Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scientific Opinion - Public Assessment Report	
Product	Sebetralstat
EAMS indication	Sebetralstat is indicated for the treatment of hereditary angioedema (HAE) attacks in adult and adolescents aged 12 years and older.
Company	Kalvista Pharmaceuticals Limited
EAMS number	46326/001
EAMS Scientific Opinion date	19/03/2025

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 Sebetralstat?

Sebetralstat is the active substance of a medicine, which is taken orally.

What is Sebetralstat used to treat/diagnoses/prevent?

Sebetralstat is indicated for the treatment of hereditary angioedema (HAE) attacks in adult and adolescents aged 12 years and older.

How is Sebetralstat used?

The recommended dose is ONE tablet to be taken at the earliest sign that you are having an attack. Swallow the tablet whole with some water, if required. The tablet can be taken with or without food.

An additional dose of ONE tablet may be taken if symptoms persist.

Subjects who are taking a strong CYP3A4 inhibitors should treat a HAE attack with a single dose of 300 mg only.

How does Sebetralstat work?

Sebetralstat works by blocking the activity of plasma kallikrein and helps reduce the levels of bradykinin. When taken at the start, or during an attack, this will stop further progression of the attack and the symptoms of swelling and pain.

How has Sebetralstat been studied?

The efficacy of Sebetralstat for the treatment of hereditary angioedema (HAE) attacks in adult and adolescent patients aged 12 years and older was demonstrated in the KONFIDENT trial, a randomised, double-blind, placebo-controlled, three-way cross-over design.

A total of 110 patients treated 264 attacks; 87 treated with 300 mg Sebetralstat, 93 treated with 600 mg Sebetralstat, and 84 treated with placebo. Attacks ranged in severity from mild to very severe and occurred in all anatomic locations. Following treatment of each attack an additional dose could be taken if needed. The primary efficacy endpoint was the time to beginning of symptom relief, assessed using the Patient Reported Global Impression of Change (PGI-C). The PGI-C required patients to assess their attack symptoms using a seven-point scale (“much worse” to “much better”). To achieve the primary endpoint, a patient had to report a positive and sustained response on the PGI-C within 12 hours.

When should Sebetralstat not be given?

Sebetralstat is not recommended if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby.

What are the benefits and risks of Sebetralstat?

Benefits

For the primary endpoint, time to symptom relief favoured Sebetralstat, with median times of 1.61 hours for the 300 mg dose and 1.79 hours for the 600 mg dose, compared with 6.72 hours for placebo.

For key secondary endpoints, the median time to reduction in severity of attacks favoured sebetralstat, with median times of 9.27 hours for the 300 mg dose, 7.75 hours for the 600 mg dose, and greater than 12 hours for placebo. The median time to complete HAE attack resolution favoured sebetralstat compared to placebo for both 300mg and 600mg.

Risks

The most common side-effects related to Sebetralstat is dyspepsia and fatigue.

Why has Sebetralstat been given a positive Early Access to Medicine Scientific opinion?

Hereditary angioedema is a seriously debilitating disease that has a major impact on quality of life and current treatment formulations are limited to injectable formulations that are more complicated to carry around and administer compared to Sebetralstat which can be taken orally. In addition to the practical advantages of Sebetralstat, it has demonstrated to have equivalent efficacy to commonly used C1 esterase inhibitors through indirect comparison studies. Sebetralstat has an acceptable safety profile

and avoids the risk of injection-site related adverse reactions. Therefore, the benefit-risk profile of Sebetralstat is considered positive.

What are the uncertainties?

For patients taking potent CYP33A4 inhibitors exposure of Sebetralstat is expected to be significantly increased. In healthy volunteers given doses of 600mg whilst on potent CYP3A4 inhibitor drugs, the Cmax value is very close to the concentration value calculated from the QT analysis as giving rise to a QT prolongation of 10 ms (14.7- 16.9 μg/ml), higher exposure in some patients is a potential concern. As this will be the first time the drug is given in an uncontrolled setting to a wider patient population a cautious approach is recommended.

Therefore, in these circumstances, it is recommended that only one dose of Sebetralstat 300mg is given and no additional dose is taken.

Are there on-going clinical studies?

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There is no on-going study of Sebetralstat in the EAMS indication.

What measures are in place to monitor and manage risks?

A risk management plan has been developed to ensure that Sebetralstat is used as safely as possible. Based on this plan, the company that makes Sebetralstat must ensure that all healthcare professionals expected to use the medicine, as well as patients, are provided with information on the medicines 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 side effects experienced by patients receiving Sebetralstat through the scheme. Safety data will be reviewed and reported to the MHRA on a regular basis by the company.

Other information about Sebetralstat – see EAMS Treatment Protocol