Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

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 medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist physicians in prescribing this unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of this promising new 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.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for healthcare professionals

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Sebetralstat 300 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg sebetralstat.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, oval shaped, biconvex tablets debossed with KalVista logo “K” on one side and “300” on the other side.

4. CLINICAL PARTICULARS

4.1 EAMS therapeutic indication

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

4.2 Posology and method of administration

Posology

The recommended dose of sebetralstat is 300 mg administered at the earliest recognition of an attack. An additional dose may be taken ifthere are no signs of improvement.

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

Special populations

Elderly population
No dose adjustment is required for patients above 65 years of age (see section 5.2).

Renal impairment
No dose adjustment is required for patients with renal impairment.

Hepatic impairment
No dose adjustment of sebetralstat is required for patients with mild or moderate hepatic impairment (Child-Pugh A or B). Use of sebetralstat in patients with severe hepatic impairment (Child-Pugh C) is not recommended.

Paediatric population
The safety and efficacy of sebetralstat in children under 12 years of age have not been established.
No data are available.

Method of administration

For oral use. The film-coated tablets can be taken with or without food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Laryngeal attacks: Following treatment of laryngeal attacks with sebetralstat, advise patients to seek immediate medical attention.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on sebetralstat

Sebetralstat is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Quinidine, a P-gp inhibitor, increased the maximum concentration (C_{max}) of sebetralstat by 18% and the AUC of sebetralstat by 14%. Sebetralstat exposure may be increased with concomitant administration of P-gp inhibitors, however no dose adjustment is required.

Eltrombopag, a BCRP inhibitor, increased the C_{max} of sebetralstat by 12%, however the AUC of sebetralstat remained unchanged. Sebetralstat peak levels may be increased with concomitant administration of BCRP inhibitors, however no dose adjustment is required.

Sebetralstat is a substrate of CYP3A4.

Itraconazole, a strong CYP3A4 inhibitor, increased the C_{max} of sebetralstat by 135% and the AUC by 420%. The moderate CYP3A4 inhibitor verapamil increased the C_{max} of sebetralstat by 76% and the AUC by 102%. Co-administration with the weak CYP3A4 inhibitor cimetidine caused no increase in the C_{max} or AUC of sebetralstat. Subjects who are taking a strong CYP3A4 inhibitors should treat a HAE attack with a single dose of 300 mg only.

Phenytoin, a strong CYP3A4 inducer, reduced the C_{max} of sebetralstat by 66% and the AUC by 83%. The moderate CYP3A4 inducer efavirenz reduced the C_{max} of sebetralstat by 63% and the AUC by 79%. Co-administration with the weak CYP3A4 modafinil reduced the C_{max} of sebetralstat by 11% and the AUC by 21%. In patients taking strong or moderate CYP3A4 inducers, it is recommended that a HAE attack is treated with a single dose of 900 mg (3 x 300 mg tablets). No dose adjustment is required when taking weak CYP3A4 inducers.

In patients with moderate hepatic impairment who are taking a strong CYP3A4 inhibitor a single dose of 300 mg is recommended when treating an HAE attack.

Effects of sebetralstat on other medicinal products

No clinical DDI studies assessing the effect of sebetralstat on other medicinal products have been performed. Given the intermittent use of sebetralstat and its rapid absorption and elimination, the potential of sebetralstat to be a precipitant of CYP- and transporter-mediated DDIs is low. In vitro data suggests possible inhibition of CYP2C9 and CYP3A4, and of transporters OATP1B3, OAT3, OCT2, MATE1, and MATE2-K and BCRP. Caution should be taken when dosing with narrow therapeutic index substrates of these enzymes and transporters.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

It is recommended that women of childbearing potential use effective, medically appropriate contraception during treatment with sebetralstat.

Pregnancy

There are no data from the use of sebetralstat in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Sebetralstat is not recommended during pregnancy.

Breast-feeding

It is unknown whether sebetralstat or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of sebetralstat and/or its metabolites in milk (see section 5.3).

A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from sebetralstat therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data regarding the effects of sebetralstat on human fertility. No effect on fertility was observed in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Sebetralstat has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of sebetralstat is based on data from the double-blind, randomised, placebo-controlled, crossover KONFIDENT trial in which 110 patients with HAE, aged 12 years and older, treated at least one attack. Patients treated each attack with either 300 mg sebetralstat, 600 mg sebetralstat or placebo. Patients ranged in age from 13 to 74 years of age; 60% were female and 40% were male; 84% were Caucasian. There were 24 patients (22%) on long-term prophylactic therapy during the trial which included lanadelumab, berotralstat, and C1-INH.

No patients discontinued study drug prematurely due to adverse reactions and there were no SAEs related to treatment. No deaths occurred in the trial.

The safety profile of sebetralstat was consistent across all subgroups of patients.

Safety data are also available from the controlled Phase 2 trial and the ongoing, open-label, long-term safety trial KONFIDENT-S. The safety profile in these trials is consistent with that seen in the KONFIDENT trial. Overall 198 patients have treated 879 HAE attacks with sebetralstat.

Tabulated list of adverse reactions

The frequency of all adverse reactions listed in the table below is defined using the following convention:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1. Summary of adverse reactions by system organ class and frequency

System Organ Class	Adverse Reaction	Frequency
Gastrointestinal disorders	Dyspepsia	Common
General disorders and administration site conditions	Fatigue	Common

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No case of overdose has been reported in clinical trials.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other haematological agents, drugs used in hereditary angioedema, ATC code: B06AC08.

Mechanism of action

Sebetralstat is a competitive, reversible inhibitor of plasma kallikrein. Plasma kallikrein is a serine protease that cleaves high molecular weight kininogen (HK) releasing bradykinin (BK) which increases vascular permeability through activation of BK receptors causing oedema. Sebetralstat inhibits the cleavage of HK to BK, preventing activation of the BK receptors and halting the progression of HAE attacks. Sebetralstat also inhibits the positive feedback mechanism of the kallikrein kinin system by plasma kallikrein, thereby reducing factor XIIa and additional plasma kallikrein generation.

Pharmacodynamic effects

Concentration-dependent inhibition of plasma kallikrein, measured as a reduction from baseline of specific enzyme activity, was demonstrated to be rapid, with near complete suppression of plasma kallikrein as early as 15 minutes after dosing in patients with HAE.

Clinical efficacy and safety

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.

There was a statistically significant faster time to the beginning of symptom relief for both dose levels compared to placebo (Table 2, Figure 1).

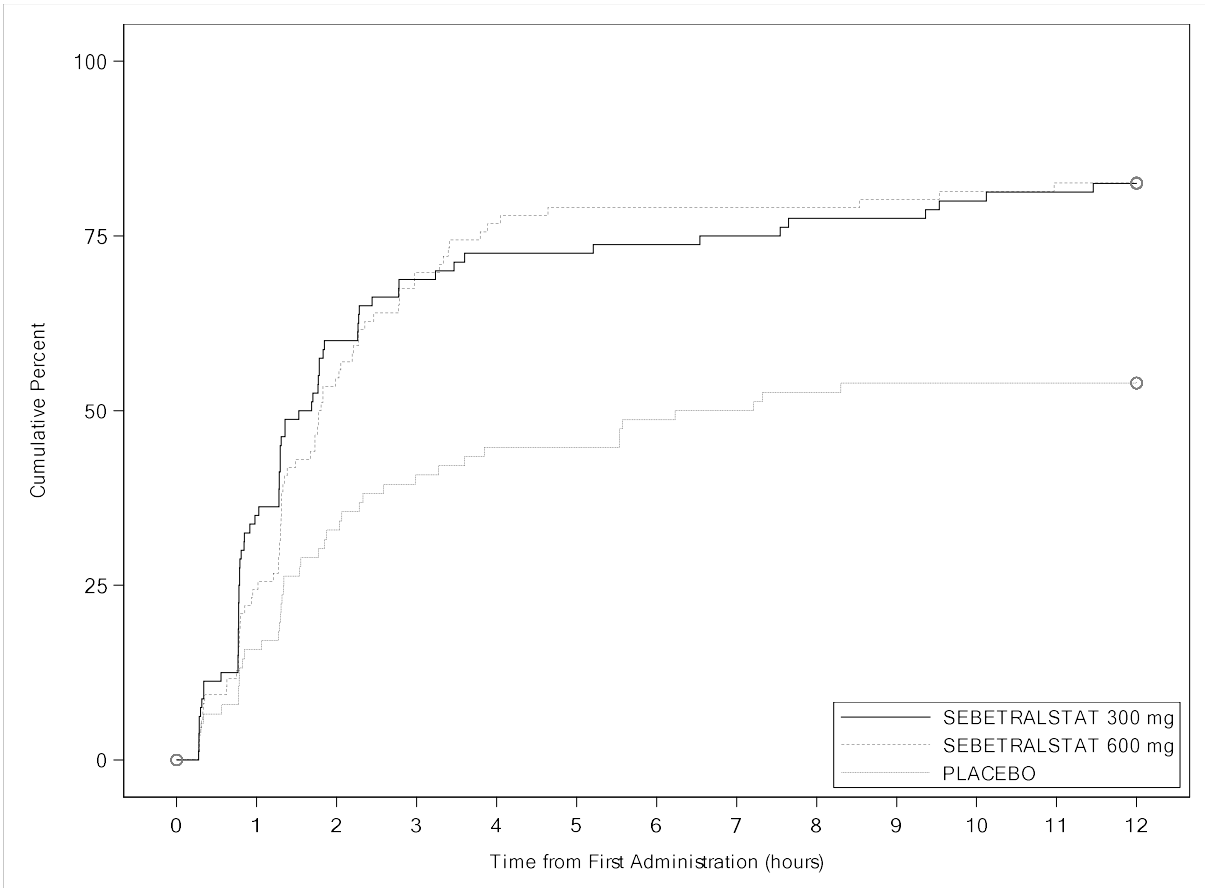
Table 2. KONFIDENT Trial - Time to beginning of symptom relief within 12 hours of dosing

	300 mg Sebetralstat	600 mg Sebetralstat	Placebo
N	87	93	84
Median (95% CI)	1.61	1.79	6.72

	(1.28, 2.27)	(1.33, 2.27)	(2.33, NE)
Adjusted p-value (sebetralstat vs. placebo)	<0.0001	0.0013	-

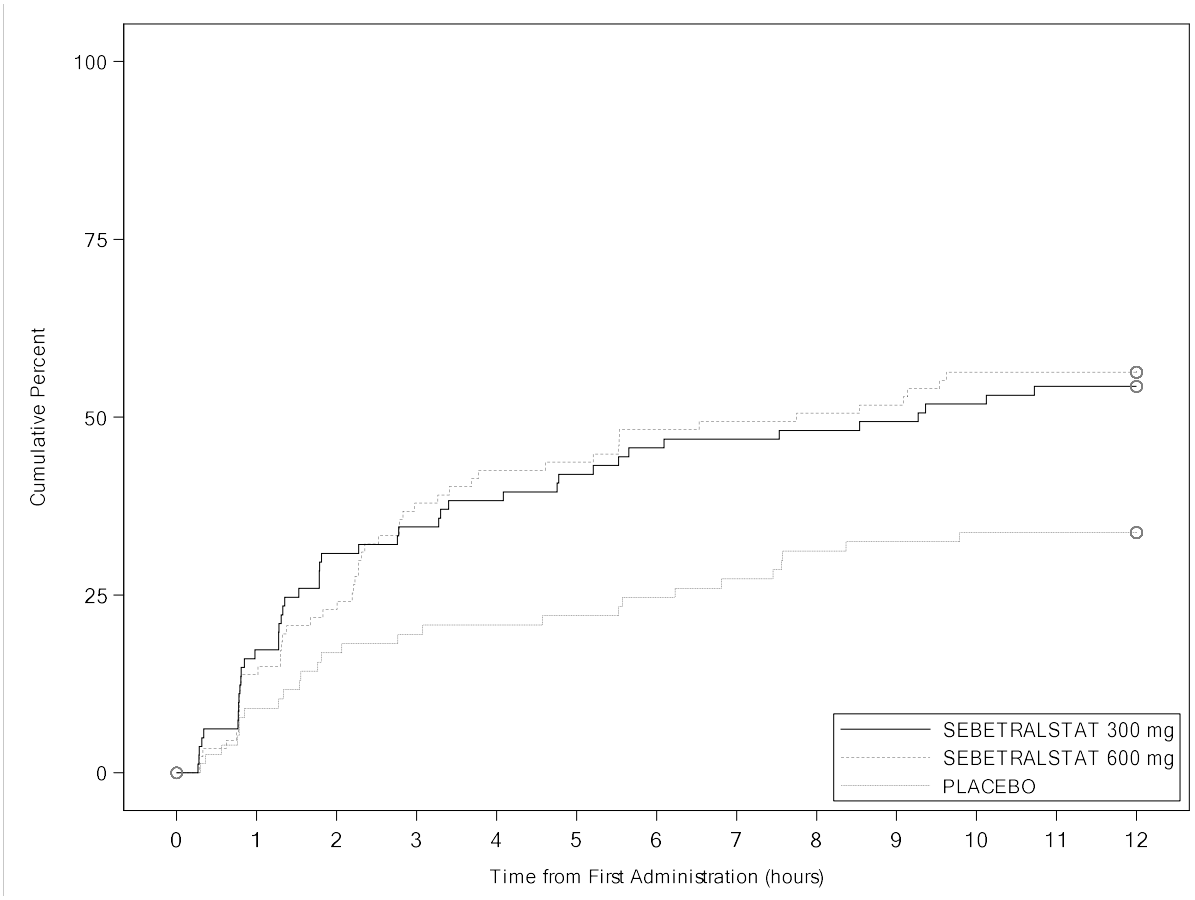
NE = not evaluable at 12 hours

Figure 1. KONFIDENT Trial – Kaplan-Meier plot for time to beginning of symptom relief within 12 hours of dosing



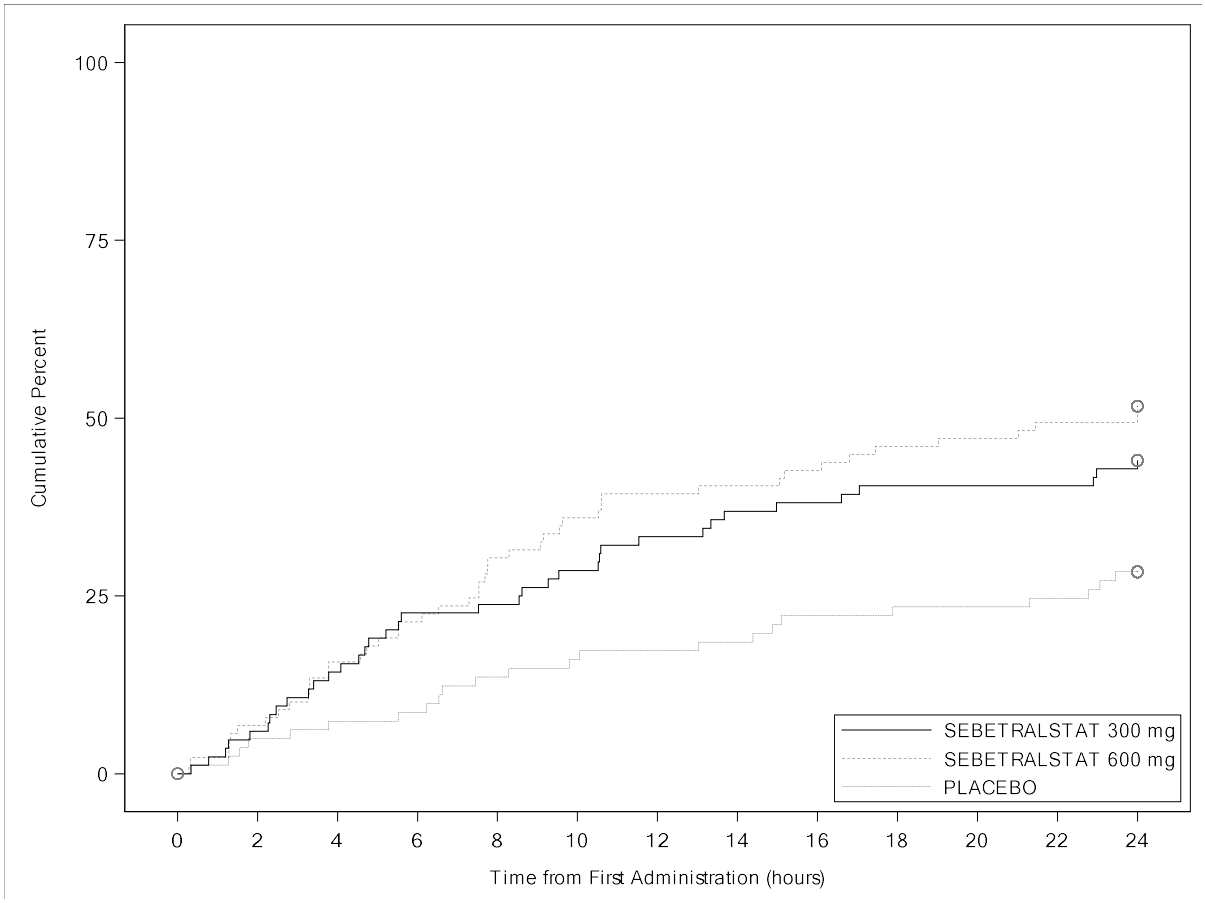
The first key secondary endpoint was time to reduction in severity on the Patient Global Impression of Severity (PGI-S) within 12 hours of dosing. There was a statistically significant faster time to reduction in severity for 300 mg sebetralstat (adjusted p=0.0036) and 600 mg sebetralstat (adjusted p=0.0032) compared to placebo (Figure 2).

Figure 2. KONFIDENT Trial - Kaplan-Meier plot for time to reduction in severity within 12 hours of dosing



The second key secondary endpoint was time to complete attack resolution defined as “none” on PGI-S. There was a statistically significant faster time to complete attack resolution for 300 mg sebetralstat (adjusted p=0.0022) and 600 mg sebetralstat (adjusted p<0.0001) compared to placebo (Figure 3).

Figure 3. KONFIDENT Trial - Kaplan-Meier plot for time to complete attack resolution within 24 hours of dosing



Treatment with sebetralstat reduced cumulative anxiety over 12 hours after dosing compared to placebo.

Assessment of primary and key secondary efficacy endpoint results in the KONFIDENT trial in all subgroups, including sex, race, age, baseline attack severity, baseline attack location, time from onset of attack to treatment, use of long-term prophylactic treatment and geography were consistent with the results in the overall population.

In the open-label KONFIDENT-S trial, patients treat multiple attacks with sebetralstat for up to 2 years. To date, 84 patients (including 12 adolescents) have treated a total of 640 attacks. The median number of attacks treated was 5 and ranged from 1-37 attacks. The median time from onset of attack to treatment was 9 minutes. For adolescent patients the median time from onset of attack to treatment was 3 minutes. The efficacy results were consistent with the results of the KONFIDENT trial (Table 2). Efficacy was maintained with repeated treatments.

In the Phase 3 trials a total of 18 laryngeal attacks have been treated with sebetralstat.

<u>Paediatric population</u>

The KONFIDENT trial included 13 paediatric patients aged 12 to <18 years of age. The safety and efficacy in paediatrics were consistent with that observed in adults.

The safety and efficacy of sebetralstat in paediatric patients aged <12 years of age have not been established.

The Medicines & Healthcare products Regulatory Agency as deferred the obligation to submit the results of studies with sebetralstat in one or more subsets of the paediatric population in the treatment of hereditary angioedema (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After a dose of 300 mg, sebetralstat was rapidly absorbed with peak plasma concentrations occurring at approximately 1 hour.

Food effect

In an evaluation of food effect, no difference in the AUC of sebetralstat was observed following a dose of 600 mg sebetralstat with a high-fat meal, there was an approximately 29% reduction in C_{max}, and median T_{max} was delayed by 2 hours.

Sebetralstat can be taken with or without food.

Distribution

Plasma protein binding in humans is approximately 77%. After a dose of 600 mg radiolabelled sebetralstat, the blood to plasma ratio of radioactivity was approximately 0.65. The geometric mean apparent volume of distribution (Vz/F) was 208 L after a dose of 300 mg.

Elimination

After a dose of 300 mg, the geometric mean elimination half-life of sebetralstat was 3.7 hours. The geometric mean apparent clearance (CL/F) was 38.5 L/h.

Metabolism
Sebetralstat is primarily metabolised by CYP3A4. After a dose of 600 mg radiolabelled sebetralstat, sebetralstat represented 64.1% of the total plasma radioactivity AUC_{0-24}, with 11 metabolites, each accounting for between 0.39% and 7.1% of the total radioactivity AUC_{0-24}. The most prevalent plasma metabolite is not pharmacologically active.

Excretion
After a dose of 600 mg radiolabelled sebetralstat to healthy male subjects, approximately 32% of radioactivity was excreted in urine and 63% was excreted in faeces. Approximately 8.7% and 12.5% of the dose was recovered in the urine and faeces, respectively, as unchanged sebetralstat. Sebetralstat is mainly eliminated by hepatic metabolism via the faeces.

Linearity/non-linearity

Across a dose range of 5 mg to 600 mg, the C_{max} of sebetralstat was proportional to dose; the AUC was greater than dose proportional, likely due to emergence of a longer terminal elimination phase at higher doses.

Special Populations

Hepatic impairment
The pharmacokinetics of 600 mg sebetralstat were studied in patients with mild and moderate hepatic impairment (Child-Pugh Class A or B). In patients with mild hepatic impairment C_{max} was increased by 7% and AUC by 16% compared to patients with normal hepatic function. In patients with moderate hepatic impairment, C_{max} was increased by 63% and AUC was increased by 100%. Physiologically-based pharmacokinetic modelling predicted that in patients with severe hepatic impairment (Child-Pugh Class C), C_{max} would increase by 36% and AUC by 280% compared to patients with normal hepatic function.

No dose adjustment is required for patients with mild or moderate hepatic impairment. Use of sebetralstat in patients with severe hepatic impairment is not recommended.

Renal impairment
Sebetralstat is not primarily renally eliminated and is not administered as a chronic treatment. Sebetralstat pharmacokinetics have not been studied in patients with renal impairment. No dose adjustment is required.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity and carcinogenic potential.

Carcinogenicity of sebetralstat was evaluated in a 26-week study in rasH2-Tg transgenic mice and a 104-week study in rats. There were no increases in malignant tumours and no evidence of carcinogenicity in either species at any dose level. Exposure at the highest doses (on an AUC basis) were 0.9 and 1.7 times the maximum recommended human dose (MRHD) in male and female mice respectively, and 34 times MRHD in rats.

An embryofoetal development study conducted in pregnant rats administered sebetralstat at exposures (on an AUC basis) 18 times the MRHD revealed no evidence of harm to the developing foetus. At higher exposures (on an AUC basis) of 72 times the MRHD, there were embryofoetal losses and a low incidence of malformations (cleft palates and ventricular septal defects). There were no effects in a rat pre-and-post natal development study, where exposure in pregnant female rats (on an AUC basis) was at least 18 times the MRHD.

An embryofoetal development study was conducted in pregnant rabbits administered sebetralstat at exposures (on an AUC basis) up to 13 times the exposure at the MRHD. Malformations were observed in all sebetralstat dose groups in this study, however, there was no clear dose response and malformations were largely consistent with those observed in historical control data, except in the high dose group. Clinical relevance is uncertain. The rabbit is not a pharmacologically relevant species.

Sebetralstathad no effects on mating or fertility in male and female rats at exposures (on an AUC basis) that were 46 times the exposure at the MRHD.

Administration of a single dose of radiolabelled sebetralstatto lactating rats resulted in similar concentrations of total radioactivity in milk and plasma, with the maximum concentration observed at 1 hour post dose. By 24 hours post dose mean levels of radioactivity in both milk and plasma were close to background.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Croscarmellose sodium
Povidone K30
Magnesium stearate

Film-coatings
Macrogol Poly(vinyl alcohol) grafted copolymer
Talc
Titanium dioxide
Glycerol monocaprylocaprate (Type 1)
Poly(vinyl alcohol)
Iron oxide yellow (E172)
Iron oxide black (E172)
Maltodextrin
Guar galactomannan
Hypromellose
Triglycerides, medium-chain

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

Tablets are packed in oPA/Al/PVC with aluminium lidding blisters.

Pack size: 6 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SCIENTIFIC OPINION HOLDER

KalVista Pharmaceuticals Ltd
Porton Science Park,
Bybrook Road,
Porton Down,
Wiltshire,
SP4 0BF, United Kingdom

8. EAMS NUMBER

46326/001

9. DATE OF SCIENTIFIC OPINION
19/03/2025

Additional information

Principle Investigator's (PI) who participated in KalVista's Phase III Open Label Extension (OLE) trial will be contacted by KalVista partner Inceptua. If the PI determines that a patient benefitted from treatment with sebetralstat in the OLE Inceptua will ask the PI to provide relevant qualifying information.

Physicians interested in enrolling a naïve patient into the EAMS will use the Inceptua IMAP portal [https://portal.inceptua.com/#/login] to submit required information and documentation.

If the physician has not previously registered with IMAP, they must first contact Inceptua [access@inceptua.com] to begin the registration process. As part of the process, the physician will need to provide relevant qualifying information, including their current medical license and their institution details via the IMAP portal.

Registered physicians will have access to program documentation including to submit the necessary essential documentation, including regulatory and/or import approval and information for each individual patient in an electronic Patient Access Form (ePAF) to request sebetralstat for that patient. Each patient request will be reviewed by KalVista for approval to enroll in the sebetralstat EAMS.

A unique anonymized identifier is assigned automatically to each patient through the IMAP portal, once the ePAF is completed. The identifier is used for all treatment orders/re-supply requests and also when

entering real-world data and Adverse Event (AE) reporting by the HCP. At this point any patient data entered into IMAP will be pseudonymized with only the HealthCare Professional (HCP) being able to link patient identity and the unique anonymized identifier.

The HCP will be notified if their patient request is approved, allowing them to submit an initial order for sebetralstat via the IMAP portal, but only once the following required documents/details have been provided:

- Regulatory and/or Import Approval;
- Confirmation of patient informed consent;
- Necessary HCP declarations within the ePAF;
- Pharmacy details for shipment of drug.

In the event that the eligibility criteria are not met for a particular patient, the request will be rejected, and the requesting physician will be notified. On occasion, it may be necessary to ask the physician to provide further information before an enrollment decision can be made.

Please see the EAMS Protocol for more information.

Contact information

Inceptua Ltd.
Vista
2 William Street
Windsor, SL4 1BA
Email: access@inceptua.com