Medicines & Healthcare products Regulatory Agency

MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for
Sebetralstat indicated for the treatment of hereditary angioedema (HAE) attacks in adult and adolescents 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 [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

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 or seriously debilitating condition** Hereditary angioedema (HAE) is a seriously debilitating condition. It is a chronic disease that often begins at a young age and presents with spontaneous swelling at multiple anatomical sites, including the gastrointestinal tract. Rarely, laryngeal attacks may occur, which can be life-threatening if not treated promptly. Due to the chronic and unpredictable nature of the disease, and the potential for serious consequences, HAE significantly affects the quality of life of those affected. As such, hereditary angioedema is considered a seriously debilitating condition. **(b) High unmet need: there is no method available/approved medicinal product or existing methods/licensed medicines have serious limitations** HAE is a time-sensitive disease in which delays in treatment can result in rapid progression of an attack and a prolonged time to symptom resolution. In other words, early treatment reduces the speed of progression and leads to faster symptom resolution. Current treatments are primarily injectable and have significant practical limitations, such as the need to carry syringes with needles, longer set-up times, and the requirement for a private space for administration. These factors contribute to psychosocial impacts, such as a preference for treatment at home or in a healthcare facility, which may result in treatment delays and anxiety related to injection-associated pain. Sebetralstat addresses an unmet need by offering an easier-to-administer oral tablet, which has the potential to improve both time to treatment and the psychosocial burden associated with injectable therapies.
2	**The medicinal product offers major advantage over existing methods in the UK** Indirect efficacy comparisons were conducted with currently used injectable treatments in the UK, namely recombinant C1 esterase inhibitors (Ruconest) and bradykinin B2 receptor antagonists (Icatibant). The results of indirect comparisons with recombinant C1 esterase inhibitors (Ruconest) demonstrated equivalent efficacy after accounting for differences in study populations and disease severity. However, indirect

	comparisons with Icatibant were inconclusive due to deficiencies in study design and a lack of data regarding patient characteristics, disease severity, endpoints, and measurement methods. Clinically, C1-INH (e.g., Ruconest) and Icatibant are the main on-demand treatment options available to patients in the UK. Apart from known allergies to rabbits, there is no strict delineation regarding which treatment option should be preferred. Therefore, it would be reasonable to conclude that if Sebetralstat demonstrates at least equivalent efficacy to Ruconest, it would be considered comparable to other on-demand treatments, including Icatibant. Considering Sebetralstat's practical advantages—such as convenience, ease of use, lower incidence of adverse events (particularly injection site-related reactions), and associated psychosocial benefits—the MHRA accepts that a major advantage over existing methods in the UK has been demonstrated.
3	**The potential adverse effects of the medicinal product are outweighed by the benefits, allowing for a conclusion of a positive benefit/risk balance** Adverse effects associated with Sebetralstat use were generally low, with common reactions including dyspepsia and fatigue. Notably, unlike injectable treatments, Sebetralstat carries no risk of injection site reactions. However, for patients taking potent CYP3A4 inhibitors, exposure to Sebetralstat is expected to be significantly increased. In healthy volunteers who received a 600 mg dose of Sebetralstat whilst on potent CYP3A4 inhibitors, the Cmax approached the concentration associated with a QT interval prolongation of 10 ms (14.7–16.9 µg/mL), based on QT analysis. Therefore, higher exposure in some patients is a potential concern. As this will be the first time the medicine is administered in an uncontrolled setting to a broader patient population, a cautious approach is advised. Accordingly, for patients taking potent CYP3A4 inhibitors, it is recommended that only a single dose of Sebetralstat 300 mg be administered, and no additional dose should be taken.
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.