Advate

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
N/0121	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/11/2023		Labelling	
II/0119/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or	20/07/2023		SmPC and Labelling	

[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).

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate 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 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 A.7 - Administrative change - Deletion of manufacturing sites				
II/0120/G	This was an application for a group of variations. B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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	22/06/2023	n/a		

	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range				
PSUSA/2200/ 202208	Periodic Safety Update EU Single assessment - octocog alfa	14/04/2023	n/a		PRAC Recommendation - maintenance
IB/0117	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/07/2022	15/03/2023	SmPC and PL	
WS/2218/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.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products	12/05/2022	15/03/2023	SmPC	
WS/2189	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and	24/02/2022	15/03/2023	SmPC and PL	

	biological/immunological medicinal products				
IA/0116/G	This was an application for a group of variations. 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 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 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 A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	08/02/2022	15/03/2023	Annex II	
IB/0114	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	04/01/2022	n/a		
IB/0112	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	03/06/2021	n/a		

	or addition) for the AS or a starting material/intermediate				
IB/0110	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	26/03/2021	n/a		
IB/0111	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/02/2021	24/02/2022	SmPC, Labelling and PL	
IB/0109	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	19/10/2020	n/a		
IA/0108	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	21/08/2020	n/a		
II/0107	B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS	23/07/2020	n/a		
PSUSA/2200/ 201908	Periodic Safety Update EU Single assessment - octocog alfa	17/04/2020	n/a		PRAC Recommendation - maintenance
T/0106	Transfer of Marketing Authorisation	21/02/2020	01/04/2020	SmPC, Labelling and	

				PL	
WS/1723	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.c.z - Container closure system of the AS - Other variation	26/03/2020	n/a		
IA/0105	A.7 - Administrative change - Deletion of manufacturing sites	20/12/2019	01/04/2020	SmPC, Annex II, Labelling and PL	
WS/1634	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	12/09/2019	n/a		
II/0100	B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	12/09/2019	n/a		
WS/1657	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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	04/07/2019	n/a		

	changes to an approved test procedure				
IA/0099	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	10/04/2019	n/a		
IB/0098	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	29/03/2019	n/a		
IB/0097	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	14/01/2019	n/a		
IB/0096	B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	06/11/2018	n/a		
IB/0095	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	02/10/2018	n/a		
II/0092	Update of section 5.1 of the SmPC in order to add new data on immune tolerance induction (ITI). This update follows final results from study PASS-INT-004; this was a prospective, multi-centre, uncontrolled, open-label, non-interventional post-authorization safety surveillance study conducted to	06/09/2018	06/06/2019	SmPC	A non-interventional prospective registry (PASS-INT-004) documented immune tolerance induction (ITI) in 44 paediatric and adult subjects of whom 36 completed ITI therapy. The data showed that immune tolerance may be achieved.

	evaluate Advate in ITI therapy in subjects with moderate or severe hemophilia A (baseline factor VIII ≤ 2%) and a high titer (> 5 BU) inhibitor to FVIII. The RMP version 16.0 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0091	Update of section 4.2 of the SmPC in order to remove a statement that the use of 2 ml presentations has not been documented for paediatric subjects below 2 years of age. This update follows final results from study 061101 listed as a category 3 study in the RMP; this was a prospective, non-interventional, post-marketing surveillance study that assessed the safety and efficacy of Advate reconstituted in 2 ml of sterile water for injection during routine clinical practice in the EU. The Package Leaflet is updated accordingly. The RMP version 15.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/06/2018	06/06/2019	SmPC and PL	The study did not support a higher risk of hypersensitivity or infusion-related reactions of the lower injection volume 2 ml in children. No new safety signals were identified. Advate 2 ml was well tolerated in patients <12 years old, none of the adverse events were considered related by the investigators. No FVIII inhibitor development was observed. No differences between the <2 years age group and subjects >2 and <12 years of age was determined with regard to safety and treatment efficacy.
IA/0094	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	17/05/2018	n/a		

II/0090	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	08/03/2018	n/a		
II/0088	Submission of the final report from study 061301 (China PTP). This is an interventional, open-label study aimed to evaluate the efficacy and safety of Advate in the treatment of previously treated patients with haemophilia A. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/01/2018	n/a		
II/0089	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/01/2018	n/a		
A31/0078	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. 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	14/09/2017	24/11/2017	SmPC and PL	Please refer to the assessment report: human coagulation factor VIII - EMEA/H/A-31/1448

	concluded in September 2017 that there is no clear and consistent evidence of a difference in the incidence of inhibitor development between the two classes of factor VIII medicines: those derived from plasma and those made by recombinant DNA technology. Due to the different characteristics of individual products within the two classes, EMA concluded that the risk of inhibitor development 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.				
II/0082/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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	12/10/2017	n/a		

	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 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				
II/0085	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	14/09/2017	n/a		
IB/0084	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	28/06/2017	n/a		
N/0086	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/06/2017	24/11/2017	Labelling and PL	
PSUSA/2200/ 201608	Periodic Safety Update EU Single assessment - octocog alfa	05/05/2017	n/a		PRAC Recommendation - maintenance
II/0083/G	This was an application for a group of variations. B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	21/04/2017	n/a		

	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				
IB/0080	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	12/01/2017	n/a		
IB/0079	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	19/08/2016	n/a		
IB/0077/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test A.7 - Administrative change - Deletion of manufacturing sites	17/08/2016	n/a		

IB/0076/G	This was an application for a group of variations. B.I.a.z - Change in manufacture of the AS - Other variation B.I.a.z - Change in manufacture of the AS - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	27/04/2016	n/a		
IB/0075	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	02/02/2016	n/a		
IB/0073/G	This was an application for a group of variations. 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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	03/09/2015	n/a		

	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IA/0074	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	11/08/2015	n/a		
II/0065/G	This was an application for a group of variations. 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 B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	23/07/2015	n/a		
IA/0072/G	This was an application for a group of variations. 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 A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	01/07/2015	24/06/2016	Annex II	

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				
IB/0071	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	18/06/2015	n/a		
IB/0070	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	17/06/2015	n/a		
IAIN/0069/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	02/06/2015	24/06/2016	Annex II and PL	
IB/0066	B.I.b.2.e - Change in test procedure for AS or	23/04/2015	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
N/0067	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/03/2015	24/06/2016	PL	
IB/0064	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	10/02/2015	n/a		
PSUSA/2200/ 201402	Periodic Safety Update EU Single assessment - octocog alfa	09/10/2014	n/a		PRAC Recommendation - maintenance
II/0060	Introduction of a post approval change management protocol related to the Active Substance B.I.e.2 - Introduction of a post approval change management protocol related to the AS	25/09/2014	n/a		Introduction of a post approval change management protocol related to the Active Substance
IAIN/0063/G	This was an application for a group of variations. 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	06/08/2014	15/01/2015	SmPC, Labelling and PL	

	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 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 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/0059/G	This was an application for a group of variations.	24/07/2014	15/01/2015	SmPC, Labelling and	

	B.II.b.1.c. Addition of a New packaging site B.II.b.z. Cange in the manufacturing process B.IV.z introduction of the alternative BAXJECT III reconstitution system 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.z - Change in manufacture of the Finished Product - Other variation B.IV.z - Quality change - Change in Medical Devices - Other variation			PL	
IB/0061	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	09/07/2014	n/a		
IB/0058	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	07/03/2014	n/a		
II/0053/G	This was an application for a group of variations. Introduction of additional new active substance manufacturing and release testing site	23/01/2014	15/01/2015	Annex II	

	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 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				
IB/0057	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	16/01/2014	n/a		
R/0052	Renewal of the marketing authorisation.	24/10/2013	20/12/2013	SmPC, Labelling and PL	Advate contains octocog alfa, a recombinant human coagulation Factor VIII produced by recombinant DNA technology in Chinese Hamster Ovary cells and belongs to the pharmacotherapeutic group of blood coagulation Factor VIII (ATC code: B02BD02). It was first approved in the EU in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) on 02 March 2004 and renewed on 26 February 2009. This is the 2nd renewal of the Marketing Authorisation for Advate. An overview of the knowledge and information submitted related to the quality, safety and efficacy aspects of the product reconfirmed the positive benefit- risk ration in the approved indication. The risk management plan is in place and is considered acceptable. The CHMP considers that the renewal can be granted with unlimited validity.

IA/0055/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	08/11/2013	n/a		
II/0049	Update of sections 4.4, 4.8 and 5.1 to update and clarify information on hypersensitivity and inhibitor occurrence and amend frequencies in the table of adverse drug reactions following the results of an integrated safety analysis from completed clinical trials. The Package Leaflet was proposed to be updated accordingly. The Labelling was update to improve clarity on the information on the expiry date after 6 months storage at room temperature. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/09/2013	20/12/2013	SmPC, Annex II, Labelling and PL	Update of sections 4.4, 4.8 and 5.1 to update and clarify information on hypersensitivity and inhibitor occurrence and amend frequencies in the table of adverse drug reactions following the results of an integrated safety analysis from 12 completed clinical trials. The Package Leaflet was proposed to be updated accordingly. The Labelling was update to improve clarity on the information on the expiry date after 6 months storage at room temperature. Changes were also implanted for compliance with the core SmPC for FVIII products (Guideline on core SmPC for human plasma derived and recombinant coagulation factor VIII products; EMA/CHMP/BPWP/1619/1999 Rev.1) and QRD template version 9.0.
IA/0054/G	This was an application for a group of variations. B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the	23/08/2013	n/a		

	Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material				
II/0051/G	This was an application for a group of variations. 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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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	25/07/2013	n/a		
II/0050	Update of sections 5.1 to include data from study 060201 where an individualised pharmacokinetic guided dosing regimen and a standard prophylactic dosing regimen were compared and update of section 5.2 of the SmPC in order to include PK data from an integrated summary of completed pharmacokinetic studies. 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 9.0.	30/05/2013	20/12/2013	SmPC, Annex II and PL	In study 060201, two long-term prophylaxis treatment schemes have been compared in 53 PTPs: an individualised pharmacokinetic guided dosing regimen (within a range of 20 to 80 IU of factor VIII per kg body weight at intervals of 72 ± 6 hours, n=23) with a standard prophylactic dosing regimen (20 to 40 IU/kg every 48 ±6 hours, n=30) . The pharmacokinetic guided dosing regimen (according to a specific formula) was targeted to maintain factor VIII trough levels ≥ 1% at the inter-dosing interval of 72 hours. The data from this study demonstrate that the two prophylactic dosing regimens are comparable in terms of

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				reduction of bleeding rate. These data were included in section 5.1 of the SmPC. Detailed pharmacokinetic results from an integrated summary of 6 completed pharmacokinetic studies were also included in section 5.2 of the SmPC.
II/0048	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	13/12/2012	n/a		
IB/0046	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	29/05/2012	n/a		
II/0045/G	This was an application for a group of variations. Change to the active substance specification and minor change to a test procedure. B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	24/05/2012	n/a		
IAIN/0047	C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the	11/05/2012	n/a		

	safety database				
IB/0044	B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	16/02/2012	10/09/2012	SmPC, Labelling and PL	
X/0041	Annex I_2.(c) Change or addition of a new strength/potency	20/10/2011	19/12/2011	SmPC, Labelling and PL	
II/0043/G	This was an application for a group of variations. Change to the active substance testing and specification. 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 B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	15/12/2011	15/12/2011		
II/0038	Update of sections 4.2, 4.4 and 5.1 of the SmPC to include information on immune tolerance induction. The MAH has taken the opportunity to update sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in line with the revised SmPC guideline with consequential changes to the Package Leaflet. The	19/05/2011	29/06/2011	SmPC, Annex II and PL	Following the currently valid Clinical Guideline, the MAH provided data from clinical studies on "Immune tolerance induction (ITI). The available information regarding ITI is described within section 5.1 of the SPC with the following wording: "Data on Immune Tolerance Induction (ITI) in patients with

	addresses of the local representatives have also been removed from the package leaflet. Annex II has been updated to reflect the new version of the Risk Management Plan (RMP version 10.0) as well as other minor editorial changes. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				inhibitors have been collected. Within a sub-study of PUP-study 060103, ITI-treatments in 11 PUPs were documented. Retrospective chart review was done for 30 subjects on ITI (study 060703) and collection of Registry data is on-going." Besides the identified risk of catheter-related complications no further risks for the patient have been identified. The following wording is proposed to be introduced into section 4.4 of the SPC:"If central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteremia and catheter site thrombosis should be considered."
IA/0042	B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material	02/03/2011	n/a		
IB/0039	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	04/10/2010	n/a		
IB/0040	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	02/09/2010	n/a		
II/0037	Additional drug product manufacturing site for Advate 2000 IU and 3000 IU. Quality changes	22/04/2010	28/04/2010		Additional drug product manufacturing site for Advate 2000 IU and 3000 IU.

II/0036	Changes in the manufacturing process of the active substance. Change(s) to the manufacturing process for the active substance	19/11/2009	25/11/2009		
II/0033	Change in shelf life of finished product. Quality changes	23/04/2009	29/05/2009	SmPC, Labelling and PL	Change in shelf life of finished product.
IB/0035	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	03/04/2009	n/a		
IB/0034	IB_42_b_Change in storage conditions of the finished/diluted/reconstituted product	30/03/2009	n/a		
II/0030	Approval of changes to the drug substance manufacturing process. Quality changes	19/02/2009	27/02/2009		Approval of changes to the drug substance manufacturing process.
R/0028	Renewal of the marketing authorisation.	18/12/2008	26/02/2009	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit/risk balance of Advate remains positive, but considers that its safety profile is to be closely monitored for the following reasons: - to follow the implementation of the registry/surveillance system further to the findings of the pharmacovigilance Inspection - to ensure appropriate implementation of the

					pharmacovigilance system / risk management plan The CHMP is of the opinion that one additional five-year renewal on the basis of pharmacovigilance grounds is required.
II/0031	Change of specifications of reagent used in drug substance purification. Quality changes	22/01/2009	26/01/2009		Change of specifications of reagent used in drug substance purification.
IA/0029	IA_05_Change in the name and/or address of a manufacturer of the finished product	25/09/2008	n/a		
IB/0027	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	30/05/2008	n/a		
X/0023	Annex I_2.(c) Change or addition of a new strength/potency	19/03/2008	22/05/2008	SmPC, Labelling and PL	The MAH applied for the approval of two additional strengths: 2000 and 3000 IU/vial. The composition of the new strengths does not differ from the compositon of the currently licensed dosage strengths, except for the amount of recombinant coagulation factor VIII. The overall benefit/risk ratio for the two new strengths is considered positive.
II/0026	Quality changes	21/02/2008	28/02/2008		
II/0025	Update of or change(s) to the pharmaceutical documentation	13/12/2007	21/12/2007		
II/0024	Quality changes	15/11/2007	22/11/2007		

II/0022	Update of Summary of Product Characteristics and Package Leaflet	21/06/2007	24/07/2007	SmPC and PL	The MAH applied for a type II variation, upon request from the CHMP following a class review of recombinant Factor VIII medicinal products, to update section 4.4 of the SPC to include a warning on cases of inhibitors as follows: '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.' The Package Leaflet has been updated accordingly.
II/0020	Quality changes	22/03/2007	28/03/2007		
IB/0021	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	20/03/2007	n/a		
II/0019	Update of Summary of Product Characteristics, Labelling and Package Leaflet	14/12/2006	17/01/2007	SmPC, Annex II, Labelling and PL	The MAH applied for an update of the SPC to Section 4.8 undesirable effects, following integrated analysis of safety data across all completed and ongoing clinical trials with corresponding amendments to the Package Leaflet. In addition, changes were implemented in all annexes in compliance with the latest QRD template.
II/0018	Quality changes	14/12/2006	17/01/2007	SmPC, Labelling and PL	
II/0016	Quality changes	24/08/2006	11/09/2006		
N/0017	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/08/2006	n/a	PL	

II/0015	Change(s) to the manufacturing process for the active substance Change(s) to the manufacturing process for the active substance	23/03/2006	27/03/2006		
II/0012	Quality changes	26/01/2006	02/02/2006		
II/0014	Quality changes	17/11/2005	22/11/2005		
II/0009	The Marketing Authorisation Holder applied for changes to the reconstitution device (BAXJET) used to transfer the solvent into the finished product vial and the reconstituted product into the syringe. The new device is called BAXJET II. In addition, the other ancillaries are removed from the pack containing the medicinal product (i.e. 1 x mini infusion set, 1 x 10 ml sterile disposable syringe, 2 x alcohol swabs, 2 x plasters). Change(s) to (an) ancillary medical device(s)	13/10/2005	15/11/2005	SmPC, Labelling and PL	This change has no impact on the medical use of the product.
II/0013	Quality changes	14/12/2005	20/10/2005		
IB/0011	IB_37_a_Change in the specification of the finished product - tightening of specification limits	31/08/2005	n/a		
IA/0010	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	12/08/2005	n/a	Annex II	

II/0008	Quality changes	26/05/2005	01/06/2005		
IB/0006	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	03/05/2005	n/a		
IA/0007	IA_09_Deletion of manufacturing site	22/03/2005	n/a		
II/0004	Extension of Indication	18/11/2004	21/12/2004	SmPC, Labelling and PL	Introduction In this variation the MAH presented additional data from a phase 2/3 study (protocol 060101) on pharmacokinetics, immunogenicity, efficacy and safety in the use of Advate in previously treated paediatric patients (PTPs) with haemophilia A. Based on the data analysed the MAH sought an extension of the existing clinical indication to include children under the age of 6 and proposed to delete the following sentence "Currently there are insufficient data in children less than 6 years of age to recommend the use of ADVATE." in section 4.2 of the SPC and corresponding changes in the PL. Further, the MAH proposed to amend sections 4.8 and 5.2 of the SPC. Consequential changes have been introduced in the PL. The MAH also took this opportunity to bring Annex III in line with the latest QRD template. Description of study 060101 This is an ongoing, multi-centre, open-label, prospective, uncontrolled clinical study of at least 50 paediatric PTPs under 6 years of age with severe or moderately severe haemophilia A (baseline factor VIII = 2%). The overall study consists of 2 parts:

					- Part 1 is an open-label evaluation of the pharmacokinetics and short-term safety of Advate following a single dose of 50 ± 5 IU/kg body weight; - Part 2 is an open-label determination of the immunogenicity, haemostatic efficacy, and safety of Advate. Subjects are to continue to receive Advate for at least 50 exposure days or a total treatment time of 6 months, whichever comes first. The treatment regimen is determined by the site investigator (i.e., standard prophylaxis [25 to 50 IU/kg, 3 to 4 times per week], modified prophylaxis, or on-demand treatment). Results and discussion Over the 18-month period covered by the interim report, 53 paediatric PTPs < 6 years of age were given a single infusion of Advate in Part 1 of this study for the determination of pharmacokinetic and safety data parameters. Forty of these subjects have been seen for at least one interval stud
II/0003	Quality changes	16/09/2004	22/09/2004		
II/0001	Change(s) to shelf-life or storage conditions	29/07/2004	04/08/2004		