NovoEight

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0035	Update of section 5.1 of the SmPC to include the results of the completed study in previously FVIII-treated patients PASS Guardian 5 NN70083553 which was a post-authorisation safety study required as part of the RMP.	01/10/2020		SmPC	Update of section 5.1 of the SmPC to include the results of the completed study in previously FVIII-treated patients PASS Guardian 5 NN70083553 which was a post-authorisation safety study required as part of the RMP. For more information, please refer to the Summary of Product Characteristics.

[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).

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IAIN/0036	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	03/09/2020	n/a		
PSUSA/10138 /201910	Periodic Safety Update EU Single assessment - turoctocog alfa	14/05/2020	n/a		PRAC Recommendation - maintenance
II/0033/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.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	30/01/2020	n/a		
II/0030/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to	31/10/2019	15/10/2020	SmPC, Labelling and PL	During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated injections.

	new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In a single dose pharmacokinetic study in adult patients the maximum exposure (Cmax) and the total exposure (AUC) increased with increasing body mass index (BMI) indicating that dose adjustments may be required. An increase in dose may be required for underweight patients (BMI <18.5 kg/m2) and a decrease in dose may be required for obese patients (BMI ≥30 kg/m2), but there is insufficient data to recommend specific dose adjustments. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable. When using an in vitro thromboplastin time (aPTT)-based one stage clotting assay for determining factor VIII activity in patients' blood samples, plasma factor VIII activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. Also there can be significant discrepancies between assay results obtained by aPTT-based one stage clotting assay and the chromogenic assay according to Ph. Eur. This is of importance particularly when changing the laboratory and/or reagents used in the assay. Data on consumption of NovoEight and overall haemostatic success rates in previously untreated patients (PUP) have been provided and includes data on 60 patients aged below 6 years of age. Data on Immune Tolerance Induction (ITI) has been collected in patients with haemophilia A who had developed

					inhibitors to factor VIII. During clinical trial in PUPs, 21 patients were treated with ITI and 18 (86%) patients completed ITI with a negative inhibitor test result. A single dose pharmacokinetic trial (50 IU/kg) was performed in 35 haemophilia patients (≥18 years of age) in different BMI categories. The maximum exposure (Cmax) and the total exposure (AUC) increase with increasing BMI indicating that dose adjustments may be required for underweight (BMI <18.5 kg/m2) and obese patients (BMI ≥30 kg/m2). For more information please refer to the Summary of Product Characteristics.
WS/1681	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.2.z - Changes in the manufacturing process of the AS - Other variation	17/10/2019	n/a		
IA/0031	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	08/08/2019	n/a		
PSUSA/10138 /201810	Periodic Safety Update EU Single assessment - turoctocog alfa	16/05/2019	n/a		PRAC Recommendation - maintenance
II/0026/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	22/11/2018	24/10/2019	Annex II	

	biological/immunological product 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.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.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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				
IG/1004	A.7 - Administrative change - Deletion of manufacturing sites	19/11/2018	n/a		
IB/0027	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	12/11/2018	n/a		

R/0025	Renewal of the marketing authorisation.	31/05/2018	30/07/2018	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of NovoEight in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. Changes to the SmPC have been introduced in Section 4.2 to be in line with the "Guideline on core SmPC for human plasma derived and recombinant coagulation factor VIII products (EMA/CHMP/BPWP/1619/1999 rev.2)" to indicate regarding treatment monitoring that individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. This recommendation also include information on in vitro thromboplastin time (aPTT)-based one stage clotting assay for determining factor VIII activity in patients'. In addition section 4.2 has been updated to include a warning that in patients with existing cardiovascular risk factors, substitiution therapy with FVIII may increase the cardiovasuclar risk in line with EMA/CHMP/BPWP/1619/1999 rev.2.
II/0023	Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to introduce a less frequent regimen in adults and adolescents (>12 years), to remove the warning related to lack of efficacy and safety data in previously untreated patients and to reflect data from final results of the Guardian 2 (NN7008-3568) study and the Guardian 4 (NN7008-3809) study for Novoeight. The Package Leaflet was updated	31/05/2018	26/07/2018	SmPC and PL	The SmPC section 4.2 has been updated with the removal of the statement on previously untreated patients: "The safety and efficacy of NovoEight in previously untreated patients have not yet been established. No data are available."; and the addition of a less frequent regimen: "In adults and adolesents (>12 years) a less frequent regimen (40-60 IU/kg every third day or twice weekly) may be applicable."

	accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				In section 4.8, the table of frequency of adverse drug reactions in clinical trials was updated and a statement was added for the paediatric population: "In the trial with previously untreated patients, between 0 and 6 years of age, a total of 36 adverse reactions were reported in 32 of 59 patients exposed to NovoEight. The most frequently reported adverse reaction was Factor VIII inhibition, see section 4.4. High risk genetic mutations were identified in 91.7% of the overall and 93.3% of the high titre inhibitors. No other factors were significantly associated with inhibitor development." Finally, in section 5.1, the clinical efficacy paragraph was updated in accordance with the final results from the two studies (Guardian 2 and Guardian 4). The PL has been updated accordingly.
PSUSA/10138 /201710	Periodic Safety Update EU Single assessment - turoctocog alfa	14/06/2018	n/a		PRAC Recommendation - maintenance
II/0021/G	This was an application for a group of variations. Section 6.3 Shelf life of the SmPC has been updated as follows: - Storage of the unopened product for a single storage for three months at up to 40°C (within the approved shelf life of 30 months at 2 to 8°C). - Storage of reconstituted product for 4 hours at up to 40°C after storage for three months at up to 40°C (within the shelf life). - The shelf life of 30 months at 2-8°C including a	19/04/2018	26/07/2018	SmPC, Labelling and PL	

	single storage period of 9 months at 30°C may only be combined with an in-use shelf life of 24 hours at 5±3°C or 4 hours at up to 30°C. See SmPC for detailed information. The labelling and PIL has been updated accordingly. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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				
IG/0870	A.7 - Administrative change - Deletion of manufacturing sites	27/11/2017	n/a		
A31/0014	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	14/09/2017	15/11/2017	SmPC and PL	Please refer to the assessment report: human coagulation factor VIII - EMEA/H/A-31/1448

	maintained, varied, suspended or revoked. The EMA concluded in September 2017 that there is no clear and consistent evidence of a difference in the incidence of inhibitor development between the two classes of factor VIII medicines: those derived from plasma and those made by recombinant DNA technology. Due to the different characteristics of individual products within the two classes, EMA concluded that the risk of inhibitor development 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/0020	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	28/09/2017	n/a		
PSUSA/10138 /201610	Periodic Safety Update EU Single assessment - turoctocog alfa	09/06/2017	n/a		PRAC Recommendation - maintenance
IB/0019	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/04/2017	15/11/2017	SmPC, Annex II and Labelling	
IA/0018	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the	28/04/2017	n/a		

	dossier) - Deletion of a supplier				
IB/0017	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	23/02/2017	n/a		
IB/0015	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	14/12/2016	n/a		
PSUSA/10138 /201604	Periodic Safety Update EU Single assessment - turoctocog alfa	01/12/2016	n/a		PRAC Recommendation - maintenance
PSUSA/10138 /201510	Periodic Safety Update EU Single assessment - turoctocog alfa	13/05/2016	n/a		PRAC Recommendation - maintenance
II/0011/G	This was an application for a group of variations. Submission of a revised RMP edition 3 version 1 in order to update the following information: - inclusion criteria of the category 3 study NN7008-3553 PASS; - due date for the provision of the final CSR for study NN7008-3553. In addition, the following minor RMP updates have been implemented: - Section 3.4.4 has been updated with information about an on-going PASS study in Japan NN7008-4105; - In Annex 7 the clinical trial NN7008-3568 has been	17/12/2015	n/a		N/A

	removed from the section "Protocols for proposed and ongoing studies in Categories 1–3 of the section "Summary table of additional pharmacovigilance activities" in RMP Part 3" to align with the requirement in GVP Module; - The clinical trial NN7008-3809 has recently been updated and a new version of the protocol has been included in annex 6 to the RMP. 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 C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
PSUSA/10138 /201504	Periodic Safety Update EU Single assessment - turoctocog alfa	06/11/2015	n/a		PRAC Recommendation - maintenance
IAIN/0010	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	18/08/2015	n/a		
IB/0008	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	02/07/2015	n/a		
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/06/2015	12/05/2016	PL	

IA/0007	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	03/06/2015	12/05/2016	SmPC	
PSUSA/10138 /201410	Periodic Safety Update EU Single assessment - turoctocog alfa	07/05/2015	n/a		PRAC Recommendation - maintenance
IB/0004	To update section 4.4 of the SmPC following the Request 4 of the 1st PSUR Assessment Report dated 4 December 2014. The MAH was requested to include a warning in section 4.4 of the SmPC concerning catheter related infections/device related adverse events consistent with the core SmPC for factor VIII products. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/03/2015	12/05/2016	SmPC	
IB/0005/G	This was an application for a group of variations. 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) B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting	11/03/2015	12/05/2016	SmPC, Labelling and PL	

	material/intermediate/reagent - Tightening of specification limits				
IB/0002/G	This was an application for a group of variations. 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 B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	04/02/2015	n/a		
PSUV/0001	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance