SUMMARY OF PRODUCT CHARACTERISTICS

▼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

Ekterly 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 Therapeutic indications

Ekterly 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 Ekterly is 300 mg administered at the earliest recognition of an attack. An additional dose may be taken if needed.

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 Ekterly is required for patients with mild or moderate hepatic impairment (Child-Pugh A or B). Use of Ekterly 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.

Patients taking strong CYP3A4 inhibitors

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

Patients taking strong or moderate CYP3A4 inducers

In patients who are taking strong or moderate CYP3A4 inducers a single dose of 900 mg (3 x 300 mg tablets) is recommended when treating an HAE attack.

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 Ekterly, advise patients to seek immediate medical attention.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium free”.

Sebetralstat is an *in vitro* inhibitor of MATE1, MATE2-K and OCT2 and co-administration may raise exposure to substrates of these transporters such as metformin. Clinicians should consider monitoring blood lactate and renal function in patients who carry a higher risk for lactic acidosis.

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. In patients who are taking a strong CYP3A4 inhibitor a single dose of 300 mg is recommended when treating an HAE attack. No dose adjustment is required when taking weak or moderate CYP3A4 inhibitors.

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 an 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.

Effects of sebetralstat on other medicinal products

In vitro studies indicate that sebetralstat inhibits CYPs 2C9 and 3A4, and the transporters BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1 and MATE2-K. Clinical interaction data are not available. The potential for interaction should be considered when sebetralstat is administered to patients taking substrates of these enzymes and transporters, particularly narrow therapeutic index substrates. If possible, substrates of these drugs and transporters, should not be taken at the same time of the day as sebetralstat is used to treat an HAE attack to minimise the potential for an interaction (see section 5.2).

In vitro studies indicate that sebetralstat inhibits UGTs 1A4 and 1A9. Clinical interaction data are not available (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Ekterly in pregnant women.

Studies in pregnant rats indicate that daily sebetralstat administration was associated with embryofoetal harm at exposures higher than clinical exposures. A study in rabbits had equivocal result**s** (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Ekterly during pregnancy and in women of childbearing potential not using effective, medically appropriate contraception.

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 newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Ekterly 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 Ekterly 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

Fatigue has been reported following the use of Ekterly. This symptom may also occur as a result of an attack of HAE. Patients should be advised not to drive or use machines if they experience fatigue.

4.8 Undesirable effects

Summary of the safety profile

Ekterly has been administered to a total of 411 healthy subjects and 239 hereditary angioedema patients. In clinical studies used for registration, 1,945 HAE attacks have been treated with Ekterly.

The most common adverse reaction in HAE patients treated with Ekterly is headache (reported by 9.2% of patients). The reported events of headache were generally mild to moderate in severity, non-serious and resolved without any further intervention.

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
Nervous system disorders	Headache	Common
Gastrointestinal disorders	Dyspepsia	Common
	Nausea	Uncommon
	Abdominal pain	Uncommon
General disorders and administration site conditions	Fatigue	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Uncommon
Vascular disorders	Hot flush	Uncommon

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 Ekterly 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 Ekterly, 93 treated with 600 mg Ekterly, 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.

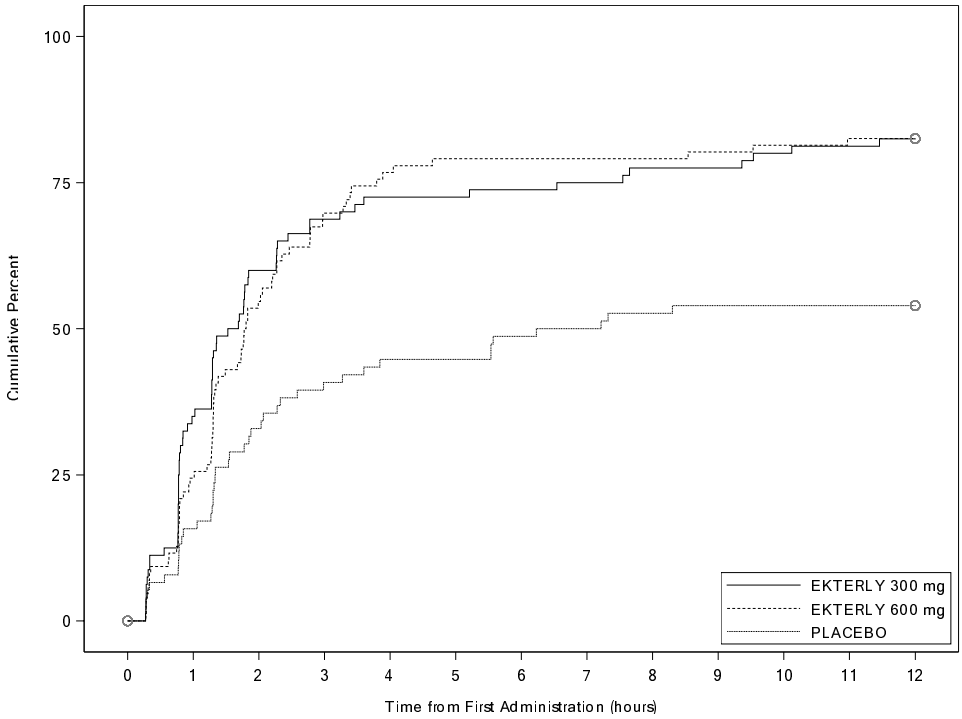
There was a statistically significant faster time to the beginning of symptom relief for 300 mg Ekterly (Bonferroni adjusted $p<0.0001$) and 600 mg Ekterly (Bonferroni adjusted $p<0.0013$) compared to placebo (Table 2, Figure 1).

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

	300 mg Ekterly	**600 mg Ekterly**	**Placebo**
N	87	93	84
Median (95% CI)	1.61 (1.28, 2.27)	1.79 (1.33, 2.27)	6.72 (2.33, NE)

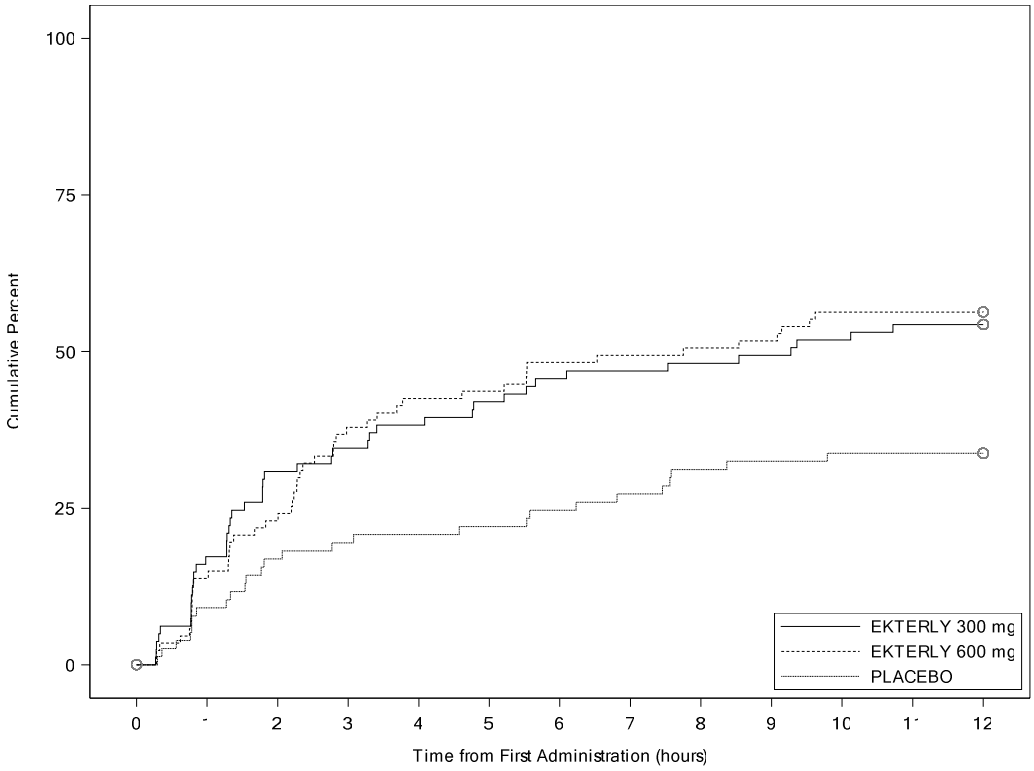
NE = not evaluable at 12 hours

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



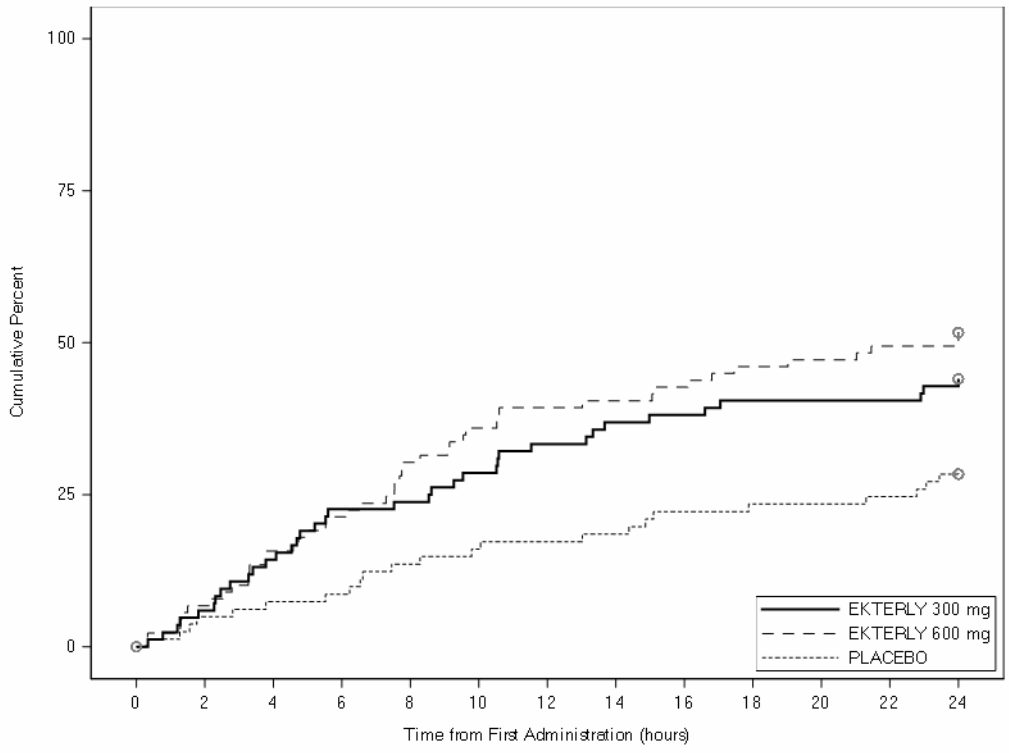
The first key secondary endpoint was time to reduction in severity on the Patient Global Impression of Severity (PGI-S) within 12 hours of dosing. There was a statistically significant faster time to reduction in severity for 300 mg Ekterly (adjusted p=0.0036) and 600 mg Ekterly (adjusted p=0.0032) compared 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 Ekterly (adjusted p=0.0022) and 600 mg Ekterly (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 Ekterly reduced cumulative anxiety over 12 hours after dosing compared to placebo.

Assessment of primary and key secondary efficacy endpoints 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 treated multiple attacks with Ekterly for up to 2 years. A total of 134 patients (including 23 adolescents) have treated 1,706 attacks. The median number of attacks treated was 8 and ranged from 1-61 attacks. The median time from onset of attack to treatment was 10 minutes. For adolescent patients the median time from onset of attack to treatment was 4 minutes. The efficacy results were consistent with the results of the KONFIDENT trial (Table 2). Efficacy was maintained with repeated treatments.

Four laryngeal HAE attacks were treated in the KONFIDENT trial (2 with 300 mg, 2 with 600 mg). In the open label KONFIDENT-S trial, 32 laryngeal attacks were treated with 600 mg. The results were similar to patients with non-laryngeal attacks with respect to time to onset of symptom relief. No events of difficulty swallowing Ekterly tablets were reported.

Paediatric population

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 Ekterly in paediatric patients aged <12 years of age have not been established. The Medicines & Healthcare products Regulatory Agency has deferred the obligation to submit the results of studies with Ekterly 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.

Ekterly 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%. (see section 4.2 and 4.5).

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.

Elderly

KONFIDENT did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients; however, age is not expected to affect exposure to Ekterly (see section 4.2).

Drug Interactions

Sebetralstat inhibited the renal/cation transporters MATE1 (IC_{50} = 8.1 µM), MATE2-K (IC_{50} = 7.8 µM) and OCT2 (IC_{50} = 5.3 µM). The effect of sebetralstat on substrates of transporters MATE1, MATE2-K and OCT2 has not been studied clinically (see section 4.4).

Weaker inhibition was observed for OAT3 (IC_{50} = 19 µM), OATP1B1 (IC_{50} = 96 µM) and OATP1B3 (IC_{50} = 60 µM). Inhibition of BCRP was weak (IC_{50} ≈ 82 µM). Sebetralstat directly inhibited CYP2C9 (IC_{50} = 30 µM) and CYP3A4 (IC_{50} ≈ 120 µM, testosterone/midazolam substrates) but showed no time-dependent inhibition of any CYP isoform. It was a weak inhibitor of UGT1A4 and UGT1A9 (IC_{50} ≈ 58–31 µM).

Clinical drug–interaction data

In dedicated DDI studies (KVD900-106 and KVD900-112) with healthy volunteers:

- Strong CYP3A4/P-gp inhibition (itraconazole 200 mg qd, 6 days) increased sebetralstat C_{max} by 135% and AUC by 420%.
- Moderate CYP3A4 inhibition (verapamil 240 mg qd, 5 days) increased C_{max} by 76% and AUC by 102%.
- Strong BCRP inhibition (eltrombopag 75 mg qd, 8 days) raised C_{max} by 12% with no AUC change.
- Strong CYP3A4 induction (phenytoin 100 mg tid, 14 days) reduced C_{max} and AUC by 66% and 83%, respectively; moderate induction (efavirenz 600 mg qd, 14 days) reduced C_{max} and AUC by 63% and 79% respectively.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated 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 unbound plasma AUC basis) were 0.2 and 0.4 times the maximum recommended human dose (MRHD), in male and female mice respectively and 5.7 times MRHD in rats.

An embryofoetal development study conducted in pregnant rats administered sebetralstat daily at exposures (on an unbound plasma AUC basis) 3 times the MRHD revealed no evidence of harm to the developing foetus. At higher exposures (on an unbound plasma AUC basis) of 12 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 unbound plasma AUC basis) was at least 3 times the MRHD.

An embryofoetal development study with daily dosing was conducted in pregnant rabbits administered exposures (on an unbound plasma AUC basis) up to 6.8 times the MRHD. A low incidence of major malformations was observed in all sebetralstat dose groups. However, there was no dose response and all malformations had been observed in historical control data. Therefore, the association with sebetralstat is equivocal and clinical relevance uncertain. The rabbit is not a pharmacologically relevant species.

Sebetralstat had no effects on mating or fertility in male and female rats at exposures (on an unbound plasma AUC basis) that were 7.7 times the exposure at the MRHD.

Administration of a single dose of radiolabelled sebetralstat to 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 (1 tablet per blister).

Pack size: 4 or 6 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

KalVista Pharmaceuticals Ltd

Porton Science Park,

Bybrook Road,

Porton Down,

Wiltshire,

SP4 0BF, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 46326/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/07/2025

10 DATE OF REVISION OF THE TEXT

15/07/2025