Medicines & Healthcare products Regulatory Agency

MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for

Cipaglucosidase alfa in conjunction with miglustat

Long-term treatment of late-onset Pompe disease (LOPD) in symptomatic adult patients who have received enzyme replacement therapy with alglucosidase alfa for ≥ 2 years

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. LOPD can present any time after infancy (>12 months) and has a 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 (ERT) with recombinant human acid α-glucosidase (rhGAA, alglucosidase alfa – Myozyme). Despite the clear benefits of alglucosidase alfa, there is a variable response in LOPD. After 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. A multi-centre cohort study recently conducted to determine the effects of 10years of ERT in adult patients with Pompe disease on various parameters including FVC and 6-minute walk distance indicate that although the majority of patients had received initial benefit of ERT, there is large interindividual variation in response patterns and duration of treatment efficacy with 35% to 63% of patients showing a secondary decline after approximately 3 to 5 years. Therefore, 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** A single-arm trial enrolled 29 adult (18-65 years old) ambulatory and non-ambulatory patients, 23 of whom were ERT-experienced (≥ 2 years of treatment with alglucosidase alfa). They were treated with cipaglucosidase alfa (20 mg/kg) every other week given 1 hour after an oral dose of miglustat (260 mg) for up to 4 years. In 16 ERT-experienced ambulatory participants, the 6-Minute Walking distance (6MWD) increased compared to baseline (~400m), by 20m after 1-2 years, and possibly further (36m) after 3 years. In these patients, the forced vital capacity (FVC) tended to remain stable. Furthermore, the median reduction in fatigue using the patient-reported outcome of the Fatigue Severity Scale was considered clinically meaningful. A double-blind randomised trial compared switching to cipaglucosidase alfa and miglustat vs continuing on alglucosidase alfa in 95 ERT-experienced adult patients (65 cipaglucosidase alfa/miglustat and 30 alglucosidase alfa). A further subset of 28 ERT-naïve patients was also enrolled. The primary endpoint was the 6-Minute Walk Test (6MWT) in the overall population, and while numerically superior, statistical significance was not achieved for cipaglucosidase alfa/miglustat compared to the alglucosidase alfa/placebo arm (p = 0.071). A pre-specified subgroup analysis was performed on the ERT-experienced population for 6MWD and FVC. The effects of the combination are consistent with those of the previous trial showing clear benefit over alglucosidase alfa in terms of motor and respiratory outcomes with a median increase in 6MWD of 9.65m *vs* a decrease of 8.9m (nominal p = 0.047) and a median increase in FVC of 0.5% *vs* a decrease of 3.2% (nominal p = 0.006), for cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo, respectively.
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 overall safety database included 114 patients treated with the combination of cipaglucosidase alfa and miglustat. The most common adverse drug reactions (ADRs) reported in ≥ 10% subjects were headache (28%), diarrhoea (20%), myalgia (19%), nausea (17%), abdominal pain (15%), fatigue (14%), muscle spasms (14%) and dizziness (10%). Infusion-associated reactions (IARs) occurred during 2-3% of all infusions of cipaglucosidase alfa and the patient incidence was similar with cipaglucosidase alfa (25%) and alglucosidase alfa (26%). Most IARs were mild or moderate in severity; the most severe (in 6 patients) included chills, dyspnoea, flushing, hypotension, pharyngeal oedema, and urticaria. Only 3 patients stopped treatment due to an IAR (anaphylactoid reaction, chills, urticaria). In the first study, antidrug antibodies were observed in all patients in the course of the treatment with variable titres; some were neutralising. Analyses based on limited interim data indicate that immunogenicity did not appear to impact cipaglucosidase alfa pharmacokinetics, IARs, or efficacy. Overall, the safety profile of cipaglucosidase alfa is broadly similar to that of Myozyme. The infusion reactions appear to be manageable in the majority of cases. Therefore, the benefit/risk balance of cipaglucosidase alfa/miglustat 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.