Medicines & Healthcare products Regulatory Agency

MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for
Berotralstat is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

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 berotralstat 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

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** Hereditary angioedema (HAE) is a rare, but serious and potentially life-threatening disorder caused by mutations in one allele of SERPING1, leading to reduced functional C1-esterase inhibitor (C1-INH) levels. It is characterised by spontaneous swellings in various parts of the body, which are unpredictable, either with or without triggers, and the risk of asphyxiation due to laryngeal oedema is lifelong. Hence, HAE is a serious and life-threatening condition that profoundly affects the lives and day-to-day functioning of many patients. **(b) High unmet need, i.e. there is no methods available or existing methods have serious limitations** There remain some patients who fail to respond to currently licensed medicinal products or are unable to use either an intravenously or subcutaneously delivered drugs. Therefore, it is likely that there are serious limitations in the use of existing licensed medicines.
2	**The medicinal product offers major advantage over existing methods in the UK** The swelling in HAE is caused by a high activity of plasma bradykinin, which is activated by kallikrein. Berotralstat blocks the activity of kallikrein, which in turn reduces bradykinin activation, and swelling in the body. 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. In the pivotal Study NCT 03485911, 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. Therefore, oral berotralstat 150 mg QD is likely to offer significant advantages over methods currently used in the UK.
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 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. Therefore, potential adverse effects of berotralstat are considered being outweighed by the benefits.
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.