24 June 2022
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Xenpozyme (olipudase alfa)
Treatment of Niemann-Pick disease
EU/3/01/056

Sponsor: Genzyme Europe B.V.

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 human acid sphingomyelinase
Other names	-
International Non-Proprietary Name	Olipudase alfa
Tradename	Xenpozyme
Orphan condition	Treatment of Niemann-Pick disease
Sponsor's details:	Genzyme Europe B.V. Paasheuvelweg 25 1105 BP Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Genzyme B.V.
COMP opinion	18 July 2001
EC decision	19 September 2001
EC registration number	EU/3/01/056
Post-designation procedural history	
Amendment of an existing orphan medicinal product designation - Opinion	17 October 2016
Amendment of an existing orphan medicinal product designation - EC decision	5 December 2016
Transfer of sponsorship	Transfer from Genzyme B.V. to Genzyme Europe B.V. – EC decision of 11 April 2002
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johann Lodewijk Hillege / Ewa Balkowiec Iskra
Applicant	Genzyme Europe B.V.
Application submission	26 October 2021
Procedure start	25 November 2021
Procedure number	EMA/H/C/00004850
Invented name	Xenpozyme
Proposed therapeutic indication	Xenpozyme is indicated as an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B. Further information on Xenpozyme can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Xenpozyme
CHMP opinion	19 May 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Cécile Dop / Elisabeth Johanne Rook
Sponsor's report submission	26 November 2021

COMP opinion (adoption via written procedure)	23 May 2022

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 in 2001 designation was based on the following grounds:

"Whereas the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- based on the submitted evidence the rationale for the use of the product in Type A disease has not been substantiated. Therefore, the condition has been limited to include only patients with Type B disease (hereinafter referred to as "the condition").
- the condition was estimated to be affecting less than 0.04 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating and life threatening due to the deleterious effects on the respiratory system and the liver and due to the significant reduction in life expectancy;
- there is, at present, no satisfactory treatment that has been authorised in the Community for patients affected by the condition.

the COMP recommends the designation this medicinal product, containing Recombinant human acid sphingomyelinase (rhASM), as an orphan medicinal product for the orphan indication: treatment of Niemann-Pick Disease type B."

2.2. Amendment of an existing orphan medicinal product designation

The COMP opinion that was the basis for the amendment of the orphan medicinal product designation in 2016 was based on the following grounds:

"Genzyme Europe BV, the sponsor of the orphan designation of a medicinal product containing recombinant human acid sphingomyelinase for treatment of Niemann-Pick disease, type B submitted on 20 July 2016 an application for amendment of the existing designation. The proposed amended indication is: treatment of acid sphingomyelinase deficiency. The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

For the purpose of amendment of an existing designation, the Committee for Orphan Medicinal Products (COMP) considered that the amended condition proposed by the sponsor should be renamed as "Niemann-Pick disease" (hereinafter referred to as "the condition").

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the amended condition with the medicinal product containing recombinant human acid sphingomyelinase was considered justified based on preliminary clinical data demonstrating that treatment improved spleen volume, liver volume and pulmonary function in patients affected by the condition;
- the condition is chronically debilitating and life threatening due to severe early onset neurological symptoms, hepatosplenomegaly, thrombocytopenia, infiltrative lung disease, atherogenic lipid

profile, osteoporosis, osteopenia, and cardiovascular disease leading to a significant reduction in life expectancy;

- the condition was estimated to be affecting less than 0.5 in 10,000 persons 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 human acid sphingomyelinase will be of significant benefit to those affected by the condition. There is one product authorised for Niemann-Pick disease type C, and no authorised products for Niemann-Pick disease type A and B. The proposed product is an enzyme replacement therapy for the treatment of patients affected by patients that can be categorised as Niemann-Pick type A and B patients. This is supported by clinical data that demonstrate that the treatment improved spleen volume, liver volume and pulmonary function in Niemann-Pick disease type B patients. 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 amendment of the designation as follows: the medicinal product containing recombinant human acid sphingomyelinase for the orphan indication: treatment of Niemann-Pick disease".

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

Niemann-Pick Disease (NPD) comprises a group of autosomal recessive inherited lysosomal storage disorders. These disorders have in common the deficient and/or very low activity of the lysosomal hydrolase, acid sphingomyelinase. Two such groups of patients are described in the literature, the first characterised by a deficiency of acid sphingomyelinase (ASM; "types A & B", caused by mutations in the SMPD1 gene), and the second is due to defective function in cholesterol transport ("type C" caused by mutations in NPC1 in approximately 95% of cases or NPC2 gene) (Schuchman and Desnick, Mol Genet Metab. 2017 Jan - Feb). Type A is characterised by early hepatosplenomegaly and profound CNS manifestations, while type B only rarely exhibit CNS manifestations. Type C patients also manifest organomegaly and neurodegeneration (Patterson and Walkley, Mol Genet Metab. 2017 Jan - Feb).

Acid sphingomyelinase (ASM) is a lysosomal phosphodiesterase that catalyzes the hydrolysis of sphingomyelin to ceramide and phosphocholine (Schuman and Desnick, 7th Ed NY, 1995). ASM activity is deficient in Niemann-Pick disease Types A and B.

NPC exhibits phenotypic heterogeneity, comprising systemic, neurological, and psychiatric features. Neonatal NPC patients frequently have an increase in bile acid concentration in the liver, and 10% of these patients die of liver failure before six months of age. The symptoms of NPC patients who survive infancy are dominated by progressive neurodegeneration, characterised by features such as cerebellar ataxia, vertical supranuclear gaze palsy, dysphagia, gait disorder with falls and dementia.

The approved therapeutic indication "Xenpozyme is indicated as an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B." falls within the scope of the designated orphan condition "Treatment of Niemann-Pick disease".

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

At the time of initial designation and review at initial marketing authorisation, the COMP agreed that the condition was chronically debilitating and life-threatening.

At the time of this review Niemann-Pick Disease is presented to the COMP to remain chronically debilitating and life-threatening disease. However, the signs and symptoms depend on the type and severity of the condition. The clinical presentation and course of NPD Type A is relatively uniform. Typically, in the first few months of life the spleen and liver will enlarge. Moderate lymphadenopathy is present and by bone marrow examination the Niemann-Pick foam cells are revealed. Early neurologic manifestations include hypotonia and muscular weakness. By 6 months of age the psychomotor retardation becomes evident, and as the infant becomes progressively weaker and hypotonic, retrogression of developmental milestones is noted. With advancing of age the loss of motor function and the deterioration of intellectual capabilities are progressively debilitating. Followed in later stages by spasticity and rigidity. Patients generally succumb before 3 years of age, due to the gradual progression of neurological symptoms (Besley and Elleder, J Inherit Metab Dis, 1986, Schuman and Desnick, 7th Ed NY, 1995).

The onset and clinical course of Type B NPD is highly variable. In the most severely affected Type B NPD patients the disease is diagnosed early in childhood by organomegaly and minor decreased pulmonary involvement which progresses with age. Severely affected individuals may experience significant pulmonary involvement by 15-20 years of age as well as liver involvement leading to life-threatening cirrhosis, portal hypertension, and ascites. Other heavily involved organ systems include bone and spleen with lesser involvement in the lymph nodes, heart, and eyes. In general, Type B patients do not have neurologic involvement and are intellectually normal. The primary cause of death is related to pulmonary complications (Besley and Elleder, J Inherit Metab Dis, 1986, Schuman and Desnick, 7th Ed NY, 1995Crocker and Farber S., Medicine 1958).

The COMP concluded that the condition remains chronically debilitating and life-threatening due to severe early onset neurological symptoms, hepatosplenomegaly, thrombocytopenia, infiltrative lung disease, atherogenic lipid profile, osteoporosis, osteopenia and cardiovascular disease leading to a significant reduction in life expectancy.

Number of people affected or at risk

At the time of designation, the prevalence (P) was agreed to be less than 0.5 per 10,000.

For this review the prevalence was presented to the COMP to remain less than 5 per 10,000 and was estimated to be 0.047 per 10,000.

For the calculation of the prevalence the sponsor calculated the sum of the prevalence for ASMD and for NPD type C.

The prevalence calculation for ASMD provided is based on the highest estimate of 0.6 per 100,000 birth prevalence seen in the epidemiology birth prevalence literature including patients across the ASMD spectrum (see Table 1). The studies have rates ranging from 0.3 to 0.6 per 100,000. The lowest (approximately 0.3/100,000) is seen in a study in the Czech Republic. The highest rate (0.6/100,000) is found in a study in Portugal. Given the limitations of the epidemiological literature, both in estimation of prevalence and distinction of subgroups at the extreme ends of the ASMD spectrum, the most conservative rate of 0.6 per 100,000 was used for the whole, combined population.

Table 1. Birth prevalence of ASMD in the general population

Author	**Publication Date**	**Location or Ethnicity**	**Study Design**	**Years of study**	**Identified cases**	**Birth Prevalence (per 100,000)**
Poorthuis et al	1999	Netherlands	Retrospective	1970-1996	NPD A+B	0.53
					NPD A: 14	0.40
					NPD A or B: 13 NPD C: 25	0.13 0.35
Meikle et al	1999	Australia	Retrospective	1980-1996	NPD A+B: 17 NPD C: 20	0.40 0.47
Pinto et al	2004	Portugal	Retrospective	1952-1991	NPD A+B: 7	0.60
				1983-2001	NPD A: 4	0.50
				1979-1985	NPD B: 3 NPD C: 9	0.10 2.2
Poupětová et al	2010	Czech Republic	Retrospective		NPD A+B: 21	0.33
				1963-2002	NPD A: 10	0.18
				1948-1996	NPD B: 11 NPD C: 54	0.15 0.91
Wittmann	2012	Hungary	Newborn Screening	Not Specified	NPD A+B	5.0
Mechtler et al.	2012	Austria	Newborn Screening	Jan – July 2010	NPD A+B	0
Elliot et al	2016	United States	Newborn Screening	Not specified	NPD A+B	2.27
Wasserstein et al	2018	United States	Newborn Screening	2013-2017	NPD A+B: 2	3.05

NPD A = infantile neurovisceral end of the ASMD spectrum;
NPD B = chronic visceral end of the ASMD spectrum;
NPD A+B = ASMD disease across the spectrum;
NPD C = type C disease

The duration of disease (D) used for the calculation will be 65 years based on the data described by McGovern and colleagues (McGovern et al., Genet Med. 2013) and the surviving population ages described by Hollak (Hollak et al., Mol Gen Metab. 2012)

Using the conservative number of 0.06/10,000 for the birth prevalence and the conservative life expectancy of 65 years from epidemiological studies, the expected total number of individuals with ASMD is 0.037 per 10,000. This calculation is here-below:

P = I x D= (4.2M births x 0.06/10,000 births) x 65 / 448M = 0.037 per 10,000 persons for the ASMD.

Since the orphan condition also entails NPD type C, the sponsor also calculated the prevalence of the NPD type C. For NPD type C, based on a recent study (in US), and birth incidence data from France, UK and Germany (1988-2002, Vanier MT, Millat G: Niemann-Pick disease type C. Clin Genet. 2003, 64: 269-281.) The prevalence of diagnosed NPD type C has been estimated at about 1 per million inhabitants (=0.01 per 10,000 persons). However, the sponsor's prevalence estimate might be underestimated, as these data were based on prevalence/incidence at birth and involve early onset NPD type C, thereby excluding late-onset patients. Moreover, based on the same European data, the COMP previously estimated the prevalence at approximately 0.1 /10,000 for NPD type C. With the availability of miglustat for the treatment of NPD-C the proportion of adolescent/adult-onset NP-C cases diagnosed in France increased 2.5-fold since 2009 compared with the 2000-2008 period due to improved awareness. (Y. Nadjar, Orphanet J Rare Dis 2018; 13(1):175)

Altogether, the COMP considered a prevalence estimate of approximately 0.1 would be in line with most recent orphan designations for the total Nieman Pick disease population in the EU including all disease types.

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

There is currently no "standard of care" treatment for the disease, and symptoms are managed with supportive measures. Splenectomy is occasionally performed for thrombocytopenia, but removal of the spleen has been known to exacerbate lung involvement. Liver transplantation is rarely performed, and bone marrow transplantation is associated with high morbidity and mortality. Palliative treatment with lipid-lowering drugs, antibiotics, and supplemental oxygen (O2) has limited benefit.

Zavesca is currently authorised for the treatment of patients with Niemann-Pick disease type C, which is an entirely different target population than patients with Niemann-Pick disease type A and B. The proposed product Xenpozyme is able to treat patients of Niemann-Pick subtypes A/B and B, for whom currently no authorised products exist.

The COMP concluded that there is no approved treatment that qualifies as a satisfactory treatment for the purpose of the examination of the significant benefit vis-à-vis Xenpozyme, as the authorised treatment options do not cover the patient population for which Xenpozyme is intended.

Significant benefit

Xenpozyme is intended for a patient population for whom no other satisfactory method is available (see above). No justification of significant benefit is therefore required.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 23 May 2022

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 Niemann-Pick disease (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life threatening due to severe early onset neurological symptoms in type A, hepatosplenomegaly, thrombocytopenia, interstitial lung disease, atherogenic lipid profile, osteoporosis, osteopenia, and cardiovascular disease leading to a significant reduction in life expectancy;
- there is, at present, no satisfactory method for the treatment of the entirety of patients covered by the therapeutic indication of Xenpozyme.

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 Xenpozyme, recombinant human acid sphingomyelinase, olipudase alfa for treatment of Niemann-Pick disease (EU/3/01/056) is not removed from the Community Register of Orphan Medicinal Products.