Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scientific Opinion - Public Assessment Report	
Product	**Cipaglucosidase alfa in conjunction with miglustat**
EAMS indication	**Long-term treatment of late-onset Pompe disease (LOPD) in adult patients with symptoms and who have received alglucosidase alfa (Myozyme) for at least 2 years.**
Company	**Amicus Therapeutics Europe Ltd**
EAMS number	**50636/0001**
EAMS Scientific Opinion date	**04 June 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 are cipaglucosidase alfa and miglustat?
Cipaglucosidase 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).
Miglustat is the active substance of a medicine, which is available as an oral capsule.

What is cipaglucosidase alfa with miglustat used to treat?
Cipaglucosidase alfa in conjunction with miglustat is used to treat 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), but also later in life (the 'late-onset' form - LOPD).

Cipaglucosidase alfa is given in conjunction with miglustat 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).

How are cipaglucosidase alfa and miglustat used?
Treatment with cipaglucosidase alfa with miglustat should be supervised by a doctor who has experience in the management of patients with late-onset Pompe disease.

Cipaglucosidase alfa is given as an infusion once every two weeks. The dose is 20 mg per kilogram body weight. 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. 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.

Miglustat is given as a single dose of 4 capsules of 65 mg if the patient weighs at least 50 kg or 3 capsules of 65 mg if the patient weighs between 30 and 50 kg. The capsules should be taken 1 hour before the start of the infusion of cipaglucosidase alfa on an empty stomach (patients have to fast 2 hours before and 2 hours after taking miglustat).

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

Miglustat, which has been absorbed in the blood after oral intake, binds with cipaglucosidase alfa when it is injected and protects it from degradation in the blood.

How have cipaglucosidase alfa and miglustat been studied?
A first study of the effects of cipaglucosidase alfa with miglustat enrolled 22 patients, aged 18 to 66 years, who had previously received enzyme replacement therapy for more than 2 years; they all received cipaglucosidase alfa with miglustat for up to 4 years.

A second study enrolled 95 adult patients, most of them having previously received enzyme replacement therapy for more than 5 years. Of these 95 patients, 65 were switched to cipaglucosidase alfa with miglustat and 30 remained on alglucosidase alfa (Myozyme) given with placebo (dummy) capsules for 52 weeks. Treatments were randomly attributed, and patients and healthcare professionals were unaware of the treatment received.

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 (for those still able to walk). Another measure was a self-assessment by the patients of the severity of 'fatigue' and its impact on their quality of life using a scale (Fatigue Severity Scale). All patients are still followed-up in the long-term.

When should cipaglucosidase alfa and miglustat not be given?
Cipaglucosidase alfa and miglustat should not be given in case of life-threatening allergic reactions to cipaglucosidase alfa or any of the other ingredients of these medicines where re-administration of the medicines was not successful.
In case of life-threatening allergic reactions to alglucosidase alfa (Myozyme), the doctor will consider the risks and benefits of administering cipaglucosidase alfa.

What are the benefits and risks of cipaglucosidase alfa in conjunction with miglustat?

Benefits
In the first study, patients treated with cipaglucosidase alfa in conjunction with miglustat had stable respiratory function after 52 weeks and half of them had an increase in walking distance of more than 20 metres. A reduction of fatigue severity was reported in most cases.

In the second study, the respiratory function was shown to be stable for 52 weeks in patients treated with cipaglucosidase alfa in conjunction with miglustat while worsening was observed in those who continued to be treated with alglucosidase alfa. Likewise, half the patients had an increase in walking distance of more than 10 metres while the walking distance tended to decrease in most patients who continued to be treated with alglucosidase alfa.

Risks
The most frequent side effects of cipaglucosidase alfa given in conjunction with miglustat (occurring in ≥ 10% patients) were headache, diarrhoea, muscle pain, nausea (feeling sick), abdominal pain, fatigue, muscle spasms and dizziness.

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

Why has cipaglucosidase alfa with miglustat 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. Cipaglucosidase alfa in conjunction with miglustat has been shown to provide stabilisation or improvement in these patients. With regard to the medicines' 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 cipaglucosidase alfa with miglustat over several years.
The company that makes these medicines will provide additional information when it becomes available.

Are there on-going clinical studies?
All clinical studies conducted with cipaglucosidase alfa with miglustat are currently on-going to collect long-term safety and effectiveness data. In addition, a study in children and adolescents (aged 0 to <18 years) is being conducted.

What measures are in place to monitor and manage risks?
A risk management plan has been developed to ensure that cipaglucosidase alfa in conjunction with miglustat is used as safely as possible. Based on this plan, the company that makes these medicines must ensure that all healthcare professionals expected to use them, as well as patients, are provided

with information on these medicines including their side effects and recommendations for minimising them.

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 cipaglucosidase alfa and miglustat through the scheme. These safety data will be reviewed and reported to the MHRA on a regular basis by the company.

Healthcare 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 medicines, 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 cipaglucosidase alfa and miglustat through an EAMS.

Other information about cipaglucosidase alfa with miglustat – see EAMS Treatment Protocols