Medicines & Healthcare products Regulatory Agency

MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for

Avalglucosidase alfa

- Treatment of late-onset Pompe disease (LOPD) in symptomatic patients who have received Pompe disease ERT with alglucosidase alfa for ≥ 2 years
- Treatment of infantile-onset Pompe disease (IOPD) in symptomatic patients ≥ 1 year old who have received Pompe disease ERT with alglucosidase alfa for ≥ 6 months

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising unlicensed medicines to UK patients that have a high unmet clinical need. A positive scientific opinion is only issued by the MHRA if the criteria for the EAMS are fulfilled, which includes demonstrating a positive benefit risk balance (quality, safety and efficacy assessment) and the ability of the pharmaceutical company to supply a medicine according to a consistent quality standard.

EAMS medicines are unlicensed medicines. The term 'unlicensed medicine' is used to describe medicines that are used outside the terms of their UK licence or which have no licence for use in the UK. GMC guidance on prescribing unlicensed medicines can be found below:

https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines

The opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of the medicine. As such this is a scientific opinion and should not be regarded as a licensed indication or a future commitment by the MHRA to licence such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMS documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

EAMS procedural assessment at the MHRA

A full assessment of the quality, safety and efficacy of [product INN or code number] has been conducted by the MHRA's assessment teams, including pharmacists, toxicologists, statisticians, pharmacokinetic and medical assessors. This assessment process also includes consideration of the quality, safety and efficacy aspects by the UK independent expert committees including Expert Advisory Groups (EAGs) and the Commission on Human Medicines (CHM):

- The Commission on Human Medicines (CHM) advises ministers on the quality, safety and efficacy of medicinal products. The Chair and Commissioners are appointed in accordance with the Code of Practice for Ministerial Appointments to Public Bodies. The Chair and

Commissioners follow a code of practice, in which they are precluded from holding personal interests. The Commission is supported in its work by Expert Advisory Groups (EAGs), covering various areas of medicine.

https://www.gov.uk/government/organisations/commission-on-human-medicines/about

- Chemistry, Pharmacy and Standards EAG, which advises the CHM on the quality in relation to safety and efficacy of medicinal products

  https://www.gov.uk/government/organisations/commission-on-human-medicines/about/membership#chemistry-pharmacy-and-standards-eag

- Clinical Trials, Biologicals and Vaccines EAG, which advises the CHM on the quality in relation to safety and efficacy of vaccines and biological products

  https://www.gov.uk/government/organisations/commission-on-human-medicines/about/membership#clinical-trials-biologicals-and-vaccines-eag

Pharmacovigilance system

A pharmacovigilance system for the fulfilment of pharmacovigilance tasks has been put in place for this EAMS medicine, including a risk management plan. As the safety profile of the EAMS medicine is not fully established it is particularly important that any harmful or unintended responses to EAMS medicines are reported. Healthcare professionals should be aware of their obligations to report adverse event information upon enrolment of any patients receiving EAMS medicines in the scheme. They will be required to follow the process which the pharmaceutical company which manufactures the EAMS medicine has in place to enable systematic collection of information on adverse events.

For more detailed information on this EAMS medicine, please refer to the Public Assessment Report, EAMS treatment protocol for healthcare professionals, EAMS treatment protocol for patients and EAMS treatment protocol for pharmacovigilance.

https://www.gov.uk/government/collections/early-access-to-medicines-scheme-eams-scientific-opinions

Justification for the fulfilment of the EAMS criteria

There are four EAMS criteria that need to be fulfilled before a medicine can enter the scheme and a positive scientific opinion is issued by the MHRA. The fulfilment of the criteria for this particular medicine is described below.

1	**(a) Life threatening and seriously debilitating condition** Pompe disease is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal acid alphaglucosidase (GAA), an enzyme that degrades glycogen. The resulting accumulation of glycogen in body tissues, especially cardiac, respiratory and skeletal muscles, disrupts the architecture and function of affected cells leading to a variety of symptoms, clinical decline, and in many cases, premature death. Disease spectrum is a continuum, generally divided into two subtypes: infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD), although there is considerable variability and overlap between these two extremes. The majority of patients with Pompe disease are classified with the late-onset subtype. • IOPD presents in the first months of life and is characterized by severe cardiomyopathy, hypotonia, respiratory failure and, without treatment, leads to death within the first year. • LOPD can present any time after infancy (>12 months) and has a more variable course. These patients usually present with slowly progressive myopathy, predominantly of the proximal muscles in the trunk, pelvic and shoulder girdles, and have a variable degree of respiratory involvement. Most patients ultimately become wheelchair bound, and as the disease progresses, many patients eventually require non-invasive or invasive ventilation. They ultimately progress to respiratory failure, the leading cause of death in these patients. The mean time from symptom onset to dependence on assisted artificial ventilation is reported to be 15 years (range 1-35 years) with symptom onset between the ages of 30 to 50 years. Invasive ventilation is required in 11 to 25% of adult patients with a higher proportion (29%) using non-invasive ventilation. Mortality in untreated LOPD patients is approximately 25 years earlier than the normal population on average, with a mean age at death of about 45 years. **(b) High unmet need: existing methods/licensed medicines have serious limitations** The current standard of care is enzyme replacement therapy with recombinant human acid α-glucosidase (rhGAA, alglucosidase alfa – Myozyme). • LOPD: Despite an initial improvement in forced vital capacity (FVC) for the majority of patients, the capacity gained over the first months is gradually lost over time with patients returning to baseline values by 36 months and followed thereafter by a slight progressive decline. In the 6-minute walking test (6MWT), the largest improvement is over the first 20 months of treatment with substantial stabilization in the following years. • IOPD: Patients treated with alglucosidase alfa may now be able to survive infancy, but as they age, the treatment limitations are becoming apparent. In a UK survey, 35% died and a further 30% became ventilator dependent. Whilst a dramatic improvement in cardiac function is seen, the treatment is not so effective in preventing the long-term development of arrhythmia. Furthermore, it has limited effect on skeletal muscle and residual motor effects. Overall, a trend of initial

	improvement followed by clinical deterioration is common amongst long-term survivors despite continued ERT. The population of patients who exhibit a clinical decline or partial response whilst receiving ERT with Myozyme has the highest unmet need as there is currently no alternative treatment.
2	**The medicinal product offers major advantage over existing methods in the UK** <u>LOPD</u> A randomised trial comparing avalglucosidase alfa to Myozyme in 100 treatment-naïve patients (16 to 78 years old) showed an improvement in FVC% predicted (2.9% vs 0.5%) and 6MWT (32m vs 2m) after 48 weeks of treatment. Subsequently, patients who switched from Myozyme to avalglucosidase alfa had a dramatic drop in urinary excretion of glucose tetrasaccharide; although not a surrogate marker, this parameter is used for patient monitoring and some data support that patients with the most marked improvement have the best clinical response. This biomarker result was associated with a small improvement in the main efficacy outcomes 1 year later, which should be put in perspective with the plateau that is likely achieved after 1 year of ERT treatment. In another trial, a small number (10) of patients showed stable disease or minor decline (FVC, 6MWT) for up to 6 years of follow-up after a switch from Myozyme. <u>IOPD</u> A trial was conducted in 22 children, 1 to 12 years old, whose clinical condition was declining or with partial response whilst on Myozyme, despite often high doses (up to 85 mg/kg over a period of 2 weeks). Over a period of 1.5 to 3 years of follow-up, functional motor outcomes showed an improvement over baseline in 15 to 18 patients depending on the score considered. In 6 patients who were initially randomised to pursue Myozyme and were switched to avalglucosidase alfa after 24 weeks, an improvement in almost all scores was reported after the switch (or no change in 2 scores). In particular, the Pompe PEDI-scale improved in all patients after the switch. In these patients, a clear drop in biomarkers such as creatine kinase and transaminases was also observed after the switch. The literature on long-term treatment with alglucosidase alfa emphasises the great heterogeneity of disease evolution as no fewer than 7 evolution profiles have been identified by some authors. This highlights the great difficulties encountered when interpreting the data provided from small patient samples. Furthermore, given the clinical condition and the lack of alternative treatment, it is considered that any improvement would qualify as a “major” advantage in the framework of the EAMS.
3	**The potential adverse effects of the medicinal product are outweighed by the benefits, allowing for a conclusion of a positive benefit/risk balance** The most common adverse drug reactions (ADRs) reported in 138 patients were hypersensitivity reactions (e.g., pruritus, rash, urticaria), headache, fatigue, nausea and chills. Infusion reactions were reported in 26% of the patients. Most occurred from 0 to 2 hours after the infusion and were of mild intensity. Anaphylaxis according to Samson criteria was reported in 2 patients (1.5%). Serious ADRs were reported in 5 patients (3.6%); a very small number of patients discontinued treatment (2; 1.4%), including one patient whose symptoms of respiratory distress met the criteria for anaphylaxis.

	Almost all treatment-naïve patients (95%) developed anti-drug antibodies (ADAs) and the occurrence of infusion reactions and hypersensitivity reactions increased with increasing ADA titres; neutralising ADAs (Nabs) were detected in 44% of treatment-naïve patients. Amongst treatment-experienced patients, 46% developed treatment-emergent ADAs (49% of adults and 38% of children); 33% of the adults developed Nabs but no Nabs were detected in paediatric patients. The incidence of infusion reactions and hypersensitivity was higher in patients who developed ADAs compared to patients who were ADA-negative. Overall, the safety profile of avalglucosidase alfa is broadly similar to that of Myozyme. The infusion reactions appear to be manageable in the majority of cases. In IOPD, all 22 children are pursuing treatment, most (18) at the dose of 40 mg/kg every other week. Therefore, the benefit/risk balance of avalglucosidase alfa is considered positive.
4	**The company is able to supply the product and to manufacture it to a consistent quality standard, including the presence of appropriate GMP certification.** The company has provided all documentation necessary to prove that the EAMS medicine is manufactured/packaged according to GMP.