EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2018
EMA/99789/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Lamzede (Recombinant human α-Mannosidase)
Treatment of α-Mannosidosis
EU/3/04/260 (EMA/OD/074/04)
Sponsor: Chiesi Farmaceutici S.p.A.

Note

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

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Table of contents

1. Product and administrative information 3

2. Grounds for the COMP opinion 4

3. Review of criteria for orphan designation at the time of marketing authorisation 4

Article 3(1)(a) of Regulation (EC) No 141/2000 4

Article 3(1)(b) of Regulation (EC) No 141/2000 6

4. COMP list of issues ..... Error! Bookmark not defined.

5. COMP position adopted on 26 January 2018 8

1. Product and administrative information

Product	
Active substance	Recombinant human α-Mannosidase
International Non-Proprietary Name	Velmanase alfa
Orphan indication	Treatment of α-Mannosidosis
Pharmaceutical form	Powder for solution for injection
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	other alimentary tract and metabolism products, enzymes (A16AB)
Sponsor's details:	Chiesi Farmaceutici S.p.A. Via Palermo 26/A 43122 Parma Italy
Orphan medicinal product designation procedural history	
Sponsor/applicant	HemeBiotech A/S
COMP opinion date	8 December 2004
EC decision date	26 January 2005
EC registration number	EU/3/04/260
Post-designation procedural history	
Sponsor's name change	From HemeBiotech A/S to Zymenex A/S – EC letter of 4 February 2005
Transfer of sponsorship	From Zymenex A/S to Chiesi Farmaceutici S.p.A. - Italy - EC decision of 22 January 2015
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	H. Hillege, M. Weise
Applicant	Chiesi Farmaceutici S.p.A.
Application submission date	30 August 2016
Procedure start date	29 September 2016
Procedure number	EMA/H/C/003922
Invented name	Lamzede
Therapeutic indication	Enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha mannosidosis Further information on Lamzede can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports
CHMP opinion date	25 January 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	I. Barisic, V. Stoyanova
Sponsor's report submission date	31 August 2016
COMP opinion date	26 January 2018

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2005 was based on the following grounds:

- α-Mannosidosis (hereinafter referred to as "the condition") was estimated to be affecting approximately 0.01 in 10,000 persons in the Community at the time the application was made;
- the condition is chronically debilitating and life-threatening, in particular due to severe clinical features (mental retardation, hearing loss, immune deficiency, myopathy, dysostosis) and premature death in severe cases;
- there is, at present, no satisfactory treatment that has been authorised in the Community for patients affected by the condition.

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

A-mannosidosis is a monogenic autosomal recessive disorder, consisting of a deficiency of lysosomal α-mannosidase (LAMAN). It is caused by mutations in the MAN2B1 gene on chromosome 19 which codes for the enzyme α-mannosidase. The effect of the enzyme deficiency is blockage of the degradation of glycoproteins, which results in the accumulation of mannose rich oligosaccharides in all tissues. Progressive lysosomal accumulation of non-degradable metabolites results in generalized cell and tissue dysfunction and multi-systemic pathologies. Depending on the residual enzymatic activity, epigenetics and disease modifying factors the disease presentation and the burden of disease differs.

The COMP confirms that the condition as designated is still valid for orphan designation. The approved therapeutic indication "enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha mannosidosis" falls within the scope of the designated orphan indication "treatment of α-Mannosidosis".

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

At the time of initial designation, the COMP agreed with the sponsor that the condition was chronically debilitating and life-threatening.

The sponsor is of the opinion that the condition remains chronically debilitating with a continuous clinical spectrum with no clear stratification of patients based on disease severity and phenotypes. Typical clinical symptoms include coarse facial characteristics, mental retardation, ataxia, hearing impairment, impaired speech, recurrent infections, skeletal abnormalities, muscular pain and weakness. The long term outcome results in irreversible clinical pathology.

Regarding the life-threatening aspects, the sponsor outlines that there is very limited published evidence on longevity in α-mannosidosis. Only one published report discusses α-mannosidosis patients over the age of 50 (Malm D et al 2008). The sponsor commissioned a survey, which has been presented to the COMP in its entirety because it has not been published. Feedback was obtained from 3 experts and 16 physicians experienced in the treatment α-mannosidosis in 9 countries. The survey did not identify patients older than 41 years of age.

The COMP confirms that the condition remains life- threatening with premature death in severe cases and chronically debilitating due to coarse facial characteristics, mental retardation, ataxia, hearing impairment, impaired speech, recurrent infections, skeletal abnormalities, muscular pain and weakness.

Number of people affected or at risk

At the time of designation the prevalence was agreed to be approximately 0.01 per 10,000. The sponsor is of the opinion that the prevalence remains less than 5 per 10,000 and is estimated to be approximately 0.02 per 10,000.

Prevalence was estimated through a survey that was commissioned by the sponsor, which has been presented to the COMP in its entirety because it has not been published. This survey was distributed to physicians and key opinion leaders across Europe. The results are based on the feedback received which comprises of 4 European key opinion leaders and 16 European physicians experienced in the treatment α-mannosidosis (table 1; data from Belgium, Denmark, France, Germany, Italy, Norway, Poland, Spain, and United Kingdom). The prevalence estimate ranges from 1:200,000 (0.05 per 10,000) to 1:4,700,000 (0.002 per 10,000), when excluding Italy with a very low prevalence figure.

It can be acknowledged that there is little published information on the epidemiology of the condition. The prevalence of α-mannosidosis reported in the literature ranges from 1:500 000-1:1 000 000 worldwide. The most conservative number from the survey indicates a prevalence of 0.05 per 10,000 in the UK. This is below the threshold defined in the orphan legislation. The COMP could designate less than 0.1 as a very conservative estimate taking into consideration the uncertainty around the lack of epidemiological data.

Table 1. Country specific prevalence rate of α-mannosidosis as per survey of physicians and key opinion leaders in Europe (source is a report commissioned by the sponsor)

Country	*Prevalence Rate*
Belgium	• No idea • 1:350,000
Czech Republic	*No feedback received – global prevalence of 1:500,000 assumed.*
Denmark	• 1:1,000,000 • 7 known patients since 1976 (1 severe infantile type, the others are of moderate type) ***(KOL)*** - Denmark: ~5.6 mio inhabitants -> 1:800,000
Finland	*No feedback received – global prevalence of 1:500,000 assumed.*
France	• Very rare
Germany	• 1:500,000 • Extremely rare, no reliable data • About 1:500,000
Hungary	*No feedback received – global prevalence of 1:500,000 assumed.*
Italy	• Very rare • 4 patients; Italy: ~60 mio inhabitants -> 1:15,000,000 • About 1 of 500,000 live birth • Not available
Netherlands	*No feedback received – global prevalence of 1:500,000 assumed.*
Norway	• 1:500,000 • 6-7 patients; Norway:~ 5,1 mio inhabitants -> 1:800,000
Poland	• 1 case in 2,400,000. (from 1988, a total of 15 cases from 13 families, for an estimated population of 36 Millions) - this is a low prevalence compared to other countries ***(KOL)***
Spain	• Not defined • 5-10 cases; Spain: ~47 mio inhabitants -> 1:4,700,000 • 10 cases confirmed by Spanish KOL • 2 patients diagnosed in Spain between 1994 and 2004
Sweden	• Less than 10 patients; Sweden: ~9.6 mio inhabitants -> 1:1,000,000
UK	• 1:200,000 • similar to published epidemiology reports: ~1:500,000 births ***(KOL)***

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 has established that there are currently no authorised products for the treatment of α-mannosidosis.

The sponsor has also established that the existing methods for treatment cannot be considered satisfactory. The most severe patients are potential candidates for haematopoietic stem cell transplantation or bone marrow transplantation. Supportive care include symptom management, medical and surgical treatment of complications (e.g. infections, skeletal deformities), and physical therapy.

Significant benefit

Significant benefit does not have to be established, because the current methods for treatment are not considered satisfactory.

4. COMP position adopted on 26 January 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.
- the prevalence of α-Mannosidosis (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be less than 0.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life- threatening leading to premature death in severe cases and chronically debilitating due to coarse facial characteristics, mental retardation, ataxia, hearing impairment, impaired speech, recurrent infections, skeletal abnormalities, muscular pain and weakness;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

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 Lamzede, recombinant human α-Mannosidase, velmanase alfa, EU/3/04/260 for treatment of α-Mannosidosis is not removed from the Community Register of Orphan Medicinal Products.