Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scientific Opinion - Public Assessment Report	
Product	**Avalglucosidase alfa**
EAMS indication	**Treatment of late-onset Pompe disease (LOPD) in patients with symptoms and who have received alglucosidase alfa (Myozyme) for at least 2 years.** **Treatment of infantile-onset Pompe disease (IOPD) in patients at least 1 year old who have symptoms and have received alglucosidase alfa (Myozyme) for at least 6 months.**
Company	**Aventis Pharma Ltd t/a Sanofi**
EAMS number	**04425/0004**
EAMS Scientific Opinion date	**05 March 2021**

Introduction
The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The MHRA scientific opinion provides benefit and risk information to physicians who may wish to prescribe the EAMS medicine under their own responsibility. More information about the scheme can be found here:
http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

The scientific 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 medicine licensed by the MHRA or a future commitment by the MHRA to license 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.

The General Medical Council's guidance on prescribing unlicensed medicines can be found here:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

What is avalglucosidase alfa?
Avalglucosidase alfa is the active substance of a medicine, which is available as a powder that is made up into a solution given by infusion (drip into a vein).

What is avalglucosidase alfa used to treat?
Avalglucosidase alfa is used to treat children from one year of age, adolescents and adults who have Pompe disease, a rare inherited disorder.

Patients with this disease do not have enough of an enzyme called acid alpha-glucosidase. This enzyme normally breaks down sugar stored as glycogen into glucose that can be used for energy by

the body's cells. If the enzyme is not present, glycogen builds up in certain tissues, particularly the muscles, including the heart and diaphragm (the main breathing muscle under the lungs). The progressive build-up of glycogen causes a wide range of symptoms, including an enlarged heart, breathing difficulties and muscle weakness. The disease can appear soon after birth (the 'infantile-onset' form - IOPD), but also later in life (the 'late-onset' form - LOPD).

Avalglucosidase alfa is given to patients treated with alglucosidase alfa (Myozyme), who have a partial response or a loss of response to this treatment after it has been given for a period of time sufficient to judge its effects (2 years in LOPD and 6 months in IOPD).

How is avalglucosidase alfa used?
Treatment with avalglucosidase alfa should be supervised by a doctor who has experience in the management of patients with Pompe disease or other inherited diseases of the same type.

Avalglucosidase alfa is given as an infusion once every two weeks. The dose is 20 mg per kilogram body weight in LOPD and 40 mg per kilogram body weight in IOPD. The infusion should start slowly and then be gradually sped up as long as there are no signs of side effects caused by the infusion. It will last approximately 4 hours for patients with LOPD and 6 hours for patients with IOPD.

Before the infusion, patients may be given medicines (anti-allergic or anti-fever) to prevent or reduce side effects caused by the infusion.

If an allergic reaction occurs during the infusion, the doctor may decide to slow down or stop the infusion, depending on the severity of the reaction. If side effects resolve, the infusion may be progressively re-started.

How does avalglucosidase alfa work?
Avalglucosidase alfa is an enzyme replacement therapy, which provides patients with the enzyme they are lacking, in this case, acid alpha-glucosidase. Avalglucosidase alfa helps to break down glycogen and stops it building up abnormally in the cells.

How has avalglucosidase alfa been studied?
The main study of the effects of avalglucosidase alfa in LOPD has enrolled 100 patients, aged 16 to 78 years, who had not previously received enzyme replacement therapy. Half of the patients were given avalglucosidase alfa (20 mg/kg every other week) and the other half alglucosidase alfa (Myozyme) for 48 weeks. Afterwards, patients treated with alglucosidase alfa were switched to avalglucosidase alfa.

The main study in IOPD enrolled 22 children aged 1 to 12 years, whose condition was either declining or partially responding to treatment with alglucosidase alfa (Myozyme). They were given avalglucosidase alfa at a dose of 20 or 40 mg/kg every other week or remained on Myozyme for 24 weeks. Afterwards, patients treated with alglucosidase alfa were switched to avalglucosidase alfa (40 mg/kg every other week).

The main measures of effectiveness were the improvement in 'forced vital capacity' (a measure of how well lungs are working) and the distance the patients could walk in six minutes or scales of mobility skills in young children. The patients are still followed-up in the long-term.

When should avalglucosidase alfa not be given?
Avalglucosidase alfa should not be given in case of life-threatening allergic reactions to avalglucosidase alfa or any of the other ingredients of this medicine where re-administration of the medicine was not successful.

In case of life-threatening allergic reactions to alglucosidase alfa (Myozyme), the doctor will consider the risks and benefits of administering avalgucosidase alfa.

What are the benefits and risks of avalglucosidase alfa?

Benefits
In LOPD, patients treated with avalglucosidase alfa for 48 weeks experienced a greater improvement in respiratory function and also in walking distance (32 metres on average) compared to those treated with Myozyme (2 metres on average). After the switch, a notable decrease in the biological marker of glycogen burden was associated with further motor improvement in these patients.

In IOPD, patients generally showed a stabilisation or improvement in their mobility skills.

Risks
The most frequent side effects of avalglucosidase alfa were associated with the infusions and included headache, nausea (feeling sick), itching, rash, hives, fatigue and chills.

Severe allergic reactions may occur, such as difficulty breathing, chest pressure, low level of oxygen in the blood, or swollen lower lip and tongue. These require the infusion to be stopped and appropriate medical treatment to be given.

Why has avalglucosidase alfa been given a positive Early Access to Medicine Scientific opinion?
If patients are not responding to enzyme replacement therapy with alglucosidase alfa, there is no other licensed treatment available. Avalglucosidase alfa has been shown to provide some level of stabilisation or improvement in these patients. With regard to the medicine's side effects, the most frequent were mild to moderate in severity.

What are the uncertainties?
Data are still limited about the long-term effectiveness of avalglucosidase alfa over several years. The company that makes avalglucosidase alfa will provide additional information when it becomes available.

Are there on-going clinical studies?
All clinical studies conducted with avalglucosidase alfa are currently on-going to collect long-term safety and effectiveness data.

What measures are in place to monitor and manage risks?
A risk management plan has been developed to ensure that avalglucosidase alfa is used as safely as possible. Based on this plan, the company that makes avalglucosidase alfa must ensure that all healthcare professionals expected to use the medicine, as well as patients, are provided with information on the medicine including the side effects and recommendations for minimising these side effects.

Information will be collected about patients before they enter the scheme. Healthcare professionals will be asked by the company to report adverse effects experienced by patients receiving avalglucosidase alfa through the scheme. These safety data will be reviewed and reported to the MHRA on a regular basis by the company.

Health care professionals involved in the management of the scheme will receive specific training from the company, which will include product information, infusion protocol, reconstitution and storage of the medicine, and adverse event reporting process.

Patients will receive an alert card summarising the important risks with the medicine and the details of their treating doctor. Patients should carry the card with them at all times to inform any other healthcare professional that they are receiving avalglucosidase alfa through an EAMS.

Other information about avalglucosidase alfa – see EAMS Treatment Protocols