation(s) | 27/07/2006 | 01/09/2006 | SmPC, Labelling and PL | |
| II/0038 | The present type II variation relates to the extension of the indication (section 4.1) to include the treatment of patients with a single demyelinating event with an active inflammatory process if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. The SPC sections 4.2, 4.4, 4.8 and 5.1 were also amended to reflect the new data generated by the variation. Furthermore, the package leaflet was amended accordingly.<br><br>Extension of Indication | 27/04/2006 | 01/06/2006 | SmPC and PL | The CHMP variation Assessment Report will be published as part of the EPAR after deletion of confidential information. |
| II/0036 | This variation relates to the revision of section 4.2 of the SPC to reflect 5 year clinical data gathered in relapsing remitting multiple sclerosis (RRMS). In addition, this variation consists of changes to sections 4.3, 4.4, 4.6, 4.8 and 5.3 to align the SPC with the most updated company reference safety datasheet and with the SPC guideline. These changes notably include the downgrading of several contra-indications and the consequential revision of the special warnings and precautions for use. The Package Leaflet has also been updated accordingly. | 27/04/2006 | 01/06/2006 | SmPC and PL | In order to evaluate the longer-term safety and efficacy of IFNB-1b treatment of RRMS, the subjects enrolled in the original pivotal RRMS studies were given the choice of continuing their treatment, in a blinded fashion for up to 5 years. Betaferon treated patients showed significant reduction in the number of relapses over the 5 year period with supportive magnetic resonance imaging data. Section 4.2 of the SPC was revised to reflect these 5 year data.<br><br>The contra-indications in pregnancy, patients with a history of severe depressive disorders and/or suicidal ideation, any patients with epilepsy not adequately controlled by |

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| | Update of Summary of Product Characteristics and Package Leaflet | | | | treatment were also reviewed, with consequential amendments of sections 4.3, 4.4 and 4.6. As these contraindications are common to all interferons beta, the CHMP Pharmacovigilance Working Party (PhVWP) performed a class review of all interferons beta authorised to provide recommendations on the need for and the nature of changes to the current contraindications. 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:<br><br>- Removal of the absolute contraindication 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<br><br>- Revision of the contraindication 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.<br><br>- Revision of the contraindication 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 |

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| R/0037 | Renewal of the marketing authorisation. | 15/09/2005 | 31/01/2006 | SmPC, Annex II, Labelling and PL | |
| II/0039 | Change(s) to the manufacturing process for the finished product | 26/01/2006 | 31/01/2006 | | |
| II/0035 | The MAH applied for a variation, following a request by the CHMP, to update section 4.4 of the SPC in order to strengthen the wording on the potential risk of severe hepatic injury and to include a recommendation on thyroid function tests for patients with a history of thyroid dysfunction. In addition, the MAH applied for a minor update of section 4.8 of the SPC to include rare cases of "bilirubin increase". The Package Leaflet has been updated accordingly.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 15/09/2005 | 27/10/2005 | SmPC and PL | Based on the review of clinical trial data, postmarketing data and literature provided by the MAH, the following warnings were added to section 4.4 of the SPC:<br><br>"Thyroid function tests are recommended regularly in patients with a history of thyroid dysfunction or as clinically indicated.<br><br>Asymptomatic elevations of serum transaminases, in most cases mild and transient, occurred very commonly in patients treated with Betaferon during clinical trials. As for other beta interferons, severe hepatic injury, including cases of hepatic failure, has been reported rarely in patients taking Betaferon. The most serious events often occurred in patients exposed to other drugs or substances known to be associated with hepatotoxicity or in the presence of comorbid medical conditions (e.g. metastasizing malignant disease, severe infection and sepsis alcohol abuse).<br><br>Patients should be monitored for signs of hepatic injury." |
| N/0034 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 04/08/2004 | n/a | PL | |

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| II/0033 | Change(s) to the manufacturing process for the active substance | 29/07/2004 | 02/08/2004 | | |
| II/0032 | Change(s) to shelf-life or storage conditions | 03/06/2004 | 12/07/2004 | SmPC, Labelling and PL | |
| II/0030 | Quality changes | 20/11/2003 | 24/11/2003 | | |
| II/0029 | Update of or change(s) to the pharmaceutical documentation | 24/07/2003 | 28/07/2003 | | |
| I/0028 | 23_Change in storage conditions | 14/11/2002 | 09/01/2003 | SmPC and PL | |
| II/0025 | Update of Summary of Product Characteristics and Package Leaflet | 26/07/2001 | 19/11/2001 | SmPC and PL | |
| I/0027 | 15_Minor changes in manufacture of the medicinal product | 20/09/2001 | 20/10/2001 | | |
| I/0026 | 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process | 16/03/2001 | 06/04/2001 | | |
| S/0024 | Annual re-assessment. | 14/12/2000 | 03/04/2001 | Annex II | |
| II/0022 | Change(s) to the test method(s) and/or specifications for the finished product | 21/09/2000 | 29/01/2001 | SmPC, Labelling and PL | |
| R/0023 | Renewal of the marketing authorisation. | 16/11/2000 | n/a | | |
| II/0021 | Quality changes | 27/07/2000 | 02/08/2000 | | |

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| I/0020 | 19_Change in specification of excipients in the medicinal product (excluding adjuvants for vaccines) | 17/05/2000 | n/a | | |
| S/0019 | Annual re-assessment.Annual reassessment Update of Summary of Product Characteristics and Package Leaflet | 19/01/2000 | 11/05/2000 | Annex II | |
| X/0017 | X-3-iv_Change or addition of a new pharmaceutical form | 23/09/1999 | 03/02/2000 | SmPC, Annex II, Labelling and PL | |
| II/0018 | Update of Summary of Product Characteristics and Package Leaflet | 20/05/1999 | 14/09/1999 | SmPC and PL | |
| S/0016 | Annual re-assessment. | 27/01/1999 | 11/05/1999 | Annex II | |
| II/0014 | Extension of Indication | 22/10/1998 | 26/01/1999 | SmPC and PL | |
| I/0015 | 17_Change in specification of the medicinal product | 10/12/1998 | n/a | | |
| II/0013 | Update of Summary of Product Characteristics and Package Leaflet | 22/07/1998 | 11/11/1998 | SmPC and PL | |
| S/0010 | Annual re-assessment. | 25/02/1998 | 08/07/1998 | Annex II | |
| I/0012 | 12_Minor change of manufacturing process of the active substance | 24/06/1998 | n/a | | |
| I/0011 | 17_Change in specification of the medicinal product | 27/05/1998 | n/a | | |

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| II/0009 | Update of Summary of Product Characteristics and Package Leaflet | 22/10/1997 | 05/02/1998 | SmPC and PL | |
| I/0007 | 15_Minor changes in manufacture of the medicinal product | 19/02/1997 | 22/05/1997 | Annex II | |
| I/0006 | 17_Change in specification of the medicinal product | 19/02/1997 | 22/05/1997 | Annex II | |
| II/0003 | Update of Summary of Product Characteristics and Package Leaflet | 20/11/1996 | 02/04/1997 | SmPC and PL | |
| I/0008 | 12_Minor change of manufacturing process of the active substance | 19/03/1997 | n/a | | |
| II/0001 | New presentation(s)<br>Update of Summary of Product Characteristics and Package Leaflet | 17/07/1996 | 21/11/1996 | SmPC, Annex II, Labelling and PL | |