6 May 2019
EMA/271276/2019
Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Esperoct (turoctocog alfa pegol)
Treatment of haemophilia A
EU/3/12/995
Sponsor: Novo Nordisk A/S

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Active substance	Pegylated recombinant factor VIII
International Non-Proprietary Name	Turoctocog alfa pegol
Initial orphan condition	Treatment of haemophilia A
Pharmaceutical form	Powder for solution for injection
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	B02BD02
Sponsor's details:	Novo Nordisk A/S Novo Alle 2880 Bagsvaerd Denmark
Orphan medicinal product designation procedural history	
Sponsor/applicant	Novo Nordisk A/S
COMP opinion date	8 March 2012
EC decision date	30 March 2012
EC registration number	EU/3/12/995
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	A. Laslop, E. Balkowiec - Iskra
Applicant	Novo Nordisk A/S
Application submission date	27 February 2018
Procedure start date	29 March 2018
Procedure number	EMA/H/C/004883/0000
Invented name	Esperoct
Therapeutic indication	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Further information on Esperoct can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/esperoct
CHMP opinion date	26 April 2019
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	K. Penttilä, B. Blöchl-Daum
Sponsor's report submission date	8 March 2018
COMP discussion and adoption of list of questions	19-21 March 2019
Sponsor's removal request	30 April 2019
Removal from the Register	6 May 2019

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2012 designation was based on the following grounds:

- haemophilia A (hereinafter referred to as "the condition") was estimated to be affecting approximately 0.7 in 10,000 persons in the European Union, at the time the application was made;
- the condition is chronically debilitating due to spontaneous bleeding episodes as well as substantially prolonged bleeding upon injury. Approximately 80-85% of bleeding episodes occur in the muscles and joints of the elbows, knees and ankles, causing acute haemarthrosis and synovitis. Recurrent bleeds in the same location lead to chronic arthropathy, muscular atrophy and deformities. In young children with severe haemophilia, spontaneous bleeds occur within the first 2 years of life, after the child starts to walk. Rare but life-threatening bleeds also occur in the central nervous system, throat, neck, and gastrointestinal tract;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that pegylated recombinant factor VIII may be of significant benefit to those affected by the condition. This is in particular with regards to improved pharmacokinetics as shown in preclinical and early clinical data, i.e. an extended half-life of the product and a longer time spent with factor VIII levels needed for normal coagulation processes. This might translate into a major contribution to patient care due to reduced number of infusions, with potential increase of the compliance to the treatment and reduction of patients' discomfort from repeated infusions.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The approved therapeutic indication "treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency)" falls within the scope of the designated orphan condition "treatment of haemophilia A" .

Intention to diagnose, prevent or treat

Turoctocog alfa pegol is a recombinant human factor VIII (FVIII) product with a specific glycoPEGylation on the O-linked glycan. The mechanism of action is based on replacement of the deficient or absent FVIII in patients with haemophilia A.

The medical plausibility is subject to a positive benefit/risk assessment of the CHMP.

Efficacy data are derived from three clinical studies: pivotal trial 3859 in adults and adolescents (main part and two extension phases); trial 3885 in the paediatric population (main part and one extension phase); and trial 3860 (surgery trial). All trials were open-label, multicentre trials.

Chronically debilitating and/or life-threatening nature

There have been no significant changes in the life-threatening and/or chronically debilitating nature of the condition since the designation of the orphan medicinal product.

The condition remains chronically debilitating due to recurrent bleedings in joints, gastrointestinal tract or in surgery, which may be also be life-threatening.

Number of people affected or at risk

There have been no significant changes in the prevalence of the condition since the time of orphan designation. The sponsor based the updated estimate of prevalence on the latest WFH Survey on the European Haemophilia A Prevalence. As compared to the initial designation the survey now included 31 countries (the 28 EU member states plus Iceland, Liechtenstein and Norway).

The sponsor concluded with an estimate of 0.75 in 10,000, which is not significantly different from the figure at designation and from other recent designations (0.7 in 10,000).

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor provided an up to date table with all currently authorised products for the condition (table 1). However, in the time since the sponsor provided the maintenance report emicizumab (Hemlibra), a bispecific monoclonal antibody which mimics coagulation factor VIII and damoctocog alfa pegol (Jivi), a prolonged half-life FVIII product, have also been authorized.

Table 1.

Medicine Name, active substance	Marketing Authorisation Holder	Indication
Advate, octocog alfa	Baxter AG	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). ADVATE is indicated in all age groups.
Adynovi, rurioctocog alfa pegol	Baxalta Innovations GmbH	Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).
Afstyla, lonoctocog alfa	CSL Behring GmbH	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Afstyla can be used for all age groups.
Elocta, efmoroctocog alfa	Swedish Orphan Biovitrum AB	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Elocta can be used for all age groups.

Medicine Name, active substance	Marketing Authorisation Holder	Indication
Helixate NexGen, octocog alfa	Bayer AG	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor-VIII deficiency). This preparation does not contain von Willebrand factor and is therefore not indicated in von Willebrand's disease. This product is indicated for adults, adolescents and children of all ages.
Iblias, octocog alfa	Bayer AG	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Iblias can be used for all age groups.
Kogenate Bayer, octocog alfa	Bayer AG	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor-VIII deficiency). This preparation does not contain von Willebrand factor and is therefore not indicated in von Willebrand's disease. This product is indicated for adults, adolescents and children of all ages.
Kovaltry, octocog alfa	Bayer Pharma AG	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Kovaltry can be used for all age groups.
NovoEight, turoctocog alfa	Novo Nordisk A/S	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Novoeight can be used for all age groups.
Nuwiq, simoctocog alfa	Octapharma AB	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Nuwiq can be used for all age groups.
ReFacto AF, moroctocog alfa	Pfizer Ltd	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor-VIII deficiency). ReFacto AF is appropriate for use in adults and children of all ages, including newborns. ReFacto AF does not contain von-Willebrand factor, and hence is not indicated in von-Willebrand's disease.
Vihuma, simoctocog alfa	Octapharma AB	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).Vihuma can be used for all age groups.
Voncento, human coagulation factor VIII / human von willebrand factor	CSL Behring GmbH	Von Willebrand disease (VWD): Prophylaxis and treatment of haemorrhage or surgical bleeding in patients with VWD, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated. Haemophilia A (congenital factor-VIII deficiency): Prophylaxis and treatment of bleeding in patients with haemophilia A.

There are current guidelines in Europe for patients with haemophilia (European Principles of Haemophilia Care, Haemophilia (2008), 14, pp361-374). There are also guidelines on the management of haemophilia published by the World Federation of Haemophilia (Haemophilia 2013, 19, e1-e47). The primary aim of care is to prevent and treat bleeding with the deficient clotting factor. Treatment of

severe HA presently consists of intravenous infusion of recombinant FVIII or concentrates both as prophylaxis 2-3 times per week, and “on demand” at the time of a bleed.

Significant benefit

The sponsor reports the conclusion of the protocol assistance procedure in relation to significant benefit (May 2014; EMEA/H/SA/1528/2/2012/PA/III CORRIGENDUM). At the time the COMP agreed that if the extended half-life resulted in a clinically meaningful reduction of the number of infusions this could support maintenance of orphan status. Equivalence in efficacy and a clinically relevant advantage in safety could also support significant benefit.

The sponsor at this stage argues that the significant benefit would be based on a major contribution to patient care, because Turoctocog alfa pegol could be effective with a once a week administration in a subset of patients.

Threeextended half-life FVIII products are currently authorised in the European Community: Elocta, Adynovi, and Jivi. For long-term prophylaxis, the recommended schedule of Elocta is every 3-5 days, and the recommended dose of Adynovi is twice weekly (3 to 4 days intervals). For both products, the SmPcs indicate that adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency. This means that for some patients larger intervals are possible. Indeed in the clinical studies weekly doses were also used (see e.g. weekly prophylaxis in section 5.1. of Elocta SmPc). In the case of Jivi, the dose for prophylaxis is 45-60 IU/kg every 5 days. Based on patient clinical characteristics the dose can also be 60 IU/kg every 7 days or 30-40 IU/kg two times per week.

The claim of the sponsor that Turoctocog alfa pegol results in a major contribution of patient care do not therefore appear sufficiently substantiated. The sponsor reports that in the phase 3 clinical trial 3859 turoctocog alfa pegol was tested once weekly by randomisation of patients after the main phase of the trial. When patients were randomised to once weekly prophylaxis in extension phase part 1, the median ABR was 0.00 bleeds/patient/year. When ABR was calculated for patients on once weekly dosing up to the data cut-off for extension phase part 2, median ABR was 1.82 bleeds/patient/year. The average mean prophylaxis dose was 77.1 IU/kg for the 75 IU/kg once weekly dosing regimen. The sponsor then reports that this could translate into improved adherence to prophylaxis, and fewer injection-related complications and that compared to authorised products, the treatment burden could be expected to be lowered for a sub-group of patients that can control bleedings with once weekly treatment.

The sponsor has not sufficiently substantiated the advantage compared to the currently authorised longer acting products. The discussion on significant benefit should also take into account the most recently authorized product in the EU since the time of the submission of the maintenance report. The COMP was of the opinion that even though Hemlibra is authorized for patients that have developed inhibitors, a formal discussion on significant benefit is still needed.

4. COMP list of issues

The sponsor should further discuss the significant benefit of the proposed product *vis a vis* the currently authorised FVIII products with extended half-life, and emicizumab.

The sponsor is reminded that data are needed to support any claim of significant benefit, as assumptions are not acceptable at this stage. The discussion on significant benefit should therefore include data showing that turoctocog alfa pegol actually translates into a quantifiable benefit for patients.

Comments

Following communication of the outcome of the discussion, the sponsor formally requested the withdrawal of the orphan designation on 30 April 2019, prior to responding to the list of questions.