EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



# KOGENATE Bayer

## 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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| IB/0205/G | This was an application for a group of variations.<br><br>A.7 - Administrative change - Deletion of manufacturing sites<br>B.I.z - Quality change - Active substance - Other variation<br>B.II.z - Quality change - Finished product - Other variation<br>B.II.b.2.a - Change to importer, batch release | 16/04/2018 | n/a | | |

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

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| | arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place | | | | |
| IG/0908 | 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 | 07/03/2018 | n/a | | |
| WS/1319/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><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.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 | 18/01/2018 | n/a | | |
| WS/1317/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation<br>B.I.a.2.z - Changes in the manufacturing process of | 18/01/2018 | n/a | | |

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| | the AS - Other variation | | | | |
| WS/1279 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><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 | 30/11/2017 | n/a | | |
| A31/0185 | Pursuant to Article 31 of Directive 2001/83/EC, Germany initiated a procedure on 6 July 2016 based on concerns resulting from the evaluation of data from pharmacovigilance activities.<br>The PRAC was requested to assess the potential impact of the results of the SIPPET study (which concluded that recombinant factor VIII medicines had a higher incidence of inhibitor development than plasma-derived medicines), and to issue a recommendation as to whether the marketing authorisations of these products should be maintained, varied, suspended or revoked. The EMA concluded in September 2017 that there is no clear and consistent evidence of a difference in the incidence of inhibitor development between the two classes of factor VIII medicines: those derived from plasma and those made by recombinant DNA technology. Due to the different characteristics of individual products within the two classes, EMA concluded that the risk of inhibitor development | 14/09/2017 | 16/11/2017 | SmPC and PL | Please refer to the assessment report: human coagulation factor VIII - EMEA/H/A-31/1448 |

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| | should be evaluated individually for each medicine, regardless of class. The risk for each product will continue to be assessed as more evidence becomes available. | | | | |
| IG/0822 | 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 | 14/07/2017 | n/a | | |
| IG/0806 | 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 | 31/05/2017 | n/a | | |
| PSUSA/2200/ 201608 | Periodic Safety Update EU Single assessment - octocog alpha | 05/05/2017 | n/a | | PRAC Recommendation - maintenance |
| N/0198 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 25/04/2017 | 16/11/2017 | Labelling and PL | |
| T/0197 | Transfer of Marketing Authorisation | 23/03/2017 | 11/04/2017 | SmPC, Labelling and PL | |
| WS/1125/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No | 16/03/2017 | n/a | | |

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| | 1234/2008.<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.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 | | | | |
| WS/1118/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>A.7 - Administrative change - Deletion of manufacturing sites<br>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation | 23/02/2017 | n/a | | |
| IA/0196/G | This was an application for a group of variations.<br><br>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 | 03/02/2017 | n/a | | |

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| | 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) | | | | |
| WS/1043/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<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.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 | 02/02/2017 | n/a | | |
| IA/0194/G | This was an application for a group of variations.<br><br>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure<br>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 11/01/2017 | n/a | | |

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| IA/0191/G | This was an application for a group of variations.<br><br>B.II.d.2.z - Change in test procedure for the finished product - Other variation<br>B.II.d.2.z - Change in test procedure for the finished product - Other variation<br>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 | 25/11/2016 | n/a | | |
| WS/1018 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><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 | 24/11/2016 | n/a | | |
| IA/0190 | B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation | 11/11/2016 | n/a | | |
| WS/1036 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation | 10/11/2016 | n/a | | |

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| WS/1006 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>- Implementation of QRD template version 9.1 (June 2015)<br>- Combination of the EU PIs for all five strengths (following QRD template version 9.1 and the Policy on combined Summaries of Product Characteristics (SmPCs) (June 2015). This means merging of the five strengths for KOGENATE Bayer for the Bio-set presentation, KOGENATE Bayer for the vial adapter presentation and Helixate NexGen into one EU-PI, respectively. A justification for combination of the PILs is provided.<br>- Minor editorial changes in line with the recently approved rFVIII-products Kovaltry (EMEA/H/C/003825) and Iblias (EMEA/H/C/004147). These changes are considered not to change the meaning of the text/the scientific content.<br><br>In addition the opportunity was taken to notify updates in the List of Local Representatives in the PIL section 6 for both products:<br>• KOGENATE Bayer: PT<br>• Helixate NexGen: CZ, ET, LT, LV, SK<br>The requested worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and | 15/09/2016 | 11/04/2017 | SmPC, Annex II, Labelling and PL | |

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| | Veterinary Medicinal Products - Other variation | | | | |
| WS/0938 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | 15/09/2016 | n/a | | |
| IA/0187/G | This was an application for a group of variations.<br><br>B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier<br>B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier | 12/08/2016 | n/a | | |
| IA/0182/G | This was an application for a group of variations.<br><br>B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier<br>B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier | 02/06/2016 | n/a | | |
| IG/0692 | 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 | 25/05/2016 | n/a | | |

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| | do not affect the properties of the FP | | | | |
| IAIN/0179 | B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking | 17/02/2016 | n/a | | |
| WS/0880 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation | 28/01/2016 | n/a | | |
| IA/0178/G | This was an application for a group of variations.<br><br>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<br>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<br>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 | 16/12/2015 | n/a | | |

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| N/0176 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 23/11/2015 | 11/04/2017 | PL | |
| IG/0604 | 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 | 12/08/2015 | n/a | | |
| IAIN/0174 | B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking | 17/06/2015 | n/a | | |
| IG/0562 | B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP | 05/05/2015 | n/a | | |
| IA/0172/G | This was an application for a group of variations.<br><br>A.7 - Administrative change - Deletion of manufacturing sites<br>B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State | 15/04/2015 | n/a | | |

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| WS/0654 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<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 substance which may have a significant impact on the medicinal product and is not related to a protocol | 20/11/2014 | n/a | | |
| PSUSA/2200/ 201402 | Periodic Safety Update EU Single assessment - octocog alpha | 09/10/2014 | n/a | | PRAC Recommendation - maintenance |
| WS/0557 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 24/07/2014 | n/a | | |
| N/0169 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 23/07/2014 | 11/04/2017 | PL | |
| IG/0462 | 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 | 11/07/2014 | n/a | | |
| WS/0574/G | This was an application for a group of variations following a worksharing procedure according to | 26/06/2014 | n/a | | |

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| | Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability<br>B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability | | | | |
| WS/0504/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of facilities and equipment documentation, and deletion of a manufacturing site.<br><br>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation<br>A.7 - Administrative change - Deletion of manufacturing sites | 26/06/2014 | n/a | | |
| WS/0556 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Change of the Controll test procedures of the active substance. | 22/05/2014 | n/a | | |

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| | B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | | | | |
| WS/0555/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Minor changes in the manufacturing process.<br>Update of stability data.<br><br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation | 22/05/2014 | n/a | | |
| IG/0428 | 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 | 20/03/2014 | n/a | | |
| A20/0150 | Pursuant to Article 20 of Regulation (EC) No. 726/2004, the European Commission requested the Agency to re-evaluate the benefit-risk balance of Kogenate Bayer and Helixate Nexgen in light of newly available data on the increased risk of inhibitor development in previously untreated patients compared with other factor VIII products and to give | 19/12/2013 | 20/02/2014 | SmPC and PL | Please refer to the assessment report: EMEA/H/C/000275/A-20/0150 |

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| | its opinion on whether the marketing authorisation in the approved indication should be maintained, varied, suspended or revoked.<br>The PRAC considered the publication of the results of the RODIN/PedNet study, the preliminary findings from the European Haemophilia Safety Surveillance System (EUHASS) registry and all available data submitted from clinical trials, observational studies, published literature and quality data for Kogenate Bayer and Helixate NexGen with regards to its potential risk of inhibitor development in previously untreated patients (PUPs).<br>The PRAC noted that the efficacy of Kogenate Bayer/Helixate NexGen is not questioned and, on the basis of the available data, concluded that the current results do not confirm an increased risk of developing antibodies against Kogenate Bayer and Helixate NexGen when compared with other factor VIII products in PUPs with the bleeding disorder haemophilia A.<br>The PRAC considered though that the frequency for inhibitor development in PUPs should be amended from “common” to “very common” in the section 4.8 of the SmPC and also recommended that the product information should be updated to reflect the most recent results from the RODIN study . | | | | |
| IG/0385 | 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) - | 18/12/2013 | n/a | | |

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| | Inclusion of an updated/amended PMF when changes do not affect the properties of the FP | | | | |
| WS/0463 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>PMF Second step procedure<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 | 18/12/2013 | n/a | | |
| WS/0458 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Submission of the final study report of the Leopold I study and its extension. The study was a two-part, randomised, cross-over, open-label trial to evaluate the pharmacokinetics, efficacy and safety profile of a novel formulation plasma protein-free recombinant FVIII in previously treated subjects with severe haemophilia A under prophylaxis therapy. The study compared the novel formulation with the existing one of Kogenate Bayer/Helixate NexGen and was submitted under Art. 46 of the paediatric Regulation EC/1901/2006.<br><br>C.I.13 - Other variations not specifically covered | 21/11/2013 | n/a | | The MAH submitted paediatric data for the marketed product KOGENATE Bayer from the Leopold I study in accordance with Article 46 of Regulation (EC) No 1901/2006. The PK analyses included the determination of BAY 81-8973, an investigational product, and KOGENATE Bayer. A lower AUC and t1/2 was observed for both drugs as a result of a higher clearance in the paediatric population. Section 4.2 of the SmPC already contains information on long term prophylaxis against bleeding in younger patients with severe haemophilia A, where it is suggested to have shorter dose intervals or higher doses. This information is consistent with the PK results from the study. Safety and tolerability were consistent with the known profile. No new safety concerns were identified. No changes to the product information in relation to the data submitted were considered necessary. |

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| | elsewhere in this Annex which involve the submission of studies to the competent authority | | | | |
| WS/0449 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Submission of the final report of a single dose, open-label, randomized, crossover study in subjects with severe or moderate Haemophilia A to compare the bioavailability of 2 different strengths of Kogenate FS (BAY 14-2222). The CHMP considered that no update to the product information was required.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 21/11/2013 | n/a | | As part the post-marketing commitment following the approval of the 3000 IU strength, the MAH submitted the final report of a single dose, open-label, randomized, crossover study in subjects with severe or moderate Hemophilia A to compare the bioavailability of 2 different strengths of Kogenate FS (BAY 14-2222). No new safety concerns were identified and tolerability was consistent with the other strengths of the product. Thus, no changes to the product information were considered necessary. The CHMP considers the obligation to perform a bioequivalence study for the 3000 IU strength fulfilled. |
| WS/0427/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of section 4.4 of the SmPC to include a warning on cardiovascular risk in haemophilic patients following two reports of myocardial infarction which occurred after administration of Kogenate Bayer/Helixate NexGen in patients with haemophilia A. The Package Leaflet is updated accordingly. Additional changes are made throughout the SmPC to bring it in line with the core SmPC for human plasma derived and recombinant coagulation | 19/09/2013 | 20/02/2014 | SmPC, Annex II, Labelling and PL | Haemophilic patients with cardiovascular risk factors or diseases may be at the same risk to develop cardiovascular events as non-haemophilic patients when clotting has been normalized by treatment with FVIII. Elevation of FVIII levels following administration, in particular with existing cardiovascular risk factors, might put a patient at least into the same risk for vessel closure or myocardial infarction as for the non-haemophilic population. Consequently, patients should be evaluated and monitored for cardiac risk factors. |

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| | factor VIII products. Furthermore, the PI is being brought in line with the latest QRD template version 9.0.<br><br>C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH<br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | | | | |
| IA/0154 | B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 30/04/2013 | n/a | | |
| IA/0153/G | This was an application for a group of variations.<br><br>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<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.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | 26/04/2013 | n/a | | |
| WS/0379/G | This was an application for a group of variations following a worksharing procedure according to | 25/04/2013 | n/a | | |

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| | Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Change to finished product manufacture<br>Deletion of finished product manufacturing sites<br><br>B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation<br>A.7 - Administrative change - Deletion of manufacturing sites | | | | |
| IA/0151/G | This was an application for a group of variations.<br><br>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure<br>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<br>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<br>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<br>B.III.2.b - Change to comply with Ph. Eur. or with a | 08/04/2013 | n/a | | |

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| | 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<br>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<br>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<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 | | | | |
| IB/0148 | B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place | 26/02/2013 | n/a | | |
| IG/0271 | 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 | 15/02/2013 | n/a | | |
| WS/0346 | This was an application for a variation following a worksharing procedure according to Article 20 of | 17/01/2013 | n/a | | |

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| | Commission Regulation (EC) No 1234/2008.<br><br>To introduce a change in a buffer used in the manufacture of active substance.<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 | | | | |
| IG/0244 | 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 | 12/12/2012 | n/a | | |
| IG/0242 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 28/11/2012 | n/a | | |
| WS/0289 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of section 4.8 of the SmPC with the deletion of reference to only “one” anaphylactic reaction, as more than one anaphylactic reaction report have been received. No new frequency was assigned to the ADR term ‘hypersensitivity’. No changes have been proposed for the PL.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre- | 20/09/2012 | 23/10/2012 | SmPC | The MAH reviewed cases of anaphylactic reactions from CIOMS case report forms. There were three cases that were assessed as “severe” or “life-threatening”. The MAH updated section 4.8 of the SmPC to reflect the additional cases of anaphylactic reactions. |

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| | clinical, clinical or pharmacovigilance data | | | | |
| WS/0274 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>The MAH updated section 6 of the SmPC and section 3 of the Package Leaflet (PL) in order to enhance the language with regards to the preparation and reconstitution of the product and to emphasize the use of appropriate filtration prior to administration of the product. A minor editorial change was also introduced in the PL.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | 20/09/2012 | 23/10/2012 | SmPC and PL | Following the review of complaints concerning the appearance of particulate matter present in the vial from the Bio-Set reconstitution device, the cause was identified as stemming from the sterile Bio-Set assembly or sterile rubber stopper particles which could occur during the coring process when the sterile Bio-Set needle “cores” through the rubber stopper. The MAH implemented corrective actions through better wording in the SmPC and PL to reinforce the guidance on the preparation, reconstitution and appropriate filtering prior to administration of the product. |
| IB/0144 | 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 | 17/10/2012 | n/a | | |
| IG/0187/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 | 01/06/2012 | n/a | | |

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| | 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 | | | | |
| IG/0173/G | This was an application for a group of variations.<br><br>C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD<br>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system<br>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system | 08/05/2012 | n/a | | |
| WS/0193 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of section 5.1 of the SmPC in order to add information on study results from the INFACT and the International ITI study concerning the use of octocog alfa in immune tolerance induction. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. | 15/03/2012 | 20/04/2012 | SmPC, Annex II, Labelling and PL | The applicant applied for new indication for immune tolerance induction (ITI). The CHMP considered that benefit-risk was negative for the new indication. However, it was agreed to include information on the study results of the INFACT study and the International ITI study in section 5.1 of the SmPC. |

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| | Furthermore, the PI is being brought in line with the latest QRD template version 8.0.<br><br>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | | | | |
| WS/0214 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Change to drug substance testing<br><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 | 19/04/2012 | n/a | | |
| IB/0137/G | This was an application for a group of variations.<br><br>B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol<br>B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data) | 14/04/2012 | 23/10/2012 | SmPC, Labelling and PL | |
| WS/0198 | This was an application for a variation following a worksharing procedure according to Article 20 of | 16/02/2012 | 19/03/2012 | SmPC and PL | Catheter related-infections and dysgeusia were observed in post marketing experience and in clinical trials. The |

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| | Commission Regulation (EC) No 1234/2008.<br><br>Update of section 4.4 of the SmPC to add catheter related infections and the risk of thrombosis and the inclusion of “dysgeusia” in the table of undesirable effects in section 4.8 with a frequency of "very rare/unknown". The MAH also made some minor editorial changes to the SmPC. The Package Leaflet was amended accordingly.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | | | | catheter related infections were not associated with the product itself, however, a warning on catheter-related infections and complication of thrombosis was included in the SmPC and PL since the use of octocog alfa administered via central venous access devices (CVADs) may be necessary for haemophiliac patients when frequent venous access is required for long-term prophylaxis. Dysgeusia was found to be an event with a frequency of “very rare/unknown”. |
| IG/0153/G | This was an application for a group of variations.<br><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.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.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.III.2.b - Change to comply with Ph. Eur. or with a | 06/03/2012 | n/a | | |

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| | 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<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.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.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 | | | | |
| IAIN/0135 | B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking | 23/02/2012 | n/a | | |
| WS/0213 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Changes to finished product testing.<br><br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) | 16/02/2012 | 16/02/2012 | | |

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| WS/0155/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Change to reference standards.<br><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<br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) | 16/02/2012 | 16/02/2012 | | |
| WS/0206 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Change to active substance manufacturing process.<br><br>B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line) | 19/01/2012 | n/a | | |
| IG/0131 | 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 | 08/12/2011 | n/a | | |

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| | do not affect the properties of the FP | | | | |
| IA/0113/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.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<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) | 19/08/2011 | n/a | SmPC, Labelling and PL | |
| IG/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 | 27/04/2011 | n/a | | |
| IB/0112/G | This was an application for a group of variations.<br><br>B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products<br>B.II.b.3.z - Change in the manufacturing process of | 01/04/2011 | n/a | | |

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| | the finished product - Other variation<br>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation<br>B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products | | | | |
| WS/0094 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Alternative testing site.<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 | 17/02/2011 | 17/02/2011 | | |
| WS/0083 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Change in drug product specification.<br><br>B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range | 20/01/2011 | 20/01/2011 | | |
| WS/0012 | This was an application for a variation following a worksharing procedure according to Article 20 of | 16/12/2010 | 10/01/2011 | | |

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| | Commission Regulation (EC) No 1234/2008.<br><br>Changes to in-process tests and limits in the active substance manufacture.<br><br>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | | | | |
| IG/0038/G | This was an application for a group of variations.<br><br>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV<br>C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database<br>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system | 07/01/2011 | n/a | | |
| WS/0062 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Extension in storage time.<br><br>B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol | 18/11/2010 | 20/12/2010 | SmPC, Annex II, Labelling and PL | |

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| IA/0110 | A.7 - Administrative change - Deletion of manufacturing sites | 12/10/2010 | n/a | | |
| IG/0017 | B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits | 06/08/2010 | n/a | | |
| X/0104 | Annex I_2.(c) Change or addition of a new strength/potency | 24/06/2010 | 06/08/2010 | SmPC, Labelling and PL | |
| R/0107 | Renewal of the marketing authorisation. | 24/06/2010 | 06/08/2010 | SmPC, Annex II, Labelling and PL | The quality, safety and efficacy of KOGENATE Bayer continue to be adequately and sufficiently demonstrated and the benefit/risk profile remains favourable. The CHMP is of the opinion that the renewal can be granted with unlimited validity. |
| WS/0010 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>To extend the shelf life of the product from 24 month to 30 months for the 2000 IU doses strength.<br><br>B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol | 24/06/2010 | 28/07/2010 | SmPC | |

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| WS/0020 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>To introduce a minor change in the manufacturing process of the active substance<br><br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 22/07/2010 | 22/07/2010 | | |
| IG/0012 | 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 | 21/07/2010 | n/a | | |
| IG/0009/G | This was an application for a group of variations.<br><br>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system<br>C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV<br>C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV<br>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV | 18/06/2010 | n/a | Annex II | |

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| | C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system | | | | |
| WS/0014 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Change to the specification parameters and/or limits of a reagent used in the active substance manufacture.<br><br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation | 20/05/2010 | 20/05/2010 | | |
| WS/0008 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Changes to the active substance manufacturer.<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 | 20/05/2010 | 20/05/2010 | | |
| WS/0007 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. | 20/05/2010 | 20/05/2010 | | |

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| | Change to the manufacture of 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 change requires an assessment of comparability | | | | |
| II/0108 | Change in drug product test procedure and drug product specification.<br><br>B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range | 22/04/2010 | 03/05/2010 | | Change in drug product test procedure and drug product specification. |
| II/0092 | Change in Product Information relating to stability claim for for continuous infusion.<br><br>Update of Summary of Product Characteristics, Labelling and Package Leaflet | 18/02/2010 | 26/03/2010 | SmPC, Labelling and PL | Change in Product Information relating to stability claim for for continuous infusion. |
| II/0106 | Update of Appendices and Regional Information<br><br>Quality changes | 18/02/2010 | 11/03/2010 | | |
| II/0105 | Changes to drug product manufacture.<br><br>Quality changes | 21/01/2010 | 03/02/2010 | | |
| II/0103 | Changes in the manufacture of the active substance.<br><br>Change(s) to the manufacturing process for the | 17/12/2009 | 12/01/2010 | | |

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| | active substance | | | | |
| II/0094 | Introduction of additional container closure system.<br><br>Quality changes | 17/12/2009 | 12/01/2010 | | Introduction of additional container closure system. |
| II/0096 | Change in drug substance and drug product control test.<br><br>Quality changes | 19/11/2009 | 08/12/2009 | | Change in drug substance and drug product control test. |
| II/0102 | Changes to the manufacturing process of the active substance.<br><br>Update of or change(s) to the pharmaceutical documentation<br>Change(s) to the manufacturing process for the active substance | 22/10/2009 | 12/11/2009 | | |
| II/0095 | Changes to active substance manufacturing process.<br><br>Quality changes | 22/10/2009 | 12/11/2009 | | Changes to drug substance manufacture. |
| II/0101 | Update of DDPS (Pharmacovigilance) | 24/09/2009 | 16/10/2009 | Annex II | |
| II/0100 | Minor changes to the drug product manufacturing.<br><br>Quality changes | 24/09/2009 | 06/10/2009 | | |
| 2PMF/0099 | Inclusion of the updated or amended Plasma Master File (Talecris EMEA/H/PMF/000004/04) in the marketing authorisation dossier | 29/07/2009 | n/a | | |

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| II/0093 | Changes to manufacturers.<br><br>Quality changes | 25/06/2009 | 27/07/2009 | Annex II and PL | Changes to manufacturers. |
| IA/0098 | IA_25_b_02_Change to comply with Ph. - compliance with EU Ph. update - excipient | 08/07/2009 | n/a | | |
| IA/0097 | IA_09_Deletion of manufacturing site | 09/06/2009 | n/a | | |
| II/0085 | Update of Summary of Product Characteristics, Labelling and Package Leaflet | 19/03/2009 | 24/04/2009 | SmPC, Labelling and PL | The MAH submitted a revision of the section 4.8 "Undesirable Effects" of the SPC following a MAH safety review of all available data from clinical studies. These data have been recoded from COSTART to MedDRA with subsequent revisions in the list of AEs in the table.<br><br>Consequently, the section 4 "Possible Side Effects" of the PIL has been changed. Moreover, in order to improve product handling, the pictograms have been changed. In addition, the MAH proposes editorial changes to the Product Information and linguistic correction for some countries. The list of local representatives is also revised. |
| 2PMF/0091 | Inclusion of the updated or amended Plasma Master File (Talecris EMEA/H/PMF/000004/04) in the marketing authorisation dossier | 16/04/2009 | n/a | | |
| T/0088 | Transfer of Marketing Authorisation | 06/03/2009 | 07/04/2009 | SmPC, Annex II, Labelling and PL | Transfer from Bayer HealthCare AG to Bayer Schering Pharma AG.<br><br>The transfer will take place on 01 October 2009. |

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| II/0087 | Minor changes to manufacturing in-process action levels.<br><br>Quality changes | 19/03/2009 | 24/03/2009 | | Minor changes to manufacturing in-process action levels. |
| IA/0090 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 05/03/2009 | n/a | | |
| IA/0089 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 05/03/2009 | n/a | Annex II and PL | |
| II/0083 | Update of DDPS (Pharmacovigilance) | 22/01/2009 | 04/03/2009 | Annex II | Submission of a revised detailed description of the Pharmacovigilance System by the MAH. Consequently the annex II of the product information is revised. |
| IB/0086 | IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient | 02/02/2009 | n/a | | |
| II/0082 | Approval of additional drug product tests to be performed at an already licensed batch control testing site.<br><br>Quality changes | 20/11/2008 | 28/11/2008 | | |
| MF/0067 | 2PMF (2nd step of PMF certification procedure) | 27/11/2008 | n/a | | |
| IB/0084 | IB_30_b_Change in supplier of packaging components - replacement/addition | 06/11/2008 | n/a | | |
| II/0080 | Additional finished product control test to be carried at one of the finished product testing sites. | 23/10/2008 | 28/10/2008 | | Additional finished product control test to be carried at one of the finished product testing sites. |

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| | Quality changes | | | | |
| II/0079 | Changes to the in-process control testing of the active substance.<br><br>Quality changes | 23/10/2008 | 28/10/2008 | | Changes to the in-process control testing of the active substance. |
| II/0075 | Introduction of a new facility at a currently approved manufacturing site.<br><br>Quality changes | 25/09/2008 | 02/10/2008 | | Introduction of a new facility at a currently approved manufacturing site. |
| MF/0081 | 2PMF (2nd step of PMF certification procedure) | 24/09/2008 | n/a | | |
| II/0078 | Approval of addition of further finished product control tests to the Bayer SPA testing site.<br><br>Quality changes | 24/07/2008 | 29/07/2008 | | |
| II/0077 | | 24/07/2008 | n/a | | |
| II/0076 | Change to the active substance manufacture without impact on the benefit/risk balance of the product.<br><br>Quality changes | 30/05/2008 | 11/06/2008 | | |
| II/0072 | Quality changes | 19/03/2008 | 28/03/2008 | | |
| II/0069 | Change(s) to the manufacturing process for the finished product | 21/02/2008 | 26/02/2008 | | |

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| MF/0074 | 2PMF (2nd step of PMF certification procedure) | 22/02/2008 | n/a | | |
| II/0070 | Quality changes | 24/01/2008 | 29/01/2008 | | |
| IA/0073 | IA_28_Change in any part of primary packaging material not in contact with finished product | 24/01/2008 | n/a | | |
| X/0056 | X-3-iii_Addition of new strength | 18/10/2007 | 18/12/2007 | SmPC, Labelling and PL | |
| IA/0071 | IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site | 17/12/2007 | n/a | | |
| II/0068 | Quality changes | 15/11/2007 | 21/11/2007 | | |
| II/0061 | Update of Summary of Product Characteristics, Labelling and Package Leaflet | 20/09/2007 | 30/10/2007 | SmPC, Annex II, Labelling and PL | The MAH applied for a type II variation to update section 4.8 of the SPC with information on inhibitor development. The following wording was agreed with the CHMP: "In clinical studies, KOGENATE Bayer has been used in the treatment of bleeding episodes in 37 previously untreated patients (PUPs) and 23 minimally treated pediatric patients (MTPs, defined as having equal to or less than 4 exposure days). Five out of 37 (14%) PUP and 4 out of 23 (17%) MTP patients treated with KOGENATE Bayer developed inhibitors: Overall 6 out of 60 (10%) with a titer above 10 BU and 3 out of 60 (5%) with a titer below 10 BU. The median number of exposure days at the time of inhibitor detection in these patients was 9 days (range 3 - 18 days). The median number of exposure days in the clinical studies was 114 (range: 4-478). Four of the five patients, who had not achieved 20 exposure days at the end of the study, |

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| | | | | | ultimately achieved more than 20 exposure days in post-study follow-up and one of them developed a low titer inhibitor. The fifth patient was lost to follow-up.<br>In clinical studies with 73 previously treated patients (PTP, defined as having more than 100 exposure days), followed over four years, no de-novo inhibitors were observed.<br>In extensive post-registration studies with KOGENATE Bayer, involving more than 1000 patients the following was observed: Less than 0.2% PTP developed de-novo inhibitors. In a subset defined as having less than 20 exposure days at study entry, less than 11% developed de-novo inhibitors."<br>The Package leaflet has been updated accordingly.<br>In addition, the Product Information has been updated to comply with the QRD template (version 7.2) and to include minor editorial and linguistic changes. The list of local representatives has also been updated.<br>The MAH applied for a type II variation, upon request from the CHMP following a class review of recombinant Factor VIII medicinal products, to update section 4.4 of the SPC to include a warning on c |
| II/0066 | Quality changes | 20/09/2007 | 27/09/2007 | | |
| II/0062 | Quality changes | 20/09/2007 | 27/09/2007 | | |
| II/0057 | Quality changes | 19/07/2007 | 25/07/2007 | | |
| II/0058 | Update of Summary of Product Characteristics and Package Leaflet | 21/06/2007 | 24/07/2007 | SmPC and PL | The MAH applied for a type II variation, upon request from the CHMP following a class review of recombinant Factor VIII medicinal products, to update section 4.4 of the SPC to include a warning on cases of inhibitors as follows: |

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| | | | | | 'Cases of recurrence of inhibitors (low titre) have been observed after switching from one recombinant factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development.'<br><br>The Package Leaflet has been updated accordingly. |
| IA/0065 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site | 16/07/2007 | n/a | | |
| IA/0064 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site | 11/07/2007 | n/a | | |
| IA/0063 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 11/07/2007 | n/a | | |
| MF/0060 | 2PMF (2nd step of PMF certification procedure) | 08/06/2007 | n/a | | |
| IB/0059 | IB_30_b_Change in supplier of packaging components - replacement/addition | 25/05/2007 | n/a | | |
| II/0055 | Quality changes | 26/04/2007 | 02/05/2007 | | |
| II/0051 | Update of Summary of Product Characteristics and Package Leaflet | 14/12/2006 | 29/01/2007 | SmPC and PL | The MAH applied to introduce an additional mode of administration i.e. continuous infusion. Consequently, amendments to sections 4.2, 4.4, 5.2, 6.3 and 6.6 of the SPC are introduced by the Applicant in this variation. The Package Leaflet is amended accordingly. Furthermore, minor linguistic corrections in the SPC, Package Leaflet as well as amendments to the list of local |

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| | | | | | representatives in the Package Leaflet are included in addition to the inclusion of the two new Member States (Bulgaria and Romania). |
| IB/0052 | IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient | 13/12/2006 | n/a | | |
| IA/0054 | IA_16_b_Submission of new TSE certificate relating to active substance - other substances | 05/12/2006 | n/a | | |
| II/0046 | Quality changes | 21/09/2006 | 27/09/2006 | | |
| IB/0048 | IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient | 13/09/2006 | n/a | | |
| IA/0049 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 09/08/2006 | n/a | | |
| IA/0050 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 08/08/2006 | n/a | | |
| II/0044 | New presentation(s) | 28/06/2006 | 07/08/2006 | SmPC, Labelling and PL | |
| II/0045 | Quality changes | 28/06/2006 | 03/07/2006 | | |
| II/0041 | Change(s) to the manufacturing process for the active substance | 01/06/2006 | 08/06/2006 | | |
| MF/0043 | 2PMF (2nd step of PMF certification procedure) | 19/04/2006 | n/a | | |

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| T/0042 | Transfer of Marketing Authorisation | 13/03/2006 | 03/04/2006 | SmPC, Labelling and PL | Transfer of MAH from Bayer AG to Bayer HealthCare AG. |
| IB/0038 | IB_42_a_01_Change in shelf-life of finished product - as packaged for sale | 29/03/2006 | n/a | SmPC, Labelling and PL | |
| II/0040 | Change(s) to the test method(s) and/or specifications for the active substance | 23/03/2006 | 28/03/2006 | | |
| IB/0039 | IB_30_b_Change in supplier of packaging components - replacement/addition | 27/01/2006 | n/a | | |
| MF/0036 | 2PMF (2nd step of PMF certification procedure) | 25/01/2006 | n/a | | |
| II/0033 | Quality changes | 14/12/2005 | 19/12/2005 | | |
| N/0037 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 09/12/2005 | n/a | Labelling and PL | |
| IB/0034 | IB_30_b_Change in supplier of packaging components - replacement/addition | 15/11/2005 | n/a | | |
| II/0030 | Quality changes | 13/10/2005 | 19/10/2005 | | |
| R/0028 | Renewal of the marketing authorisation. | 23/06/2005 | 07/09/2005 | | |
| IB/0032 | IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient | 31/08/2005 | n/a | | |
| IA/0031 | IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) | 09/08/2005 | n/a | | |

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| II/0029 | Change(s) to the manufacturing process for the finished product | 27/07/2005 | 05/08/2005 | | |
| II/0026 | Change(s) to the manufacturing process for the active substance | 23/06/2005 | 30/06/2005 | | |
| II/0027 | Change(s) to the manufacturing process for the active substance | 26/05/2005 | 03/06/2005 | | |
| II/0025 | Quality changes | 26/05/2005 | 03/06/2005 | | |
| II/0024 | Quality changes | 16/03/2005 | 22/03/2005 | | |
| II/0021 | Deletion of redundant final container testing in USA and deletion of final container tests.<br><br>Quality changes | 15/12/2004 | 22/12/2004 | | |
| II/0020 | Changes in manufacturing and specifications of starting materials used in the manufacture of the active substance.<br><br>Quality changes | 15/12/2004 | 22/12/2004 | | |
| N/0022 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 25/11/2004 | n/a | PL | |
| IA/0023 | IA_28_Change in any part of primary packaging material not in contact with finished product | 25/11/2004 | n/a | PL | |

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| X/0016 | Annex I_2.(d) Change or addition of a new pharmaceutical form | 23/06/2004 | 21/09/2004 | SmPC, Labelling and PL | |
| II/0019 | Change(s) to the test method(s) and/or specifications for the active substance | 23/06/2004 | 01/07/2004 | | |
| II/0018 | Change in formulation<br>Change(s) to shelf-life or storage conditions | 24/03/2004 | 23/06/2004 | SmPC, Labelling and PL | 6.1 List of excipients, 6.3 Shelf lifeChange in the formulation of the drug product to include polysorbate 80, and a consequential change to provide information on stability of the drug product after reconstitution in the SPC. |
| II/0017 | Change(s) to the manufacturing process for the finished product | 24/03/2004 | 23/06/2004 | SmPC, Labelling and PL | 6.4 Special precautions for storageChange in the storage conditions to allow storage for up to 2 months at room temperature (up to 25C). |
| II/0014 | Update of the pharmaceutical documentation.<br><br>Update of or change(s) to the pharmaceutical documentation | 20/11/2003 | 16/12/2003 | | |
| II/0013 | Changes to test method.<br><br>Change(s) to the test method(s) and/or specifications for the active substance | 22/10/2003 | 28/10/2003 | | |
| I/0015 | 12a_Change in specification of starting material/intermediate used in manuf. of the active substance | 22/09/2003 | 24/09/2003 | | |
| I/0012 | 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process | 13/12/2002 | 31/01/2003 | Annex II and PL | |

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| II/0009 | Update of Summary of Product Characteristics and Package Leaflet | 19/09/2002 | 05/12/2002 | SmPC and PL | |
| II/0011 | Quality changes | 17/10/2002 | 23/10/2002 | | The Marketing Authorisation Holder has submitted the annual update of the Plasma Master File for the year 2002. In addition, the Marketing Authorisation Holder has also taken the merger of the industry organisations (ABRA to PPTA) and the plasma supplier name changes (NABI/ZLB, Sera-Tec/BioLife) into account. |
| II/0010 | Change(s) to the test method(s) and/or specifications for the active substance | 19/09/2002 | 25/09/2002 | | After the review of in-process control and final container results from 100 commercial lots, the Marketing Authorization Holder applied for a change in the limits for specifications and action limits for in-process controls and final container tests, including those for the microbial load of the combine UF/DF (Ultra Filtrate/Dia Filtrate) purification lot(s). |
| II/0004 | Update of or change(s) to the pharmaceutical documentation | 30/05/2002 | 05/06/2002 | | |
| I/0008 | 15_Minor changes in manufacture of the medicinal product<br>16_Change in the batch size of finished product | 25/04/2002 | 30/04/2002 | | |
| II/0007 | Quality changes | 13/12/2001 | 17/12/2001 | | |
| I/0006 | 23_Change in storage conditions | 13/08/2001 | 24/10/2001 | SmPC, Labelling and PL | |
| II/0002 | Update of or change(s) to the pharmaceutical documentation | 19/10/2000 | 10/05/2001 | | |

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| I/0003 | 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process | 12/10/2000 | 20/12/2000 | | |
| II/0001 | Quality changes | 16/11/2000 | 23/11/2000 | | |