



## Helixate NexGen (SRD)

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification <sup>1</sup> issued on	Commission Decision Issued <sup>2</sup> / amended on	Product Information affected <sup>3</sup>	Summary
PSUSA/2200/201908	Periodic Safety Update EU Single assessment - octocog alpha	17/04/2020	n/a		PRAC Recommendation - maintenance
IG/1068/G	This was an application for a group of variations.  B.IV.1.a.1 - Change of a measuring or administration	11/10/2019	n/a		

<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).



	<p>device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking</p> <p>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</p>				
IG/1079	<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>	26/03/2019	n/a		
IG/0981/G	<p>This was an application for a group of variations.</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.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier</p>	10/10/2018	n/a		
IG/0971	<p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p>	10/08/2018	n/a		
IG/0952	<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</p>	27/06/2018	n/a		

	do not affect the properties of the FP				
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		
IB/0197/G	This was an application for a group of variations.  B.I.z - Quality change - Active substance - Other variation  B.II.z - Quality change - Finished product - Other variation	01/03/2018	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.  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.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	18/01/2018	n/a		

	<p>Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation</p> <p>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation</p>				
WS/1279	<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.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</p>	30/11/2017	n/a		
A31/0178	<p>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.</p> <p>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</p>	14/09/2017	16/11/2017	SmPC and PL	Please refer to the assessment report: human coagulation factor VIII - EMEA/H/A-31/1448

	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 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/0190	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/0189	Transfer of Marketing Authorisation	23/03/2017	11/04/2017	SmPC, Labelling and PL	
WS/1125/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p> <p>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</p>	16/03/2017	n/a		
WS/1118/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p>	23/02/2017	n/a		

IA/0188	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		
WS/1043/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p> <p>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</p>	02/02/2017	n/a		
IA/0186/G	<p>This was an application for a group of variations.</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.a - Change in test procedure for the finished product - Minor changes to an approved test</p>	11/01/2017	n/a		

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	procedure				
WS/1018	<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.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</p>	24/11/2016	n/a		
WS/1036	<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.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation</p>	10/11/2016	n/a		
WS/1006	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <ul style="list-style-type: none"> <li>- Implementation of QRD template version 9.1 (June 2015)</li> <li>- 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</li> </ul>	15/09/2016	11/04/2017	SmPC, Annex II, Labelling and PL	



	<p>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.</p> <p>- Minor editorial changes in line with the recently approved rFVIII-products Kovaltry (EMA/H/C/003825) and Iblis (EMA/H/C/004147). These changes are considered not to change the meaning of the text/the scientific content.</p> <p>In addition the opportunity was taken to notify updates in the List of Local Representatives in the PIL section 6 for both products:</p> <ul style="list-style-type: none"> <li>• KOGENATE Bayer: PT</li> <li>• Helixate NexGen: CZ, ET, LT, LV, SK</li> </ul> <p>The requested worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.</p> <p>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation</p>				
WS/0938	<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.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p>	15/09/2016	n/a		

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IA/0180	B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)	12/08/2016	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 do not affect the properties of the FP	25/05/2016	n/a		
IB/0174	B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation	06/04/2016	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.  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/0172/G	This was an application for a group of variations.  B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)  B.III.2.b - Change to comply with Ph. Eur. or with a	16/12/2015	n/a		

	<p>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</p> <p>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</p> <p>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</p>				
N/0170	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/10/2015		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		
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/0167/G	This was an application for a group of variations.	15/04/2015	n/a		

	<p>A.7 - Administrative change - Deletion of manufacturing sites</p> <p>B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier</p>				
WS/0654	<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.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>	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	<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>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation</p>	24/07/2014	n/a		
N/0164	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/07/2014	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	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p> <p>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</p>	26/06/2014	n/a		
WS/0504/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of facilities and equipment documentation, and deletion of a manufacturing site.</p> <p>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation</p> <p>A.7 - Administrative change - Deletion of</p>	26/06/2014	n/a		

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	manufacturing sites				
WS/0556	<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>Change of the Controll test procedures of the active substance.</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>	22/05/2014	n/a		
WS/0555/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Minor changes in the manufacturing process. Update of stability data.</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation</p>	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) -	20/03/2014	n/a		

	Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
A20/0143	<p>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 its opinion on whether the marketing authorisation in the approved indication should be maintained, varied, suspended or revoked.</p> <p>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).</p> <p>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.</p> <p>The PRAC considered though that the frequency for</p>	19/12/2013	20/02/2014	SmPC and PL	Please refer to the assessment report: EMEA/H/C/000276/A-20/0143

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	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				
IA/0157	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	10/02/2014	n/a		
IA/0156/G	This was an application for a group of variations.  B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	10/02/2014	n/a		
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) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	18/12/2013	n/a		
WS/0463	This was an application for a variation following a	18/12/2013	n/a		



	<p>worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>PMF Second step procedure</p> <p>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</p>				
WS/0458	<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>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.</p> <p>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</p>	21/11/2013	n/a		<p>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.</p>

WS/0449	<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>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.</p> <p>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</p>	21/11/2013	n/a		<p>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.</p>
WS/0427/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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 factor VIII products. Furthermore, the PI is being brought in line with the latest QRD template version</p>	19/09/2013	20/02/2014	SmPC, Annex II, Labelling and PL	<p>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.</p>

	<p>9.0.</p> <p>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</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>				
IA/0147	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/0146/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS</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.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p>	26/04/2013	n/a		
WS/0379/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No	25/04/2013	n/a		

	<p>1234/2008.</p> <p>Change to finished product manufacture Deletion of finished product manufacturing sites</p> <p>B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation A.7 - Administrative change - Deletion of manufacturing sites</p>				
IA/0144/G	<p>This was an application for a group of variations.</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.III.2.b - Change to comply with Ph. Eur. or with a</p>	08/04/2013	n/a		

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	<p>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</p> <p>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</p> <p>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</p>				
IG/0271	<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>	15/02/2013	n/a		
WS/0346	<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>To introduce a change in a buffer used in the manufacture of 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</p>	17/01/2013	n/a		

	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	<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>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.</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>	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.
WS/0274	<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>The MAH updated section 6 of the SmPC and section</p>	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

	<p>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.</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>				<p>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.</p>
IB/0138	<p>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</p>	17/10/2012	n/a		
IG/0187/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>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>	01/06/2012	n/a		
IG/0173/G	<p>This was an application for a group of variations.</p>	08/05/2012	n/a		

	<p>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</p> <p>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</p> <p>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</p>				
WS/0193	<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>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. Furthermore, the PI is being brought in line with the latest QRD template version 8.0.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or</p>	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.



	modification of an approved one				
WS/0214	<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>Change to drug substance testing</p> <p>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</p>	19/04/2012	n/a		
IB/0132/G	<p>This was an application for a group of variations.</p> <p>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</p> <p>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)</p>	14/04/2012	23/10/2012	SmPC, Labelling and PL	
WS/0198	<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>Update of section 4.4 of the SmPC to add catheter related infections and the risk of thrombosis and the</p>	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 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

	<p>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.</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>				<p>via central venous access devices (CVADs) may be necessary for haemophilic 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".</p>
IG/0153/G	<p>This was an application for a group of variations.</p> <p>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)</p> <p>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)</p> <p>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)</p> <p>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</p>	06/03/2012	n/a		

	<p>Member State</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.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)</p> <p>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</p>				
IAIN/0130/G	<p>This was an application for a group of variations.</p> <p>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</p> <p>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</p>	22/02/2012	n/a		
WS/0213	<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>Changes to finished product testing.</p>	16/02/2012	16/02/2012		

	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
WS/0155/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Change to reference standards.</p> <p>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</p> <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>	16/02/2012	16/02/2012		
WS/0206	<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>Change to active substance manufacturing process.</p> <p>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)</p>	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 do not affect the properties of the FP	08/12/2011	n/a		
IA/0110/G	This was an application for a group of variations.  A.1 - Administrative change - Change in the name and/or address of the MAH 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	22/08/2011	n/a	SmPC, Labelling and PL	
WS/0094	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.  Alternative testing site.  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.	20/01/2011	20/01/2011		

	<p>Change in drug product specification.</p> <p>B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range</p>				
WS/0012	<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>Changes to in-process tests and limits in the active substance manufacture.</p> <p>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p>	16/12/2010	10/01/2011		
IG/0038/G	<p>This was an application for a group of variations.</p> <p>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV</p> <p>C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database</p> <p>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</p>	07/01/2011	n/a		

IB/0109/G	<p>This was an application for a group of variations.</p> <p>B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation</p> <p>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</p>	07/01/2011	n/a		
WS/0062	<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>Extension in storage time.</p> <p>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</p>	18/11/2010	20/12/2010	SmPC, Annex II, Labelling and PL	
IA/0108	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/0102	Annex I_2.(c) Change or addition of a new strength/potency	24/06/2010	06/08/2010	SmPC, Labelling and	

				PL	
R/0105	Renewal of the marketing authorisation.	24/06/2010	06/08/2010	SmPC, Annex II, Labelling and PL	
WS/0010	<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>To extend the shelf life of the product from 24 month to 30 months for the 2000 IU doses strength.</p> <p>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</p>	24/06/2010	28/07/2010	SmPC	
WS/0020	<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>To introduce a minor change in the manufacturing process of the active substance</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p>	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	21/07/2010	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				
IG/0009/G	<p>This was an application for a group of variations.</p> <p>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</p> <p>C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV</p> <p>C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV</p> <p>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV</p> <p>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</p>	18/06/2010	n/a	Annex II	
WS/0014	<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>Change to the specification parameters and/or limits of a reagent used in the active substance manufacture.</p>	20/05/2010	20/05/2010		

	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
WS/0008	<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>Changes to the active substance manufacturer.</p> <p>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</p>	20/05/2010	20/05/2010		
WS/0007	<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>Change to the manufacture of finished product.</p> <p>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</p>	20/05/2010	20/05/2010		
II/0106	Change in drug product test procedure and drug product specification.	22/04/2010	03/05/2010		Change in drug product test procedure and drug product specification.

	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range				
II/0091	Change in Product Information relating to stability claim for continuous infusion.  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 continuous infusion
II/0104	Update of Appendices and Regional Information  Quality changes	18/02/2010	11/03/2010		
II/0103	Changes to drug product manufacture.  Quality changes	21/01/2010	03/02/2010		
II/0101	Changes in the manufacture of the active substance.  Change(s) to the manufacturing process for the active substance	17/12/2009	12/01/2010		
II/0093	Introduction of additional container closure system.  Quality changes	17/12/2009	12/01/2010		Introduction of additional container closure system.
II/0095	Change in drug substance and drug product control test.  Quality changes	19/11/2009	08/12/2009		Change in drug substance and drug product control test .

II/0100	<p>Changes to the manufacturing process of the active substance.</p> <p>Update of or change(s) to the pharmaceutical documentation</p> <p>Change(s) to the manufacturing process for the active substance</p>	22/10/2009	13/11/2009		
II/0094	<p>Changes to active substance manufacturing process.</p> <p>Quality changes</p>	22/10/2009	13/11/2009		Changes to drug substance manufacturing process.
II/0099	Update of DDPS (Pharmacovigilance)	24/09/2009	16/10/2009	Annex II	The Detailed Description of the Pharmacovigilance System has been updated (Version 9.7) to reflect the integration of the companies' pharmacovigilance systems (Bayer and Schering AG). Consequently, Annex II has been updated with the standard text including new version number of the agreed DDPS.
II/0098	<p>Minor changes to the drug product manufacturing.</p> <p>Quality changes</p>	24/09/2009	06/10/2009		
2PMF/0097	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		
II/0092	<p>Changes to manufacturers.</p> <p>Quality changes</p>	25/06/2009	27/07/2009	Annex II and PL	Changes to manufacturers.

IA/0096	IA_09_Deletion of manufacturing site	09/06/2009	n/a		
II/0084	Update of Summary of Product Characteristics, Labelling and Package Leaflet	19/03/2009	24/04/2009	SmPC, Labelling and PL	<p>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.</p> <p>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.</p>
2PMF/0090	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/0087	Transfer of Marketing Authorisation	06/03/2009	07/04/2009	SmPC, Annex II, Labelling and PL	<p>Transfer from Bayer HealthCare AG to Bayer Schering Pharma AG.</p> <p>The transfer will take place on 01 October 2009.</p>
II/0086	Minor changes to manufacturing in-process action levels.  Quality changes	19/03/2009	26/03/2009		Minor changes to manufacturing in-process action levels.
IA/0089	IA_05_Change in the name and/or address of a manufacturer of the finished product	05/03/2009	n/a		

IA/0088	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/0082	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/0085	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	02/02/2009	n/a		
IB/0083	IB_30_b_Change in supplier of packaging components - replacement/addition	02/02/2009	n/a		
II/0080	Approval of additional drug product tests to be performed at an already licensed batch control testing site.  Quality changes	20/11/2008	28/11/2008		
MF/0067	2PMF (2nd step of PMF certification procedure)	27/11/2008	n/a		
IB/0081	IB_30_b_Change in supplier of packaging components - replacement/addition	31/10/2008	n/a		
II/0077	Additional finished product control test to be carried at one of the finished product testing sites.  Quality changes	23/10/2008	28/10/2008		Additional finished product control test to be carried at one of the finished product testing sites.
II/0076	Changes to the in-process control testing of the active substance.	23/10/2008	28/10/2008		Changes to the in-process control testing of the active substance.

	Quality changes				
II/0073	Introduction of a new facility at a currently approved manufacturing site.  Quality changes	25/09/2008	02/10/2008		Introduction of a new facility at a currently approved manufacturing site.
MF/0079	2PMF (2nd step of PMF certification procedure)	24/09/2008	n/a		
IB/0078	Addition of alternative supplier for venipuncture set.  IB_30_b_Change in supplier of packaging components - replacement/addition	08/09/2008	n/a		
II/0075	Approval of addition of further finished product control tests to the Bayer SPA testing site.  Quality changes	24/07/2008	29/07/2008		
II/0074	Change to the active substance manufacture without impact on the benefit/risk balance of the product.  Quality changes	30/05/2008	11/06/2008		
II/0071	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		
MF/0072	2PMF (2nd step of PMF certification procedure)	22/02/2008	n/a		

II/0070	Quality changes	24/01/2008	29/01/2008		
X/0056	Annex I_2.(c) Change or addition of a new strength/potency	18/10/2007	18/12/2007	SmPC, Labelling and PL	
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	<p>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:</p> <p>"In clinical studies, Helixate Nexgen 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 Helixate Nexgen 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, 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.</p> <p>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.</p> <p>In extensive post-registration studies with Helixate Nexgen, involving more than 1000 patients the following was</p>

Medicinal product no longer authorised



					<p>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.'</p> <p>The Package leaflet has been updated accordingly.</p> <p>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.</p>
II/0066	Quality changes	20/09/2007	27/09/2007		
II/0062	Quality changes	20/09/2007	27/09/2007		
II/0058	Update of Summary of Product Characteristics and Package Leaflet	21/06/2007	24/07/2007	SmPC and PL	<p>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:</p> <p>'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.'</p> <p>The Package Leaflet has been updated accordingly.</p>
II/0057	Quality changes	19/07/2007	24/07/2007		
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		
II/0055	Quality changes	26/04/2007	02/05/2007		
II/0051	Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	26/01/2007	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 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/0042	Quality changes	21/09/2006	26/10/2006	SmPC and PL	
II/0045	Quality changes	21/09/2006	27/09/2006		
IB/0047	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		
IA/0048	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	08/08/2006	n/a		
II/0044	Quality changes	28/06/2006	03/07/2006		
II/0040	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		
T/0041	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/0037	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/0039	Change(s) to the test method(s) and/or specifications for the finished product	23/03/2006	28/03/2006		
IB/0038	IB_30_b_Change in supplier of packaging components - replacement/addition	27/01/2006	n/a		
MF/0034	2PMF (2nd step of PMF certification procedure)	25/01/2006	n/a		

II/0031	Quality changes	14/12/2005	19/12/2005		
N/0035	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/0032	IB_30_b_Change in supplier of packaging components - replacement/addition	15/11/2005	n/a		
II/0028	Change(s) to the manufacturing process for the active substance	13/10/2005	19/10/2005		
R/0026	Renewal of the marketing authorisation.	23/06/2005	07/09/2005		
IB/0030	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	31/08/2005	n/a		
IA/0029	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		
II/0027	Change(s) to the manufacturing process for the finished product	27/07/2005	05/08/2005		
II/0024	Change(s) to the manufacturing process for the active substance	23/06/2005	30/06/2005		
II/0025	Change(s) to the manufacturing process for the active substance	26/05/2005	03/06/2005		
II/0023	Quality changes	26/05/2005	03/06/2005		

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II/0022	Quality changes	16/03/2005	22/03/2005		
II/0020	Deletion of redundant final container testing in USA and deletion of final container tests.  Quality changes	15/12/2004	22/12/2004		
II/0019	Changes in manufacturing and specifications of starting materials used in the manufacture of the active substance.  Quality changes	15/12/2004	22/12/2004		
N/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/11/2004	n/a	PL	
II/0018	Change(s) to the test method(s) and/or specifications for the active substance	23/06/2004	01/07/2004		
II/0017	Change(s) to the manufacturing process for the finished product	24/03/2004	23/06/2004	SmPC, Labelling and PL	6.1 List of excipients, 6.3 Shelf life Change 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/0016	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 storage Change in the storage conditions to allow storage for up to 2 months at room temperature (up to 25C).
II/0014	Update of pharmaceutical documentation.  Update of or change(s) to the pharmaceutical	20/11/2003	16/12/2003		The Marketing Authorisation Holder applied for the annual update for 2003 of the Plasma Master File including changes to the following sections: II P 2 - Plasma Origin

	documentation				and Epidemiological Data; II P 3 - Selection and Exclusion Criteria - Qualification of Donor; II P 4 - Screening Tests for Markers of Infection; II P 6 - Plasma Collection Materials; II P 7 - Plasma Quality and II P 8 - Standard Contract between Manufacturer and Plasma Supplier.
II/0013	Changes to test method.  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	
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		
II/0010	Change(s) to the test method(s) and/or specifications for the active substance	19/09/2002	25/09/2002		
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	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		
II/0001	Quality changes	16/11/2000	23/11/2000		
I/0003	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	12/10/2000	n/a		

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