



Ceprothin

Procedural steps taken and scientific information after the authorisation

| Application number | Scope | Opinion/ Notification ¹ issued on | Commission Decision Issued ² / amended on | Product Information affected ³ | Summary |
|--------------------|---|--|--|---|---------|
| II/0143/G | This was an application for a group of variations. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal | 27/03/2025 | 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).



| | | | | | |
|-----------|--|------------|-----|--|--|
| | product and is not related to a protocol B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits | | | | |
| IA/0142 | B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State | 14/11/2024 | n/a | | |
| II/0141 | 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 | 07/11/2024 | n/a | | |
| IAIN/0140 | 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 | 14/05/2024 | n/a | | |
| IA/0139 | B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 13/05/2024 | n/a | | |
| IA/0138 | B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State | 20/10/2023 | n/a | | |

| | | | | | |
|-------------------|---|------------|------------|-----------------------|---|
| IB/0137 | B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 02/10/2023 | n/a | | |
| IA/0136 | B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer | 19/07/2023 | n/a | | |
| IB/0135 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 03/07/2023 | 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 | 12/05/2023 | n/a | | |
| PSUSA/2563/202207 | Periodic Safety Update EU Single assessment - human protein c | 16/03/2023 | n/a | | PRAC Recommendation - maintenance |
| II/0127 | Extension of indication to include long-term prophylaxis (deletion of wording 'short-term' and currently listed conditions) of purpura fulminans and coumarin induced skin necrosis in patients with severe congenital protein C deficiency, based on a re-analysis of long-term prophylaxis data from the pivotal Study 400101; a phase 2/3 clinical study undertaken to evaluate PK, safety and efficacy of CEPROTIN in | 10/11/2022 | 16/12/2022 | SmPC, Annex II and PL | Please refer to Scientific Discussion 'Ceprotin-H/C/000334/II/0127' |

| | | | | | |
|-----------|---|------------|------------|----|--|
| | <p>patients with severe congenital PC deficiency for the treatment of acute thrombotic episodes, for short-term thromboembolic prophylaxis and for long-term prophylactic treatment. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated and the Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes in sections 4.4 and 4.8 the SmPC and Package Leaflet.</p> <p>Version 2.0 of the RMP has also been submitted. In addition, MAH took the opportunity to correct the address of the manufacturer of the biological active substance in Annex II following variation EMEA/H/C/000334/IAIN/0126/G.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | | | | |
| 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 do not affect the properties of the FP | 13/07/2022 | n/a | | |
| N/0131 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 01/07/2022 | 16/12/2022 | PL | |
| IA/0130 | B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier | 30/05/2022 | n/a | | |

| | | | | | |
|-------------|---|------------|------------|-----------------|--|
| IA/0128/G | <p>This was an application for a group of variations.</p> <p>B.II.c.4.z - Change in synthesis or recovery of a non-pharmacopoeial or novel excipient - Other variation</p> <p>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)</p> | 16/05/2022 | n/a | | |
| IAIN/0126/G | <p>This was an application for a group of variations.</p> <p>A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient</p> <p>A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release</p> <p>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)</p> <p>A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient</p> <p>A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or</p> | 17/01/2022 | 16/12/2022 | Annex II and PL | |

| | | | | | |
|-----------|---|------------|------------|--|--|
| | <p>manufacturer of a novel excipient</p> <p>A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient</p> <p>A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient</p> <p>A.1 - Administrative change - Change in the name and/or address of the MAH</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p> <p>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)</p> | | | | |
| T/0125 | Transfer of Marketing Authorisation | 07/12/2021 | 16/12/2021 | | |
| II/0122 | B.II.e.4.b - Change in shape or dimensions of the container or closure (immediate packaging) - The change in shape or dimensions concerns a fundamental part, which may have a significant impact on the delivery, use, safety or stability of the FP | 16/12/2021 | n/a | | |
| II/0121/G | <p>This was an application for a group of variations.</p> <p>B.I.a.1.e - Change in the manufacturer of AS or of a</p> | 16/12/2021 | n/a | | |

| | | | | | |
|-----------|---|------------|-----|--|--|
| | <p>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</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>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</p> | | | | |
| II/0124/G | <p>This was an application for a group of variations.</p> <p>B.II.z - Quality change - Finished product - Other variation</p> <p>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</p> | 25/11/2021 | n/a | | |
| IAIN/0123 | <p>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</p> | 08/07/2021 | n/a | | |
| IB/0120 | <p>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)</p> | 05/07/2021 | n/a | | |

| | | | | | |
|-------------------|---|------------|------------|----------------------------------|-----------------------------------|
| IA/0119/G | <p>This was an application for a group of variations.</p> <p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> <p>B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits</p> <p>B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation</p> <p>B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p> <p>B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised</p> <p>B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits</p> | 06/05/2021 | n/a | | |
| PSUSA/2563/202007 | Periodic Safety Update EU Single assessment - human protein c | 11/03/2021 | n/a | | PRAC Recommendation - maintenance |
| IB/0117 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 28/10/2020 | 19/10/2021 | SmPC, Annex II, Labelling and PL | |
| IAIN/0116 | B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier | 27/08/2020 | 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/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 | 29/05/2020 | n/a | | |
| IA/0114 | B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer | 10/04/2020 | n/a | | |
| T/0113 | Transfer of Marketing Authorisation | 10/01/2020 | 04/02/2020 | SmPC, Labelling and PL | |
| IAIN/0112 | B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing | 28/11/2019 | 04/02/2020 | Annex II and PL | |
| IB/0110 | B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | 09/07/2019 | n/a | | |
| IAIN/0111/G | This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or | 20/06/2019 | n/a | | |

| | | | | | |
|-------------------|---|------------|-----|--|-----------------------------------|
| | <p>deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer</p> <p>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</p> | | | | |
| PSUSA/2563/201807 | <p>Periodic Safety Update EU Single assessment - human protein c</p> | 14/03/2019 | n/a | | PRAC Recommendation - maintenance |
| II/0107/G | <p>This was an application for a group of variations.</p> <p>B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol</p> <p>B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place</p> | 18/10/2018 | n/a | | |
| II/0106/G | <p>This was an application for a group of variations.</p> <p>B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits</p> <p>B.II.e.4.b - Change in shape or dimensions of the container or closure (immediate packaging) - The</p> | 18/10/2018 | n/a | | |

| | | | | | |
|-----------|--|------------|------------|-------------|--|
| | change in shape or dimensions concerns a fundamental part, which may have a significant impact on the delivery, use, safety or stability of the FP | | | | |
| WS/1431 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS</p> | 13/09/2018 | n/a | | |
| II/0104 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 13/09/2018 | 04/10/2019 | SmPC and PL | |
| IB/0102/G | <p>This was an application for a group of variations.</p> <p>A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p> <p>B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where</p> | 15/05/2018 | n/a | | |

| | | | | | |
|-----------|--|------------|------------|------------------|--|
| | <p>batch control/testing takes place</p> <p>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation</p> <p>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p> <p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> | | | | |
| 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 | 25/04/2018 | n/a | | |
| N/0101 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 30/08/2017 | 04/10/2019 | Labelling and PL | |
| IAIN/0100 | 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 | | |
| WS/1085 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate</p> | 21/04/2017 | n/a | | |

| | | | | | |
|-------------------|---|------------|-----|--|-----------------------------------|
| | from an already approved manufacturer | | | | |
| PSUSA/2563/201607 | Periodic Safety Update EU Single assessment - human protein c | 09/03/2017 | n/a | | PRAC Recommendation - maintenance |
| IB/0096/G | This was an application for a group of variations. B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test | 31/01/2017 | n/a | | |
| IA/0099 | B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | 11/01/2017 | n/a | | |
| IB/0097 | B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | 15/12/2016 | n/a | | |
| II/0093 | C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required | 15/09/2016 | n/a | | Not applicable. |
| 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) - | 11/07/2016 | n/a | | |

| | | | | | |
|-------------------|--|------------|-----|--|-----------------------------------|
| | Inclusion of an updated/amended PMF when changes do not affect the properties of the FP | | | | |
| IB/0092/G | This was an application for a group of variations. 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.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 01/07/2016 | n/a | | |
| 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 | 25/04/2016 | n/a | | |
| PSUSA/2563/201507 | Periodic Safety Update EU Single assessment - human protein c | 17/03/2016 | n/a | | PRAC Recommendation - maintenance |
| IB/0090/G | This was an application for a group of variations. B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | 22/02/2016 | n/a | | |
| IB/0089 | B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including | 28/01/2016 | n/a | | |

| | | | | | |
|-------------|---|------------|-----|--|--|
| | replacement or addition) | | | | |
| IB/0088 | B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 22/12/2015 | n/a | | |
| II/0086/G | <p>This was an application for a group of variations.</p> <p>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</p> <p>B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> | 08/10/2015 | n/a | | |
| IAIN/0085/G | <p>This was an application for a group of variations.</p> <p>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</p> <p>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</p> | 21/05/2015 | n/a | | |

| | | | | | |
|-------------------|--|------------|------------|-----------------------|-----------------------------------|
| IB/0084 | B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation | 21/05/2015 | n/a | | |
| IB/0083 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 05/05/2015 | 20/05/2016 | SmPC, Annex II and PL | |
| N/0082 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 13/03/2015 | 20/05/2016 | PL | |
| PSUSA/2563/201407 | Periodic Safety Update EU Single assessment - human protein c | 12/03/2015 | n/a | | PRAC Recommendation - maintenance |
| IB/0081 | B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 16/01/2015 | n/a | | |
| IB/0078/G | This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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 | 15/05/2014 | n/a | | |
| 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 | 24/04/2014 | n/a | | |

| | | | | | |
|-------------------|---|------------|-----|--|-----------------------------------|
| IB/0076 | B.I.a.3.z - Change in batch size (including batch size ranges) of AS or intermediate - Other variation | 16/04/2014 | n/a | | |
| PSUSA/2563/201307 | Periodic Safety Update EU Single assessment - human protein c | 06/03/2014 | n/a | | PRAC Recommendation - maintenance |
| IA/0074 | 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 | 20/11/2013 | n/a | | |
| IB/0073 | B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation | 16/08/2013 | n/a | | |
| IA/0072 | B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 03/07/2013 | n/a | | |
| WS/0350 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Use of an alternative albumin as excipient B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation | 27/06/2013 | n/a | | |
| IAIN/0071 | 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) - | 31/05/2013 | n/a | | |

| | | | | | |
|-----------|--|------------|-----|--|--|
| | Inclusion of an updated/amended PMF when changes do not affect the properties of the FP | | | | |
| IAIN/0070 | 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 | 12/04/2013 | n/a | | |
| IA/0068 | A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS | 08/10/2012 | n/a | | |
| IB/0067 | B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer | 30/07/2012 | 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 | 18/06/2012 | n/a | | |
| IA/0065 | 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 | 11/11/2011 | n/a | | |

| | | | | | |
|-----------|---|------------|------------|----------------------------------|--|
| II/0064 | <p>Update of section 4.8 of the SmPC to include a new adverse drug reaction 'injection site reaction' Section 4 of the package leaflet has been updated accordingly. In addition, a crossreference regarding information on Parvovirus B19 has been included in section 4.6 and the adverse drug reactions in section 4.8 of the SmPC were re-ordered by MedDRA System Organ Class. Furthermore, the product information was updated according to the QRD template version 7.3.1 and the MAH also took the opportunity to update the list of all local representatives in the Package Leaflet and insert a correction of the postcode for the batch release site and DS manufacturer site.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p> | 22/09/2011 | 27/10/2011 | SmPC, Annex II, Labelling and PL | One case report of 'Injection site reaction' was reported in the post-marketing setting The patient experienced redness and burning sensation of the vein at the puncture site and several centimeters around following infusion with Ceprotin. The events occurred occasionally after some therapy episodes and resolved the day after infusion. This event was evaluated with a probable causal relationship between the use of the medicinal product and injection site reaction (temporal association and positive rechallenge). The ADR has been added to the post-marketing experience in SmPC section 4.8 with the frequency of 'not known'. Section 4 of the package leaflet has been updated accordingly. |
| IB/0063 | B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place | 06/09/2011 | n/a | | |
| IB/0061 | B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation | 17/06/2011 | n/a | | |
| IA/0062/G | <p>This was an application for a group of variations.</p> <p>B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier</p> | 01/06/2011 | n/a | | |

| | | | | | |
|-----------|--|------------|------------|--|--|
| | <p>of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP</p> <p>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</p> | | | | |
| II/0060 | <p>Change in the manufacturing process of the active substance</p> <p>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</p> | 14/04/2011 | 20/04/2011 | | |
| IA/0059/G | <p>This was an application for a group of variations.</p> <p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p> <p>B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information</p> | 16/12/2010 | n/a | | |

| | | | | | |
|-----------|--|------------|------------|--|--|
| IB/0058 | B.II.b.z - Change in manufacture of the Finished Product - Other variation | 30/09/2010 | n/a | | |
| IB/0057 | B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer | 29/07/2010 | n/a | | |
| IA/0056 | To include the PMF Annual Update 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 | 20/05/2010 | n/a | | |
| II/0054 | Addition of Baxter Manufacturing S.p.A, Rieti / Italy as an alternative manufacturing site for Factor IX eluate. Change(s) to the manufacturing process for the active substance | 18/02/2010 | 01/03/2010 | | |
| 2PMF/0055 | Inclusion of the updated or amended Plasma Master File (Baxter EMEA/H/PMF/000003/04) in the marketing authorisation dossier | 08/01/2010 | n/a | | |
| IB/0053 | IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release | 03/04/2009 | n/a | | |
| IB/0052 | IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient | 28/01/2009 | n/a | | |

| | | | | | |
|---------|--|------------|------------|-------------|--|
| IB/0051 | IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient | 02/12/2008 | n/a | | |
| MF/0050 | 2PMF (2nd step of PMF certification procedure) | 26/06/2008 | n/a | | |
| II/0049 | Change(s) to the manufacturing process for the finished product | 24/01/2008 | 30/01/2008 | | |
| II/0046 | Update of Summary of Product Characteristics and Package Leaflet | 21/06/2007 | 10/08/2007 | SmPC and PL | <p>The MAH applied for a type II variation to update sections 4.2 and 5.1 of the SPC to include information on dosing in paediatric patients as follows:</p> <p>"Based on the limited clinical experience in children from reports and studies covering 83 patients, dosing guidelines for adult subjects are considered valid for neonatal and paediatric patient population (see section 5.1). In rare and exceptional cases, subcutaneous infusion of 250-350 IU/kg was able to produce therapeutic protein C plasma levels in patients with no intravenous access."</p> <p>Further details on the reports and studies in paediatric patients are also included in section 5.1 of the SPC.</p> <p>In addition, a slight linguistic adjustment to section 4.8 of the SPC was made in order to clarify the assignment of three reported ADRs to one single patient.</p> <p>The contact details for Spain in the list of local representatives in the Package Leaflet has also been updated.</p> |

| | | | | | |
|---------|--|------------|------------|----------------------------------|--|
| II/0047 | Update of or change(s) to the pharmaceutical documentation | 19/07/2007 | 01/08/2007 | | |
| MF/0048 | 2PMF (2nd step of PMF certification procedure) | 21/06/2007 | n/a | | |
| II/0044 | Update of Summary of Product Characteristics and Package Leaflet | 16/11/2006 | 03/01/2007 | SmPC and PL | The MAH applied for an update of the SPC section 4.8 and 5.2 and the PL to include data of the clinical trial 040101 submitted to EMEA in January 2006. The PL is updated accordingly. The MAH applied also to include comments received from QRD during the renewal procedure. (SPC Section 2, 4.4, 6.6 and 9). |
| II/0045 | Quality changes | 14/12/2006 | 19/12/2006 | | |
| R/0042 | Renewal of the marketing authorisation. | 01/06/2006 | 28/07/2006 | SmPC, Annex II, Labelling and PL | The renewal was granted with unlimited validity and PSURs will be submitted on a yearly basis. |
| MF/0043 | 2PMF (2nd step of PMF certification procedure) | 30/06/2006 | n/a | | |
| II/0041 | Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product | 23/03/2006 | 29/03/2006 | | |
| II/0040 | Change(s) to the manufacturing process for the active substance | 23/03/2006 | 29/03/2006 | | |
| MF/0039 | 2PMF (2nd step of PMF certification procedure) | 25/01/2006 | n/a | | |
| S/0037 | Annual re-assessment. | 17/11/2005 | 19/01/2006 | SmPC, Labelling and | |

| | | | | PL | |
|---------|--|------------|------------|------------------------------|---|
| S/0035 | Annual re-assessment. | 15/12/2004 | 07/03/2005 | Annex II | <p>On the basis of the data submitted, the overall benefit/risk ratio of Ceprotin in the authorised indications has not been changed and remains favourable. However, the CHMP considered that there was a need to make minor editorial changes to the Product Information as part of the annual reassessment procedure and agreed on the updated SPC set out in Annex I and the updated labelling and package leaflet set out in Annex III of the Commission Decision.</p> <p>The CHMP agreed to revise the Specific Obligations set out in Annex II.C to the Commission Decision.</p> <p>The CHMP agreed that the Marketing Authorisation should remain under exceptional circumstances.</p> <p>All remaining Specific Obligations will be reviewed at the intervals indicated in the Marketing Authorisation or at the time of the next annual review together with the benefit/risk profile of the medicinal product.</p> |
| IB/0036 | IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release | 02/03/2005 | n/a | | |
| II/0034 | The MAH applied for an extension of shelf life of the final product from 24 to 36 months. Change(s) to shelf-life or storage conditions | 29/07/2004 | 27/09/2004 | SmPC, Labelling and PL | |
| II/0033 | Change(s) to the manufacturing process for the active substance | 29/07/2004 | 02/08/2004 | | |
| II/0031 | Update of or change(s) to the pharmaceutical documentation | 24/03/2004 | 30/03/2004 | | |

| | | | | | |
|---------|--|------------|------------|----------|---|
| S/0027 | Annual re-assessment. | 20/11/2003 | 23/02/2004 | Annex II | <p>On the basis of the data submitted, the overall benefit/risk ratio of Ceprotin in the authorised indications has not been changed and remains favourable.</p> <p>The CPMP agreed to revise the Specific Obligations set out in Annex II.C to the Commission Decision. The CPMP agreed that the Marketing Authorisation should remain under exceptional circumstances.</p> <p>All remaining Specific Obligations will be reviewed at the intervals indicated in the Marketing Authorisation or at the time of the next annual review together with the benefit/risk profile of the medicinal product.</p> |
| I/0030 | 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process | 17/12/2003 | 19/01/2004 | | |
| I/0028 | 24a_Change in test procedure for starting material/intermediate used in manuf. of active substance | 16/10/2003 | 22/10/2003 | | |
| II/0023 | Quality changes | 25/09/2003 | 01/10/2003 | | |
| I/0019 | 15a_Change in IPCs applied during the manufacture of the product | 24/07/2003 | 28/07/2003 | | |
| I/0025 | 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process | 10/07/2003 | 17/07/2003 | | |
| S/0016 | Annual re-assessment. | 19/03/2003 | 30/06/2003 | Annex II | <p>On the basis of the data submitted, the overall benefit/risk ratio of Ceprotin in the authorised indications has not been changed and remains favourable.</p> <p>The CPMP agreed to revise the Specific Obligations set out in Annex II.C to the Commission Decision. The CPMP agreed</p> |

| | | | | | |
|---------|--|------------|------------|--|--|
| | | | | | that the Marketing Authorisation should remain under exceptional circumstances. All remaining Specific Obligations will be reviewed at the intervals indicated in the Marketing Authorisation or at the time of the next annual review together with the benefit/risk profile of the medicinal product. |
| II/0020 | Update of or change(s) to the pharmaceutical documentation | 22/05/2003 | 02/06/2003 | | |
| I/0022 | 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process | 26/05/2003 | 02/06/2003 | | |
| I/0024 | 15a_Change in IPCs applied during the manufacture of the product | 08/05/2003 | n/a | | |
| I/0021 | 26_Changes to comply with supplements to pharmacopoeias | 12/03/2003 | 17/03/2003 | | |
| II/0015 | Quality changes | 20/02/2003 | 03/03/2003 | | |
| II/0014 | Change(s) to the test method(s) and/or specifications for the active substance | 18/12/2002 | 09/01/2003 | | |
| I/0018 | 26_Changes to comply with supplements to pharmacopoeias | 20/12/2002 | 08/01/2003 | | |
| I/0017 | 17_Change in specification of the medicinal product | 20/12/2002 | 08/01/2003 | | |
| II/0012 | Quality changes | 17/10/2002 | 22/10/2002 | | |
| I/0013 | 12a_Change in specification of starting | 16/09/2002 | 24/09/2002 | | |

| | | | | | |
|---------|--|------------|------------|----|--|
| | material/intermediate used in manuf. of the active substance | | | | |
| II/0010 | Quality changes | 22/08/2002 | 09/09/2002 | | |
| I/0011 | 24a_Change in test procedure for starting material/intermediate used in manuf. of active substance | 10/07/2002 | 12/07/2002 | | |
| I/0006 | 15_Minor changes in manufacture of the medicinal product | 30/05/2002 | 07/06/2002 | | |
| I/0007 | 25_Change in test procedures of the medicinal product | 25/04/2002 | 06/05/2002 | | |
| I/0009 | 24a_Change in test procedure for starting material/intermediate used in manuf. of active substance | 15/03/2002 | 19/03/2002 | | |
| N/0008 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 15/03/2002 | 18/04/2002 | PL | |
| I/0005 | 24a_Change in test procedure for starting material/intermediate used in manuf. of active substance | 21/12/2001 | 21/01/2002 | | |
| II/0002 | Quality changes | 15/11/2001 | 28/11/2001 | | |
| I/0004 | 24a_Change in test procedure for starting material/intermediate used in manuf. of active substance | 26/10/2001 | n/a | | |

| | | | | | |
|---------|--|------------|------------|--|--|
| II/0003 | Quality changes | 20/09/2001 | 08/10/2001 | | |
| I/0001 | 12_Minor change of manufacturing process of the active substance | 20/09/2001 | 08/10/2001 | | |