23 August 2018
EMA/505941/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for marketing authorisation application

Mepsevii (vestronidase alfa)
Treatment of Mucopolysaccharidosis Type VII
EU/3/12/973 (EMA/OD/127/11)
Sponsor: Ultragenyx Germany GmbH

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

Product	
Active substance	Recombinant human beta-glucuronidase
International Non-Proprietary Name	Vestronidase alfa
Orphan indication	Treatment of mucopolysaccharidosis type VII (Sly syndrome)
Pharmaceutical form	Solution for infusion
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	A16AB
Sponsor's details:	Ultragenyx Germany GmbH Stadtquartier Friedrichstr. 191 10117 Berlin Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	NDA Regulatory Science Ltd Prime House Challenge Court Barnett Wood Lane Leatherhead Surrey KT22 7DE United Kingdom
COMP opinion date	11/01/2012
EC decision date	21/03/2012
EC registration number	EU/3/12/973
Post-designation procedural history	
Transfer of sponsorship	- Transfer from NDA Regulatory Science Ltd - to NDA Group AB – EC decision of 20/12/2013 - Transfer from NDA Group AB to Ultragenyx UK Limited – EC decision of 07/05/2015 - Transfer from Ultragenyx UK Limited to Ultragenyx Germany GmbH – EC decision of 26/09/2016
Marketing authorisation	
Rapporteur / co-Rapporteur	J. Lodewijk Hillege/ A. Moreau
Applicant	Ultragenyx Germany GmbH
Application submission date	30/03/2017
Procedure start date	18/05/2017
Procedure number	EMEA/H/C/004438/0000
Invented name	Mepsevii

Therapeutic indication	Mepsevii is indicated for treatment of Mucopolysaccharidosis VII (MPS VII; Sly syndrome) for patients of all ages Further information on Mepsevii can be found in the European public assessment report (EPAR) on the Agency's website http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/004438/human_med_002269.jsp&mid=WC0b01ac058001d124
CHMP opinion date	28/06/2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	G. O'Dea/ I. Barisic
Sponsor's report submission date	5/04/2017
COMP discussion	19-21/06/2018
COMP opinion date	3/07/2018

2. Grounds for the COMP opinion

The COMP opinion on the orphan medicinal product designation was based on the following grounds:

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

- Mucopolysaccharidosis type VII (Sly syndrome) (hereinafter referred to as "the condition") was estimated to be affecting approximately 0.001 in 10,000 persons in the European Union, at the time the application was made;
- the condition is life-threatening and chronically debilitating due to the development skeletal and physical abnormalities with many patients dying in childhood;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

The COMP recommends the designation of this medicinal product, containing recombinant human beta-glucuronidase, as an orphan medicinal product for the orphan indication: treatment of mucopolysaccharidosis type VII (Sly syndrome).

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

Mucopolysaccharidosis VII also known as Sly syndrome or MPS VII is an autosomal recessive lysosomal storage disorder that is characterised by the deficiency of activity of β-glucuronidase (GUS). In the absence of GUS, chondroitin sulfate, dermatan sulfate and heparan sulfate are only partially degraded and the partially degraded fragments accumulate in the lysosomes of many tissues, eventually leading to cellular and organ dysfunction (Montaño A et al, 2016).

The GUS gene is located on chromosome 7q11.21–7q11.22 spanning 20 kb and containing 12 exons. Isolation and characterisation of the human GUS cDNA facilitated the investigation of allelic heterogeneity in patients with MPS VII. To date 49 unique, disease-causing mutations have been reported in patients with MPS VII. Mutations are distributed along the whole gene and include missense mutations (78.6%), nonsense mutations (12.6%), deletions (5.8%) and splice-site mutations (2.9%).

Phenotypical characteristics of patients with MPS VII resemble those of MPS I and MPS II (short stature, skeletal dysplasia, hepatosplenomegaly, hernias, cardiac involvement, decreased pulmonary function and cognitive impairment). In MPS VII, however, one unique and distinguishing clinical feature is the unexpectedly high proportion of patients that have a history of non-immune hydrops fetalis (NIHF). Hydrops fetalis (fetal hydrops) is a serious foetal condition defined as abnormal accumulation of fluid in two or more foetal compartments, including ascites, pleural effusion, pericardial effusion, and skin oedema. In some patients, it may also be associated with polyhydramnios and placental oedema

The clinical presentation and disease progression of MPS VII span a wide severity spectrum. Most patients with MPS VII have cognitive impairment, hepatosplenomegaly and skeletal dysplasia. However, affected patients show a wide range of clinical signs and symptoms, from early, severe, multisystem manifestations to milder phenotypes with later onset and normal or near-normal intelligence. Although patients with MPS VII may present with hydrops foetalis at birth and only survive a few months, rare patients with milder manifestations of MPS VII have survived into the fifth decade of life. The most severe form of MPS VII disease is characterised by the presence of NIHF (a more severe form of hydrops foetalis).

The COMP has designated this condition once before. The literature continues to describe the condition as a distinct medical entity. The COMP accepted this condition for the purpose of the review of the Maintenance of Orphan Designation.

The approved therapeutic indication "*Vestronidase alfa is indicated for the treatment of non-neurological manifestations of Mucopolysaccharidosis VII (MPS VII; Sly syndrome) for patients of all ages*" falls within the scope of the designated orphan indication "*treatment of mucopolysaccharisosis VII*".

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

Most patients with MPS VII have cognitive impairment, hepatosplenomegaly and skeletal dysplasia. Repeated upper respiratory and pulmonary infections which required antibiotics are reported as common in the first 2 years of life. Hearing impairment is common and is believed to contribute to delayed speech development.

Common causes of death included complications of hydrops foetalis with respiratory and renal failure, heart disease, decreased pulmonary function and/ or obstructive airway disease, complication of bone marrow transplantation and aspiration.

Death is premature in the majority of cases. It has been reported that 50% of patients die by the age of 1 year primarily due to complications of hydrops foetalis, respiratory failure and renal failure. After this age mortality seems to be primarily due to heart disease, complications of bone marrow transplantation (BMT) and pulmonary failure reported as the main causes of death (Montaño A et al, 2016). Only a small percentage survives into adulthood.

Number of people affected or at risk

It is noted in the literature that MPS VII is an ultra-rare disorder and precise epidemiological data are scarce (Montaño A et al, 2016).

The prevalence calculation is based on two sources: a recent publication by Montano A et al in 2016 and data collected by the sponsor through their interaction with specialist centres in Europe.

The sponsor highlights the publication in their revised prevalence calculation which states:" *This global systematic survey of physicians caring for MPS VII patients worldwide (International MPS VII Clinical Survey) was commissioned by the sponsor and conducted by Dr. Adriana Montano (Montano et al. 2016). Medical geneticists globally were queried regarding all identified MPS VII cases to characterize the population more systematically than could be performed from the literature. A total of 56 patients were identified and information collected. Of the 56 patients, 53% were confirmed alive, 36% were dead, and the status of 11% was unknown. The geographical distribution of patients with MPS VII showed they were predominantly from Brazil (27%), USA (20%), Germany (18%), Argentina (11%) and Spain (7%). Fifteen patients were identified in member countries of the European Union (Germany [10 patients], Spain [4 patients]; Lithuania [1 patient]). The sponsor's internal outreach efforts also identified 20 living patients in different member states of the EU (France [5 patients], Spain [5 patients], Portugal [4 patients], Netherlands [2 patients], Germany [2 patients], Czech Republic [1 patient], Lithuania [1 patient])".*

The authors of this article note that: "*Overall the frequency of this disease is estimated to be 1:300 000–1:2 000 000. Many patients may have been missed because of early death in utero since the most frequent phenotype may be hydrops fetalis in the antenatal form. Others may have died in early infancy without diagnosis*".

The prevalence calculation is based on a total derived from the 15 patients identified in the publication and 20 identified by the sponsor irrespective of the potential for overlap. The total number of patients in Europe is therefore estimated to be 35. This absolute number was divided by the total population for Europe which in 2017 was 511,750,300. From these assumptions the sponsor proposed that the prevalence of the condition in Europe of 0.001 in 10,000.

The current updated information provided by the sponsor confirms the assumptions made at the time of the initial orphan designation in 2011 where the information was not as current. The COMP maintained the prevalence at 0.001 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

There are currently no authorised treatments for mucopolysaccharidosis VII (Sly Syndrome). The current management of these patients is palliative treatment and bone marrow transplantation (BMT). Palliative therapies currently are the basic therapeutic approach and including corrective surgeries, oxygen supplementation, antibiotics, non-steroidal anti-inflammatory drugs and physical therapy. (Montaño A et al, 2016).

Limited results suggest that BMT can slow or even prevent further neurological complications, but has little to no effect on the skeletal disease unless it has been performed in neonates (Aldenhoven et al. 2015, Bailey L. 2008, Sands MS et al, 1993). The main limitations of BMT in MPS have been the difficulty in finding appropriate donors and the high morbidity and mortality after BMT.

Significant benefit

Not applicable.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 3 July 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 mucopolysaccharidosis Type VII (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 0.001 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 cognitive impairment, hepatosplenomegaly and skeletal dysplasia. Fifty percent of patients die by the age of 1 year primarily due to complications of hydrops foetalis, respiratory failure and renal failure;
- 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 Mepsevii, vestronidase alfa, EU/3/12/973 for treatment of mucopolysaccharidosis type VII (Sly syndrome) is not removed from the Community Register of Orphan Medicinal Products.