NovoSeven

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
IAIN/0119	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	23/02/2023	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).

IB/0118	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/01/2023		SmPC	
II/0117	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	01/09/2022	n/a		
II/0116	Extension of indication to include treatment of severe postpartum haemorrhage when uterotonics are insufficient to achieve haemostasis. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is also updated in accordance. Version 8.0 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/04/2022	24/05/2022	SmPC and PL	Please refer to Scientific Discussion 'NovoSeven II-116'
PSUSA/1245/ 202012	Periodic Safety Update EU Single assessment - eptacog alfa	02/09/2021	n/a		PRAC Recommendation - maintenance
IA/0115	To delete the vial-vial presentations (EU/1/96/006/004-007) for NovoSeven, Powder and solvent for solution for injection 1 mg, 2mg, 5 mg, 8 mg. B.II.e.5.b - Change in pack size of the finished	07/06/2021	29/09/2021	SmPC, Labelling and PL	

	product - Deletion of a pack size(s)				
II/0109/G	This was an application for a group of variations. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other	14/01/2021	n/a		

	variation B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation				
IB/0113	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	18/12/2020	n/a		
IB/0112	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation	18/12/2020	n/a		
IA/0111	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	06/11/2020	n/a		
IB/0110	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/10/2020	29/09/2021	SmPC, Annex II, Labelling and PL	
II/0106	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	17/10/2019	16/10/2020	SmPC	In hospital settings only, reconstitution must take place in controlled and validated aseptic conditions by adequately trained staff. Under these conditions, chemical and physical stability has been demonstrated for 24 hours at 25°C when stored in a 50 ml syringe (polypropylene). If not used immediately, the conditions prior to use are the responsibility of the user and the in-use storage time must not be longer than as stated above. For more information please refer to the Summary of Product Characteristics.

IB/0108	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	25/07/2019	n/a		
IA/0107/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	18/07/2019	n/a		
II/0104	Extension of Indication to include patients with Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available, based on a prospective observational registry and literature references. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in section 4.8 of the SmPC and in Package Leaflet. The updated RMP version 7.1 has been agreed within this procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	18/10/2018	20/11/2018	SmPC and PL	Please refer to Scientific Discussion EMEA/H/C/000074/II/0104.
PSUSA/1245/	Periodic Safety Update EU Single assessment -	12/07/2018	n/a		PRAC Recommendation - maintenance

201712	eptacog alfa				
II/0101/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	17/05/2018	n/a		
IB/0105	B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	15/05/2018	n/a		
IA/0102	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	14/12/2017	n/a		
IG/0870	A.7 - Administrative change - Deletion of manufacturing sites	27/11/2017	n/a		
IA/0099	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	28/04/2017	n/a		

IB/0097	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)	03/02/2017	n/a		
IB/0098/G	This was an application for a group of variations. B.I.b.1.a - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits for medicinal products subject to OCABR B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	11/01/2017	n/a		
II/0092	Update of section 4.4 of the SmPC in order to delete sucrose warning (also affecting section 2 of the SmPC). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes/corrections and updates in sections 4.8, 6.4, 6.5 and 6.6 of the SmPC and in the Package Leaflet. Moreover, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10 (combined SmPC has been introduced). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	08/12/2016	26/01/2017	SmPC, Annex II, Labelling and PL	

	data				
II/0093	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	10/11/2016	n/a		
IA/0096	A.7 - Administrative change - Deletion of manufacturing sites	15/09/2016	n/a		
IB/0095	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	28/07/2016	n/a		
IB/0094/G	This was an application for a group of variations. B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	19/07/2016	n/a		
II/0089	Submission of the Final Study Report NN7025-3601: Prospective Observational Study on NovoSeven room temperature (VII25) in patients with Haemophilia A and B. The study was intended to monitor prospectively for decreased therapeutic response and the development of neutralising antibodies towards FVII (FVII inhibitors). The submission of this study report addresses MEA 046.4 and an updated RMP	26/05/2016	n/a		

	version 6.1 is provided. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0091/G	This was an application for a group of variations. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	25/02/2016	n/a		
II/0090/G	This was an application for a group of variations. Deletion of the 3 strengths; 1.2 mg (60 KIU), 2.4 mg (120 KIU), 4.8 mg (240 KIU) – MA numbers EU/1/96/006/001-003. The SmPC, labelling and Package Leaflet have been revised accordingly with deletion of the affected presentations. Update of the conditions in Annex II; consequential deletion of the content in the Annex IID related to additional risk minimisation measures (potential risk of medication errors related to the 3 strengths above). Consequential deletion of Annex 127a. C.I.7.b - Deletion of - a strength	21/01/2016	26/01/2017	SmPC, Annex II, Labelling and PL	N/A

	C.I.7.b - Deletion of - a strength C.I.7.b - Deletion of - a strength C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IAIN/0088	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	18/08/2015	n/a		
IA/0087	A.7 - Administrative change - Deletion of manufacturing sites	29/07/2015	n/a		
PSUSA/1245/ 201412	Periodic Safety Update EU Single assessment - eptacog alfa	09/07/2015	n/a		PRAC Recommendation - maintenance
IB/0084	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	03/03/2015	n/a		
II/0083	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	26/02/2015	n/a		
II/0082	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch	20/11/2014	n/a		

	control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method				
IB/0081	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	08/09/2014	n/a		
PSUV/0080	Periodic Safety Update	10/07/2014	n/a		PRAC Recommendation - maintenance
N/0079	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/05/2014	26/01/2017	Labelling and PL	
II/0073	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC with information from an observational registry F7HAEM-3578. The Package Leaflet is updated accordingly. Editorial amendments have been proposed throughout the PI. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/11/2013	18/12/2013	SmPC, Annex II, Labelling and PL	In an observational registry (F7HAEM-3578) covering subjects with congenital FVII deficiency, the median dose for long term prophylaxis against bleeding in 22 paediatric patients (below 12 years of age) with Factor VII deficiency and a severe clinical phenotype was 30 µg/kg (range 17 µg/kg to 200 µg/kg; the dose most often used was 30 µg/kg in 10 patients) with a median dose frequency of 3 doses per week (range 1 to 7; the dose frequency most often reported was 3 per week in 13 patients). In the same registry 3 out of 91 surgical patients experienced thromboembolic events. The summary of product characteristics has been updated to include these data and the relevant pharmacokinetic information. It is also stated under posology recommendations that limited clinical experience in long term prophylaxis has been gathered in the paediatric population below 12 years of age, with a severe clinical phenotype. Dose and frequency of injections for prophylaxis should be

					based on clinical response and adapted to each individual. Changes have been made to the product information to bring it in line with the Quality review of document (QRD) template version 9.0.
IB/0078	B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	06/12/2013	n/a		
II/0074	Update of section 4.5 of the SmPC in order to include a recommendation not to combine Factor VII with FXIII and section 5.3 to include the relevant preclinical information. The Package Leaflet is updated accordingly. An editorial change was made to section 4.8 of the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	18/12/2013	SmPC and PL	Results from a cardiovascular model study in cynomolgus monkeys already submitted and evaluated within the marketing application for the product NovoThirteen, where rFVIIa was administered concomitantly with rFXIII suggest that the combination of the two products could have a synergic effect which could lead to thrombus and death. The results are highlighted in section 5.3 of the SmPC. As a consequence a recommendation not to combine the products is included in section 4.5 of the SmPC. This update of the product information of Novoseven is in line with the recommendations in the product information of NovoThirteen. An editorial change was made for clarification in section 4.8 of the SmPC to make reference to "reports of inhibitory antibodies against NovoSeven …".
IG/0280	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/04/2013	n/a		
IA/0076/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	22/03/2013	n/a		

	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer				
IA/0075	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	22/03/2013	n/a		
II/0071	Change to the active substance specification B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	17/01/2013	n/a		
II/0072/G	This was an application for a group of variations. B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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	20/09/2012	24/10/2012	SmPC, Labelling and PL	

	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 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 B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
II/0068	Changes to the active substance manufacturing process. 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	16/02/2012	16/02/2012		
II/0069	The MAH has submitted a type II variation to update section 4.8 with the inclusion of intracardiac	17/11/2011	13/01/2012	SmPC and PL	A safety signal has been identified and as a consequence the MAH has submitted a type II variation to update section

	thrombus as an example of arterial thromboembolic events – at the request of the CHMP following the assessment of the latest PSUR. An editorial amendment was also introduced. The Package leaflet was updated accordingly. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				4.8 with the inclusion of intracardiac thrombus as an example of arterial thromboembolic events – at the request of the CHMP. The frequency was classified as "not known". The section 4 of the Package leaflet was also updated.
IB/0070	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	25/11/2011	n/a		
II/0067	Extension of active substance storage time. B.I.d.1.a.3 - Stability of AS - Change in the re-test period/storage period - Extension of storage period of a biological/immunological AS not in accordance with an approved stability protocol	17/11/2011	17/11/2011		
IB/0066	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	06/06/2011	n/a		
II/0065/G	This was an application for a group of variations. Changes to the active substance manufacture and in-	14/04/2011	29/04/2011		

	process testing. 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 B.I.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS				
IG/0048/G	This was an application for a group of variations. C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	11/03/2011	n/a	SmPC, Annex II and Labelling	
II/0063	Changes to the drug substance manufacturing process.	21/10/2010	03/11/2010		Changes to the drug substance manufacturing process.

	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				
II/0064/G	This was an application for a group of variations. 1) Addition of single dose presentation of Novoseven 8 mg. 2) Extension of shelf life of the 1, 2 and 5 mg presentations from 24 to 36 months. B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, and biological/immunological multidose parenteral medicinal products 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	23/09/2010	28/10/2010	SmPC, Annex II, Labelling and PL	
IA/0062	IA_09_Deletion of manufacturing site	18/06/2009	n/a	Annex II	
II/0060	Update of Summary of Product Characteristics and Package Leaflet	23/04/2009	28/05/2009	SmPC and PL	Further to a CHMP request to bring all NovoSeven presentations in line and in accordance with current guidelines the MAH submitted a type II variation concerning sections 4.6, 4.8, and 4.9. In addition, following

					a PSUR review by the CHMP, and a MAH safety analysis to their own database including clinical trials and Post Marketing Experience data the MAH updated section 4.8 and section 4.9. In sections 4.6 the paragraph regarding lactation was amended as follows: It is unknown whether rFVIIa is excreted in human breast milk. The excretion of rFVIIa in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with NovoSeven should be made taking into account the benefit of breast-feeding to the child and the benefit of NovoSeven therapy to the woman. An updated number of cases of overdose was introduced in section 4.9 with other minor modifications. Finally section 4.8 was completely revised in accordance with the safety analysis of post marketing and clinical trials as well as the current SmPC guideline recommendations. In particular, the table listing undesirable effects was revised both for frequency and nature of adverse drug reactions mentioned. Specific subsections were also introduced under the table in section 4.8. In particular, a higher risk of arterial thrombotic events observed from a meta-analysis of pooled data from placebo controlled trials was added in section 4.8, with a clear statement that NovoSeven should not be used outside the approved indications. The Package Leaflet has been updated accordingly.

					Furthermore, minor wording changes have been introduced to the Product Information.
II/0061	Move of QC testing site. Analytical procedures and specifications remain the same. Quality changes	22/01/2009	28/01/2009		Move of QC testing site. Analytical procedures and specifications remain the same.
II/0057	The MAH has applied to amend the Product Information texts of all NovoSeven presentations in accordance with current guidelines, further to a request of the CHMP in the context of the procedure EMEA/H/C/0074/X/55 (FUM 045 and FUM 047). Consequently, minor changes are introduced in the sections 2, 4.1, 4.2, 4.3, 4.4, 4.6, 4.8, 6.1, 6.4, 6.5 and 6.6 of the SPC, Annex II and Annex III are updated. Furthermore, the MAH has taken the opportunity to align the Product Information texts for the NovoSeven presentations (EU/1/96/006/001-003) with the Product Information texts for the new room temperature stable formulation (EU/1/96/006/004-006). Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/07/2008	25/08/2008	SmPC, Annex II, Labelling and PL	The MAH has applied to amend the Product Information texts of all NovoSeven presentations in accordance with current guidelines, further to a request of the CHMP in the context of the procedure EMEA/H/C/0074/X/55 (FUM 045 and FUM 047). Consequently, minor changes are introduced in the sections 2, 4.1, 4.2, 4.3, 4.4, 4.6, 4.8, 6.1, 6.4, 6.5 and 6.6 of the SPC, Annex II and Annex III are updated. Furthermore, the MAH has taken the opportunity to align the Product Information texts for the NovoSeven presentations (EU/1/96/006/001-003) with the Product Information texts for the new room temperature stable formulation (EU/1/96/006/004-006).
IA/0059	Replacement of vial adaptor for 1.2, 2.4 and 4.8 mg presentations. IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	15/08/2008	n/a	SmPC and PL	

II/0058	Approval of an alternate freeze-dryer for the medicinal product and consequential upscale of batch size. Quality changes	24/07/2008	29/07/2008		
X/0055	Approval of the extension of the drug product range of Novoseven with three presentations of a new below 25°C stable formulation and new strengths of 1, 2 and 5 mg per vial. Annex I_2.(c) Change or addition of a new strength/potency	21/02/2008	25/04/2008	SmPC, Labelling and PL	In order to make storage and transport of NovoSeven more convenient for the users, a new drug product formulation allowing storage <25°C has been developed. The new formulation involves the introduction of two new excipients. Furthermore, in order to facilitate the calculation of the dose needed for the individual patient, the drug product presentations of the new formulation will comprise three single use vials of 1, 2, and 5 mg of lyophilized rFVIIa per vial. Reconstitution with the appropriate volumne of the Histidine solvent will provide 1.0 mg rFVIIa/ml for each strength. Comparative characterisation studies confirmed that the change in formulation does not lead to changes in the physical and chemical characteristics of rFVIIa. There are no changes of indications, dose recommendations, undesirable effects or warnings and precautions, as compared to the current formulation of NovoSeven. Overall, based on the available data, the benefit/risk of the new formulation of NovoSeven was considered positive. A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns and that additional risk

					minimisation activities were required.
II/0056	Change(s) to the test method(s) and/or specifications for the active substance	13/12/2007	19/12/2007		
II/0054	Update of Summary of Product Characteristics	19/07/2007	03/09/2007	SmPC	The MAH applied for a type II variation to update section 5.2 Pharmacokinetic properties of the SPC based on the results from two pharmacokinetic studies. The pharmacokinetics of NovoSeven were investigated in 35 healthy Caucasian and Japanese healthy subjects. The pharmacokinetic profiles indicated dose proportionality and were similar across sex and ethnic groups. In a study in 12 paediatric (2-12 years) and 5 adult patients with haemophilia A and B with inhibitors in non bleeding state, dose proportionality was established in children for the investigated doses of 90 and 180 ?g per kg body weight. Mean clearance was approximately 50% higher in paediatric patients relative to adults and increased towards a lower age. Consequently, section 4.2 of the SPC was updated with regards to dosing information in children as follows: "Dosing in children Current clinical experience does not warrant a general differentiation in dosing between children and adults, although children have faster clearance than adults. Therefore, higher doses of rFVIIa may be needed in paediatric patients to achieve similar plasma concentrations as in adult patients (see section 5.2)." Minor editorial changes to the SPC are also included.
II/0053	Update of Summary of Product Characteristics and Package Leaflet	24/01/2007	05/03/2007	SmPC and PL	The CHMP adopted an update of section 4.2 'Posology and method of administration' in the SPC with an alternate dose

					recommendation. In addition to the current recommendation of 90 g /kg, which may be repeated as required, a single dose of 270 g/kg/body weight is recommended for the treatment of mild to moderate bleeding episodes in haemophilia A or B patients with inhibitors to factor VIII or factor IX in order to achieve rapid haemostasis and reduce the number of injections. This is based on clinical data from 2 double-blind clinical studies and relevant literature data. The section 4.4 is updated with a warning for the elderly population since there is no clinical experience in this population. The PL is updated accordingly.
II/0052	Update of Summary of Product Characteristics and Package Leaflet	16/11/2006	04/01/2007	SmPC and PL	The MAH applied for a type II variation to add information on 'hepatic thrombotic events' in section 4.8 of the SPC in order to clarify that in the vast majority of cases these patients were predisposed due to liver disease or liver surgery. In addition, the MAH took the opportunity to make a few minor editorial and linguistic changes in the SPC and the PL.
II/0048	Change(s) to the manufacturing process for the active substance	16/11/2006	21/11/2006		
II/0051	Changes in the manufacturing process of the active substance Change(s) to the manufacturing process for the active substance	18/10/2006	23/10/2006		Changes in the manufacturing process of the active substance

II/0046	Additional manufacturing site of drug substance Change(s) to the manufacturing process for the active substance	27/07/2006	21/08/2006	Annex II	
II/0047	Update of Summary of Product Characteristics and Package Leaflet	28/06/2006	04/08/2006	SmPC and PL	Update of Section 4.8 of the SPC to include cases of anaphylactic reactions reported in the PMS following the 13th PSUR. The package leaflet has been updated accordingly. In addition the MAH proposed minor changes in sections 4.2, 5.1, 5.2 and package leaflet.
IB/0049	IB_30_b_Change in supplier of packaging components - replacement/addition	28/06/2006	n/a		
II/0045	Change(s) to the manufacturing process for the finished product	23/02/2006	07/03/2006		
R/0043	Renewal of the marketing authorisation.	14/12/2005	09/02/2006	SmPC, Annex II, Labelling and PL	Unlimited validity of the MA granted in February 2006 subject to clinical follow up measures. The MAH should submit PSURs every 18 months until further notice.
II/0041	Introduction of new device for reconstitution and a changed package. Change(s) to container	13/10/2005	16/11/2005	SmPC, Labelling and PL	This variation recomends the introduction of new device for reconstitution and a changed package, as applied by the MAH. The MAH proposed a new vial adaptor to facilitate the transfer of water from the solvent vial to the NovoSeven vial. The change of device concerns a substitution of the current transfer needle with a needle-free vial adaptor for the reconstitution process of NovoSeven. Due to different size of the proposed vial, the dimensions of the outer packaging box are changed. Moreover, in the redesigned packaging

					box the current plastic tray is replaced by a carton tray, and a separate inner-carton for the powder and solvent vials is introduced for the fixation of the vials. As a consequence of the changes, the SPC and PIL have also been adapted. The MAH proposed a new vial adaptor to facilitate the transfer of water from the solvent vial to the NovoSeven vial. This change aims to improve the current reconstitution procedure preventing the risk of the current transfer needle with stick injuries in patients and health care professionals. Changes related to the reconstitution procedure are included in the package leaflet. Pictures have also been added to make the description of the reconstitution procedure more user-friendly. On the basis of the information provided by the MAH, the CHMP recomended the aproval of the new proposed vial adaptor and the change on the dimensions of the packaging box.
II/0039	Change(s) to the test method(s) and/or specifications for the finished product	15/09/2005	03/10/2005		
II/0038	Change(s) to the test method(s) and/or specifications for the active substance	15/09/2005	03/10/2005		
II/0040	Change(s) to shelf-life or storage conditions	21/04/2005	27/04/2005		
II/0034	Quality changes	21/10/2004	26/10/2004		

II/0035	Update of or change(s) to the pharmaceutical documentation	29/07/2004	03/08/2004		
II/0031	Update of Summary of Product Characteristics and Package Leaflet	25/09/2003	27/01/2004	SmPC and PL	
II/0030	Update of Summary of Product Characteristics and Package Leaflet	25/09/2003	27/01/2004	SmPC, Labelling and PL	
II/0029	Extension of Indication	22/10/2003	27/01/2004	SmPC and PL	
II/0028	Extension of Indication	22/10/2003	27/01/2004	SmPC and PL	
II/0027	Changes to the shelf life of the powder for injection to 36 months; changes to the shelf life of the solvent to 36 months. Change(s) to shelf-life or storage conditions	24/07/2003	08/10/2003	SmPC	
I/0032	24_Change in test procedure of active substance	22/08/2003	22/09/2003		
I/0025	15_Minor changes in manufacture of the medicinal product	20/02/2003	10/03/2003		
I/0024	16_Change in the batch size of finished product	20/02/2003	10/03/2003		
I/0023	24_Change in test procedure of active substance 25_Change in test procedures of the medicinal product	21/11/2002	09/12/2002		

I/0022	18_Synthesis or recovery of non-pharmacopoeial excipients in the medicinal products	15/07/2002	15/07/2002		
I/0021	12_Minor change of manufacturing process of the active substance	25/04/2002	29/04/2002		
I/0020	12_Minor change of manufacturing process of the active substance	25/04/2002	29/04/2002		
II/0018	Update of Summary of Product Characteristics and Package Leaflet	01/03/2001	20/06/2001	SmPC and PL	
I/0019	26_Changes to comply with supplements to pharmacopoeias	13/03/2001	06/04/2001		
II/0015	Change(s) to the test method(s) and/or specifications for the finished product	19/10/2000	28/11/2000		
I/0016	04_Replacement of an excipient with a comparable excipient	15/09/2000	21/10/2000		
II/0014	Update of Summary of Product Characteristics and Package Leaflet	29/07/1999	08/12/1999	SmPC and PL	
I/0013	11_Change in or addition of manufacturer(s) of active substance 12_Minor change of manufacturing process of the active substance	23/02/1999	08/03/1999		
I/0012	11_Change in or addition of manufacturer(s) of active substance	23/02/1999	08/03/1999		

	12_Minor change of manufacturing process of the active substance				
II/0011	Update of or change(s) to the pharmaceutical documentation Change(s) to the test method(s) and/or specifications for the active substance	27/01/1999	08/02/1999		
II/0010	Change(s) to the test method(s) and/or specifications for the active substance	27/01/1999	08/02/1999		
II/0009	Change(s) to shelf-life or storage conditions	27/01/1999	08/02/1999		
II/0007	Change(s) to container	23/07/1998	19/11/1998	SmPC, Labelling and PL	
I/0008	20_Extension of shelf-life as foreseen at time of authorisation	15/05/1998	17/07/1998	SmPC	
I/0006	12_Minor change of manufacturing process of the active substance	24/06/1998	n/a		
II/0001	Update of Summary of Product Characteristics and Package Leaflet	23/07/1997	04/12/1997	SmPC and PL	
I/0004	12_Minor change of manufacturing process of the active substance	24/09/1997	n/a		
I/0003	12_Minor change of manufacturing process of the active substance	24/09/1997	n/a		

I/0002	12_Minor change of manufacturing process of the active substance	24/09/1997	n/a		