Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scientific Opinion - Public Assessment Report	
Product	**Berotralstat**
EAMS indication	Berotralstat is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older
Company	**BioCryst UK Ltd.**
EAMS number	**32080/0001**
EAMS Scientific Opinion date	**30 October 2020**

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 berotralstat?
Berotralstat is the active substance of a medicine, which is available as capsules for oral use.

What is berotralstat used to treat?
Berotralstat is used for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

How is berotralstat used?
Berotralstat should be taken as one capsule with one glass of water at the same time once daily. This can be done at any time of the day, with or without food.

The recommended dose for adults and adolescents from 12 years is one 150mg capsule of berotralstat daily.

No change in the dose is required for patients with mild, moderate or severely reduced kidney function or patients over 65 years. However, no dosage recommendations can be given for patients on dialysis.

No change in the dose is required for patients with reduced liver function. However, caution is required when berotralstat is prescribed to patients who have moderate or severely reduced liver function, whose body weight is <40 Kg or if there are additional independent risk factors for QTc prolongation such as electrolyte disturbances, known pre-existing QTc prolongation (either acquired or familial), or concomitant use of other drugs known to either prolong the QTc (e.g. ondansetron) or increase berotralstat drug levels (cyclosporine). Women using only desogestrel for contraception must switch to an alternative method of effective contraception, such as a barrier method, injectable progesterone, or combination oral, patches and vaginal ring hormonal contraception.

If a patient forgets to take their daily dose of berotralstat, a double dose must not be taken to make up for a forgotten capsule. The missed dose should be taken as soon as the patient remembers, but patients should take no more than one dose per day.

How does Berotralstat work?
HAE is a rare illness that causes swelling in various parts of the body, resulting in pain and limitation in daily activity. The swelling is caused by a high activity of a protein in the bloodstream, called bradykinin, which is activated by a chemical, called kallikrein. Berotralstat blocks the activity of kallikrein, which in turn reduces bradykinin activation, and swelling in the body.

How has berotralstat been studied?
The main study of the efficacy and safety of berotralstat was a randomized, double-blind, placebo-controlled Study NCT 03485911 in 120 adults or adolescents aged 12 years and over with HAE who experienced at least two investigator-confirmed attacks within the first 8 weeks of the run-in period. Patients were randomised into 1 of 3 parallel treatment arms, stratified by baseline attack rate, in a 1:1:1 ratio (berotralstat 110 mg, berotralstat 150 mg or placebo by oral administration once daily, with food) for the 24-week treatment period (Part 1). The safety was also investigated in 266 patients aged 12 years and older of the open-label, non-randomised study NCT 03472040.

When should berotralstat not be given?
Berotralstat should not be given to patients who have hypersensitivity to the drug or any of its excipients.

What are the benefits and risks of berotralstat?
Benefits
Berotralstat 150 mg produced a statistically significant and clinically meaningful reduction in the rate of HAE attacks by 44.2% compared to placebo in the first month of treatment, which was sustained in the 24-week treatment period. Amongst patients receiving 150 mg berotralstat, 58% had a ≥ 50% reduction in their HAE attack rates compared to baseline versus 25% of placebo patients. In post-hoc analyses, 50% and 23% of patients receiving berotralstat 150 mg had a ≥ 70% or ≥ 90% reduction in their HAE attack rates respectively compared to baseline versus 15% or 8% of placebo patients.

Risks
The most common adverse reactions are abdominal pain (all locations, which occurred in 21% patients in clinical trials) and diarrhoea (which occurred in 15% patients in clinical trials). These events most often occurred early after initiation of treatment and became less frequent with continued berotralstat use. Most of these events were brief and resolved without medication while berotralstat treatment was continued.

Why has berotralstat been given a positive Early Access to Medicine Scientific opinion?
The pivotal study NCT 03485911 has demonstrated clinically significant reductions in HAE attacks by berotralstat and therefore routine HAE prophylaxis using oral berotralstat is likely to provide a meaningful impact to patients in clinical practice. Given serious limitations in the use of existing licensed medicines, oral berotralstat 150 mg taken once daily is likely to offer significant advantages over methods currently used in the UK.

What are the uncertainties?

The number of patients studied in clinical trials was very small, which makes it difficult to evaluate precisely the degree of clinical benefit and the frequency and severity of side-effects with this product. Furthermore, data on the reduction of HAE attack rates and safety are still preliminary. The company that makes berotralstat will provide additional information when it becomes available.

Are there on-going clinical studies?
The main studies mentioned above are still on-going.

What measures are in place to monitor and manage risks?
A risk management plan has been developed to ensure that berotralstat is used as safely as possible. Based on this plan, the company that makes berotralstat must ensure that doctors and other healthcare professionals expected to use the medicine, as well as patients, are provided with information on the medicine. The patient in the Early Access to Medicines Scheme will receive a Patient Alert Card from their doctor with a space to capture details of their treating physician, a reminder on the posology of berotralstat and important information on the potential for drug-drug interactions and risk factors that may increase the risk of prolonging the QTc interval. In normal use the risk of QT prolongation leading to arrythmia is low with no cases reported in the clinical trials at time of EAMS approval. However the risk cannot be excluded in patients with higher exposures to berotralstat, including patients with moderate or severe hepatic impairment (Child-Pugh Class B or C), with body weight <40 kg, or those with additional independent risk factors for QTc prolongation (including a history of QTc prolongation, electrolyte disturbances and/or concomitant use of QTc prolonging medicines or medicines that increase berotralstat drug levels). Appropriate monitoring is recommended, and dose reduction may be required for concomitant use of narrow therapeutic index drugs which are substrates for CYP2D6, CYP3A4 and P-gp. The patient should always carry the card with them and should be instructed to show this to any other healthcare professional who treats the patient or provides them with advice.

Information will be collected about patients before they enter the scheme. Healthcare professionals will be asked by the company to report all adverse events and side effects experienced by patients receiving berotralstat through the scheme, as well as medication errors, overdose, and pregnancies. They will receive a physician pack and comprehensive training on the risk of adverse events and how to report these prior to commencement of patient treatment. These safety data will be reviewed and reported to the MHRA on a regular basis by the company.

Other information about berotralstat – see EAMS Treatment Protocol