27 February 2023
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for type II variation application

Reblozyl (luspatercept)
Treatment of beta-thalassaemia intermedia and major
EU/3/14/1300

Sponsor: Bristol-Myers Squibb Pharma EEIG

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Product and administrative information

Product	
Designated active substance	Recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain
Other name(s)	--
International Non-Proprietary Name	Luspatercept
Tradename	Reblozyl
Orphan condition	Treatment of beta-thalassaemia intermedia and major
Sponsor's details:	Bristol-Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 Dublin 15 D15 T867 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	IDEA Innovative Drug European Associates Limited
COMP opinion	12 June 2014
EC decision	29 July 2014
EC registration number	EU/3/14/1300
Post-designation procedural history	
Transfers of sponsorship	Transfer from IDEA Innovative Drug European Associates Limited to Celgene Europe Limited – EC decision of 26 February 2015 Transfer from Celgene Europe Limited to Celgene Europe B.V. – EC decision of 27 September 2018 Transfer from Celgene Europe B.V. to Bristol-Myers Squibb Pharma EEIG – EC decision of 12 February 2021
COMP opinion on review of orphan designation at the time of marketing authorisation	20 May 2020
Type II variation procedural history	
Rapporteur / Co-rapporteur	Daniela Philadelphy / Ewa Balkowiec Iskra
Applicant	Bristol-Myers Squibb Pharma EEIG
Application submission	8 October 2021
Procedure start	30 October 2021
Procedure number	EMA/H/C/004444/II/0009
Invented name	Reblozyl

Proposed therapeutic indication	Reblozyl is indicated in adults for the treatment of anaemia associated with transfusion-dependent and non-transfusion-dependent beta-thalassaemia. Further information on Reblozyl can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/reblozyl
CHMP opinion	26 January 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Enrico Costa
Sponsor's report submission	8 November 2021
COMP discussion and adoption	8-10 November 2022, 6-8 December 2022 and 17-19 January 2023
COMP opinion (adoption via written procedure)	31 January 2023

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2014 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain was considered justified based on preliminary clinical data showing haemoglobin increase in non-transfusion dependent patients affected by the condition;
- the condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these, in particular in beta- thalassaemia major patients;
- the condition was estimated to be affecting approximately 1 in 10,000 people in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant fusion protein consisting of a modified form of the extracellular domain of human Activin Receptor IIB linked to the human IgG1 Fc domain may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that treatment of patients with the product may improve anaemia, which is a different aspect to the target of the iron chelation products authorised. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain, as an orphan medicinal product for the orphan indication: treatment of beta-thalassaemia intermedia and major.

2.2. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2020 was based on the following grounds:

- the prevalence of beta-thalassaemia intermedia and major (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Reblozyl may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data that support a reduction in transfusion burden, in a population that is broader than the one covered by the currently authorised products. The COMP considers that this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Reblozyl, recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain, luspatercept, for treatment of beta-thalassaemia intermedia and major (EU/3/14/1300) is not removed from the Community Register of Orphan Medicinal Products.

3. Review of criteria for orphan designation at the time of type II variation

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

Beta thalassaemias are a group of inherited autosomal recessive disorders caused by genetic mutations that reduce or eliminate the expression of β-globin, which results in an α to non-α globin

chain imbalance and decrease in adult haemoglobin (HbA) tetramers in red blood cells (RBCs). Unpaired α-globin chains precipitate, leading to destruction of erythroid precursors and ineffective erythropoiesis (i.e., destruction of RBC precursors in the bone marrow) and peripheral haemolysis.

β-thalassaemia is caused by point mutations or, more rarely, deletions in the HBB gene, leading to reduced (β+) or absent (β0) synthesis of the β-chains of haemoglobin.

Historically, individuals with beta thalassemia were classified as having beta thalassemia major, intermedia, and minor (decreasing severity).

The most severe form is thalassaemia major, which is characterised by a severe (Hb 3 to 4 g/dl) transfusion dependent microcytic anaemia with genotype β0/ β0 or β0 / β+ and corresponding haemoglobin constitution of HbA2 ≥5%, HbF up to 95% and no HbA. Beta thalassaemia intermedia gives a clinical manifestation of moderate microcytic anaemia, has a genotype of β+/ β+ and on typical values on haemoglobin analysis HbA2 ≥4%, HbF up to 50%. A moderate, mild microcytic anaemia is the characteristic feature of minor beta thalassaemia (also called trait) where the genotype is β/β0 or β/β+ haemoglobin analysis and HbF is up to 5%. Subsequently, β-thalassemia has been classified Transfusion dependent (TD) β-thalassemia and Non-Transfusion Dependent (NTD) β-thalassemia (Taher, 2017).

The COMP has previously considered that individuals with beta thalassaemia trait are not to be included in the proposed orphan condition, because of their limited clinical relevance (Premawardhena A Br J Haematol. 2008;141(3):407).

The proposed therapeutic indication "Reblozyl is indicated for the treatment of adult patients with anaemia associated with non-transfusion dependent beta thalassaemia" falls within the scope of the designated orphan condition "Treatment of beta-thalassaemia intermedia and major".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The COMP has previously considered that the condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these. This view is still retained.

All of the pathophysiologic features of β-thalassaemias can be linked to the primary imbalance and accumulation of unpaired α-globin chains within the developing erythrocytes, resulting in ineffective erythropoiesis and peripheral haemolysis that led to clinical complications including chronic anaemia, primary iron overload, and hypercoagulable state (Musallam, 2013a; Taher, 2018a; Sleiman, 2018).

In the absence of transfusion therapy for the treatment of anaemia, the ineffective erythropoiesis in patients with β thalassaemia leads to i) chronic anaemia, which can worsen as patients age, and is directly and independently associated with morbidity (Taher, 2010a; Taher, 2010b; Taher, 2015; Taher, 2018), ii) iron overload due to erythroid factors produced by erythroid cells, especially under conditions of ineffective erythropoiesis and anaemia/hypoxia, that suppress hepcidin synthesis in the liver, leading to increased intestinal iron absorption and increased release of recycled iron from the reticuloendothelial system (Camaschella, 2016; Rivella, 2015) and iii) other morbidities, such as bone marrow expansion and bone changes or mineral density reduction, hypercoagulability due to haemolyzed prothrombotic red cell production and vascular disease, as well as gallstone formation due to peripheral haemolysis (Musallam, 2013d; Taher, 2017; Taher, 2018).

Non-transfusion dependent β-thalassaemia (NTDT) does not depend on regular transfusion therapy for survival. They sporadically need transfusion therapy, e.g., with significant infection, during surgery or pregnancy or for limited periods of time with growth retardation in children or when the chronic anaemia causes clinical morbidity such as splenomegaly, EMH pseudo tumours, leg ulcers.

Complications commonly seen in NTDT have been associated with iron overload, such as multisystemic iron deposition to the liver, heart, and endocrine system.

Number of people affected or at risk

The sponsor proposed a prevalence of approximately 1 in 10,000 persons.

A number of difference sources were used, as comprehensive prevalence data are not available for every EU country. These sources include (i) national databases of rare diseases (from those EU countries in which such registries are maintained), (ii) registries from patient advocacy organizations, and (iii) primary epidemiological data from peer-reviewed medical literature. Additionally, a conservative calculation of prevalence is presented based upon the number of annual conceptions carrying combinations of significant haemoglobin gene variants associated with the orphan condition (Model, 2007; Model, 2008).

The calculated prevalence of β-thalassaemia for each EU27 Member State, based on known frequencies of haemoglobin gene variants and affected conceptions is presented in Table 1 below. For countries in which gene frequency data are not available, the median prevalence value of 0.4 per 10,000 was used to estimate disease prevalence across the EU27 Member States.

Table 1. Prevalence Estimates for β-Thalassaemia in the EU27Member States

Country	**2019 Population Estimate (thousands)** [1]	**Calculated Total Number of Patients (N) Based on Affected Conceptions** [2]	**Calculated Prevalence (per 10,000 population) Based on Affected Conceptions**	**Actual Reported Prevalence (per 10,000 population)**
Austria	8,858.8	89	0.1	
Belgium	11,467.9	229	0.2	0.06 – 0.36 (Gulbis, 2009; Kattamis, 2020)
Bulgaria	7,000.0	1750	2.5	0.3 – 2.5 (Raredis, 2011; Kattamis, 2020)
Croatia	4,076.2	163	N/A (0.4) [a]	
Cyprus	875.9	4931	56.3	5.9 – 56.3 (Tefler, 2006; Kattamis, 2020)
Czech	10,649.8	426	N/A (0.4) [a]	
Denmark	5,806.1	232	0.4	0.4 (Kattamis, 2020)
Estonia	1,324.8	53	N/A (0.4) [a]	
Finland	5,517.9	55	0.1	0.1 (Kattamis, 2020)
France	67,028.0	2681	0.4	0.06 – 0.4 (Thuret, 2010; Kattamis, 2020)

Germany	83,019.2	2491	0.3	0.06 – 0.3 (Dickerhoff, 2009; Kattamis, 2020)
Greece	10,722.3	10293	9.6	2.5 - 2.9 (Voskaridou, 2012; Kattamis, 2020)
Hungary	9,772.8	391	N/A (0.4) [a]	
Ireland	4,904.2	49	0.1	0.1 (Kattamis, 2020)
Italy	60,359.5	21729	3.6	1.0 – 3.6 (WHO-TIF, 2007; Kattamis, 2020)
Latvia	1,920.0	77	N/A (0.4) [a]	
Lithuania	2,794.2	112	N/A (0.4) [a]	
Luxembourg	613.9	12	0.2	0.2 (Kattamis, 2020)
Malta	493.6	118	2.4	2.4 (Kattamis, 2020)
Netherlands	17,282.2	864	0.5	0.06 - 0.5 (Giordano,
Poland	37,972.8	1519	N/A (0.4) [a]	
Portugal	10,276.6	103	0.1	0.04 – 0.1 (WHO-TIF, 2007; Kattamis, 2020)
Romania	19,401.7	582	0.3	0.3 (Kattamis, 2020)
Slovakia	5,450.4	218	N/A (0.4) [a]	
Slovenia	2,080.9	83	N/A (0.4) [a]	
Spain	46,934.6	469	0.1	0.02 – 0.1 (Cela, 2017; Kattamis, 2020)
Sweden	10,230.2	614	0.6	0.6 (Kattamis, 2020)
EU27 total	**513,415,04**	**50,334**	**0.98** [b]	**0.06** [c]

[a] For countries in which prevalence estimates are not available (shaded cells), a median value of 0.4 per 10,000 population is used for the purpose of estimating prevalence in the EU28.
[b] Calculated as: Prevalence = 50,334/513,415,043 x 10,000
[c] Median prevalence across EU countries for which individual prevalence values are available.
Sources: [1] Eurostat, Population on 1 January; [2]: Modell, 2007; Modell, 2008

The conclusion is generally in line with previous procedures of approximately 1 per 10,000, and it was considered acceptable.

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

Based on the Thalassaemia International Federation (TIF) guidelines for the Management of NTDT (Thalassaemia International Federation TIF, 2017), current treatment options for NTDT include pharmaceutical and non-pharmaceutical interventions:

a) Pharmaceuticals: iron chelation therapy (ICT), prophylactic anticoagulant therapy, and the (at the moment off-label) use of hydroxyurea as enhancer of foetal haemoglobin (HbF). A gene therapy - autologous CD34+ cells encoding βA-T87Q-globin gene (Zynteglo) – had been authorised in the EU, but then withdrawn by the sponsor for marketing reasons.

b) Non-Pharmaceutical: RBC transfusions, splenectomy.

The sponsor presented in the Table 2 below the products authorised in the EU for the treatment of β thalassaemia intermedia and major. The COMP discussed the authorised products that would be considered satisfactory for this new target patient population and if applicable form the basis for the justification of significant benefit.

Table 2. Products authorised in the EU indicated for the treatment of β-thalassaemia intermedia and major

INN (Invented Name)	**Pharmaco-therapeutic group**	**Approved Indication in EU**
Deferoxamine/deferoxamine mesilate (Desferal)	Iron chelating agent	Iron overload - acute iron poisoning; primary and secondary haemochromatosis including thalassaemia and transfusional haemosiderosis; in patients in whom concomitant disorders (e.g. severe anaemia, hypoproteinaemia, renal or cardiac failure) preclude phlebotomy; and for the diagnosis of iron storage disease and sideroblastic anaemia, auto-immune haemolytic anaemia and other chronic anaemias.
Deferiprone (Ferriprox)	Iron chelating agent	Ferriprox monotherapy is indicated for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate. Ferriprox in combination with another chelator is indicated in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction

Deferasirox (Exjade)	Iron chelating agent	Treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. Treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups: 1) in paediatric patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years, 2) in adult and paediatric patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older, Treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

The proposed new indication for Reblozyl is: ''treatment of adult patients with anemia associated with non-transfusion dependent beta thalassemia'.

The iron chelating agents presented in the table above are used for managing iron overload. Their indication is specifically for the treatment of iron overload while the indication for Reblozyl is for the treatment of patients with anaemia. There is a recognised overlap in the NTD patients to be treated, i.e. patients having both anaemia and iron overload. However, due to fact that Reblozyl is targeting a different aspect of the condition than deferoxamine/deferoxamine mesilate (Desferal), deferiprone (Ferriprox) and deferasirox (Exjade), the latter three products are not considered as satisfactory methods, especially in treating anaemia.

Significant benefit

Not applicable.

4. COMP position adopted on 31 January 2023

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of beta-thalassaemia intermedia and major (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these, in particular in beta- thalassaemia major patients;
- at present, no satisfactory methods have been authorised in the EU for patients covered by the currently approved therapeutic indication, i.e. treatment of adult patients with non-transfusion dependent beta thalassemia associated with anaemia.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Reblozyl, recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain, luspatercept for treatment of beta-thalassaemia intermedia and major (EU/3/14/1300) is not removed from the Community Register of Orphan Medicinal Products.