ANNEX I

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 of sebetralstat.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, oval shaped (approximately 15 mm x 9 mm), 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 symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.

4.2 Posology and method of administration

The decision to initiate treatment with oral sebetralstat should be made by a healthcare professional experienced in the management of patients with HAE.

Posology

Adults and adolescents aged 12 years and older
The recommended dose is one 300 mg tablet of Ekterly administered at the earliest recognition of an attack. A second dose may be taken 3 hours after the first dose if response is inadequate, or if symptoms worsen or recur. No more than two doses should be administered in a 24 hour period.

Patients with normal C1-INH HAE (nC1 INH)
Consideration should be given to discontinuing treatment in patients with normal C1-INH HAE (nC1-INH) if a clinical response is not observed (see sections 4.4 and 5.1).

Elderly
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 (see section 5.2).

Hepatic impairment
No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh A or B).

Use in patients with severe hepatic impairment (Child-Pugh C) is not recommended (see section 5.2).

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 (see section 4.5).

Patients taking CYP3A4 inducers
No dose adjustment is required when taking weak CYP3A4 inducers.

In patients taking moderate or strong CYP3A4 inducers a single dose of 900 mg (3 x 300 mg tablets) is recommended when treating an HAE attack (see section 4.5).

Paediatric population

Safety and efficacy in children less than 12 years have not been established.
No data are available.

Method of administration

Ekterly is intended 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, patients should seek immediate medical attention. If laryngeal attack symptoms worsen after treatment, patients should be managed in an appropriate medical institution.

Normal C1 esterase inhibitor (nC1-INH)

There are no data available on the use of Ekterly in HAE patients with nC1-INH.

Some subcategories of nC1-INH HAE may not respond to treatment due to alternative pathways that do not include plasma kallikrein activation. It is recommended to perform genetic testing, if available, according to the current HAE guidelines, and to discontinue the treatment if clinical response is not observed (see sections 4.2 and 5.1).

QT prolongation

In a clinical trial dedicated to the assessment of cardiac parameters in healthy subjects, a potential of sebetralstat to extend the QT interval was detected but only at high concentrations that are not expected to be reached with the recommended dose. There are no data available for the use of sebetralstat in patients with independent risk factors for QT prolongation such as known pre-existing QT prolongation (either acquired or congenital), electrolyte disturbances, hepatic impairment, concomitant use of drugs interacting with the metabolism of sebetralstat or concomitant use of other medicinal products known to prolong the QT interval. Caution is warranted on the risk of QT prolongation in these patients, especially in patients who have more than one risk factor (see section 5.1).

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on sebetralstat

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 change in the exposure of sebetralstat. No dose adjustment is required when taking 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 inducer modafinil caused no clinically relevant change in the exposure of sebetralstat. No dose adjustment is required when taking weak CYP3A4 inducers.

In patients taking strong or moderate CYP3A4 inducers (e.g. rifampicin, efavirenz, carbamazepine, phenytoin, phenobarbital), it is recommended that an HAE attack is treated with a dose of 900 mg (3 x 300 mg tablets).

In patients with moderate hepatic impairment who are taking a strong CYP3A4 inhibitor (e.g. erythromycin, clarithromycin, itraconazole, ketoconazole, ritonavir) a single dose of 300 mg is recommended when treating an HAE attack.

Gastric Acid Reducing Agents
No dedicated *in vivo* drug-drug interaction (DDI) study with gastric acid reducing agents was performed. Thus, the effect of gastric acid reducing agents on the pharmacokinetics of sebetralstat is unknown. Caution should be used when co-administering Ekterly with gastric pH modifying agents such as antacids, proton-pump inhibitors, and histamine 2 receptor antagonists.

Effects of sebetralstat on other medicinal products

No clinical DDI studies assessing the effect of sebetralstat on other medicinal products have been performed.

In vitro data suggest that sebetralstat may inhibit CYP2C9, UGT1A4 and UGT1A9, and transporters OCT2, OATP1B3, MATE1, and MATE2-K. The clinical relevance of these findings is currently unknown. Co-administration of sebetralstat with substrates of these enzymes and transporters which have a narrow therapeutic index (e.g., warfarin, mycophenolic acid, cyclosporine, tacrolimus) should be avoided unless clinically warranted given the risk of increased pharmacokinetic exposure of these co-administered drugs and thus of toxicity. If co-administration is unavoidable, close clinical monitoring is recommended where feasible.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception during treatment with Ekterly and for a period of 24 hours after the last dose.

Pregnancy

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

Ekterly should be used during pregnancy only if the potential benefit justifies the potential risk for the fetus (e.g. for treatment of potentially life-threatening laryngeal attacks).

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/abstain from Ekterly therapy, or to discontinue breast-feeding for 24 hours after taking Ekterly, 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

Ekterly has minor influence on the ability to drive and use machines.

Dizziness 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 feel dizzy.

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 trials used for registration, 1945 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 disorder	Headache	Common
	Dizziness	Common
Gastrointestinal disorders	Vomiting	Common
	Nausea	Common
	Abdominal pain*	Common
	Diarrhoea	Common
Musculoskeletal and connective tissue disorders	Back pain	Common
Vascular disorders	Hot Flush	Common

* Includes events of abdominal pain and abdominal pain upper.

Paediatric population

In 32 adolescent patients aged 12 to < 18 years old, a total of 390 HAE attacks have been treated with sebetralstat. The safety profile was similar to that observed in adults.

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 national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported in clinical trials. There is no available information to identify potential signs and symptoms of overdose. If symptoms should occur, symptomatic treatment is recommended. There is no antidote available.

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 (PKa). By inhibiting PKa, sebetralstat blocks the cleavage of high molecular weight kininogen (HK) and the subsequent generation of bradykinin (BK), thereby halting HAE attack progression which is associated with increased vascular permeability and oedema formation. Sebetralstat also suppresses the activation of positive feedback mechanism of the kallikrein-kinin system (KKS), thereby reducing factor XIIa (FXIIa) and additional PKa production.

Clinical efficacy and safety

KONFIDENT trial

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

A total of 110 patients treated 264 attacks. The median age of the patients was 39.5 years and ranged from 13 to 74 years. This notably included 13 [11.8%] adolescents and only 4 [3.6%] elderly patients. Patients with HAE type 1 (101 patients [91.8%]) and type 2 (9 patients [8.2%]) were represented in the trial. Patients entered the trial either taking conventional on-demand treatment (86 [78.2%]) or long-term prophylactic treatment (24 [21.8%]). The baseline characteristics of the treated attacks included all attack severities (113 [42.8%] mild, 102 [38.6%] moderate, 38 [14.4%] severe and 7 [2.7%] very severe) and all anatomic locations (142 [53.8%] subcutaneous, 120 [45.5%] mucosal (of which 8 [3%] were laryngeal)).

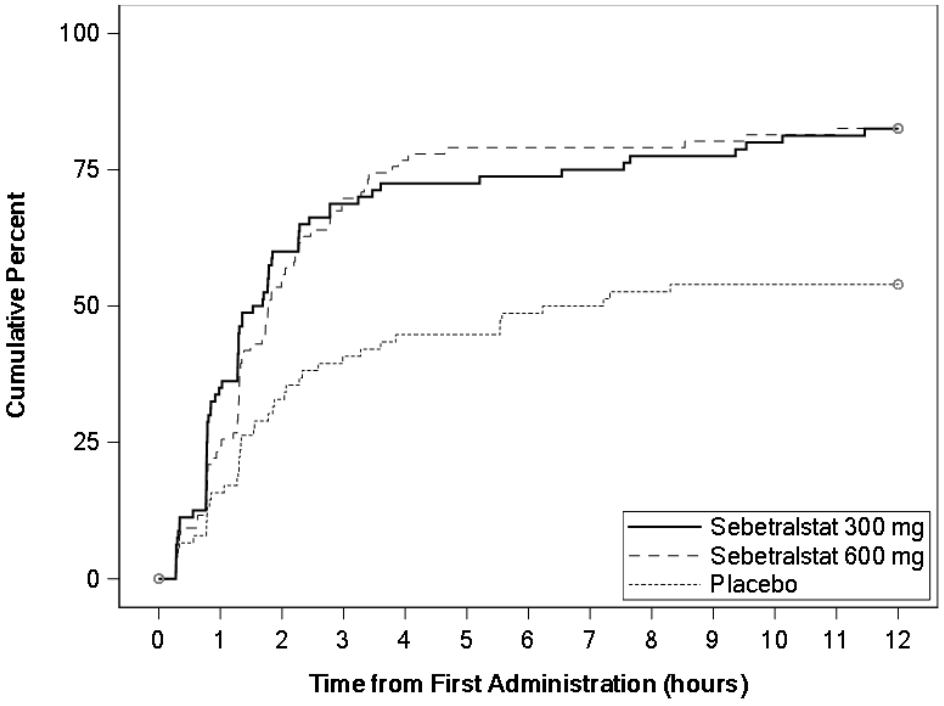
The median time to treatment (IQR) was 41 (6 to 140) minutes.

Of the 264 treated attacks, 87 were treated with 300 mg sebetralstat, 93 were treated with 600 mg sebetralstat, and 84 were treated with placebo. Following treatment of each attack, after at least 3 hours, an additional dose could be taken as determined by the patient if needed based on symptoms.

The primary efficacy endpoint was the time to beginning of symptom relief, defined as at least "a little better" (two time points in a row) within 12 hours of the first sebetralstat administration, as assessed using 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 of at least "a little better" two timepoints in a row on the PGI-C within 12 hours.

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

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

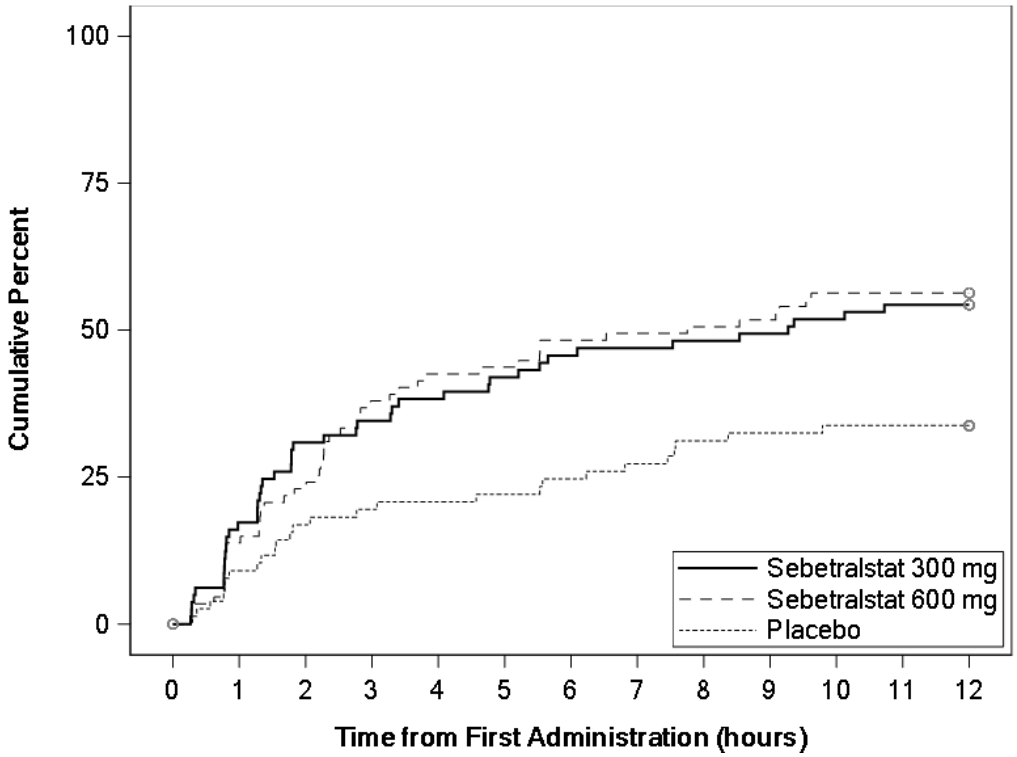


The proportions of patients who took a second dose within 12 hours were 29.9% and 37.6% for 300 mg sebetralstat and 600 mg sebetralstat respectively, which was lower than placebo, 48.8%. The proportion of patients who achieved the primary endpoint without a second administration or before a second administration of 300 mg sebetralstat or 600 mg sebetralstat was 93.9% and 95.8%, respectively.

The first key secondary endpoint was the time to first incidence of decrease in severity from baseline (two time points in a row) within 12 hours of the first sebetralstat administration on the Patient Global Impression of Severity (PGI-S). The PGI-S required patients to assess their attack symptoms using a five-point scale ("none" to "very severe"). To achieve the first key secondary endpoint, a patient had to report a positive and sustained reduction of at least one step on the PGI-S within 12 hours.

There was a statistically significant faster time to reduction in severity for 300 mg sebetralstat (Bonferroni adjusted p = 0.0036) and 600 mg sebetralstat (Bonferroni adjusted p = 0.0032) compared to placebo (Figure 2).

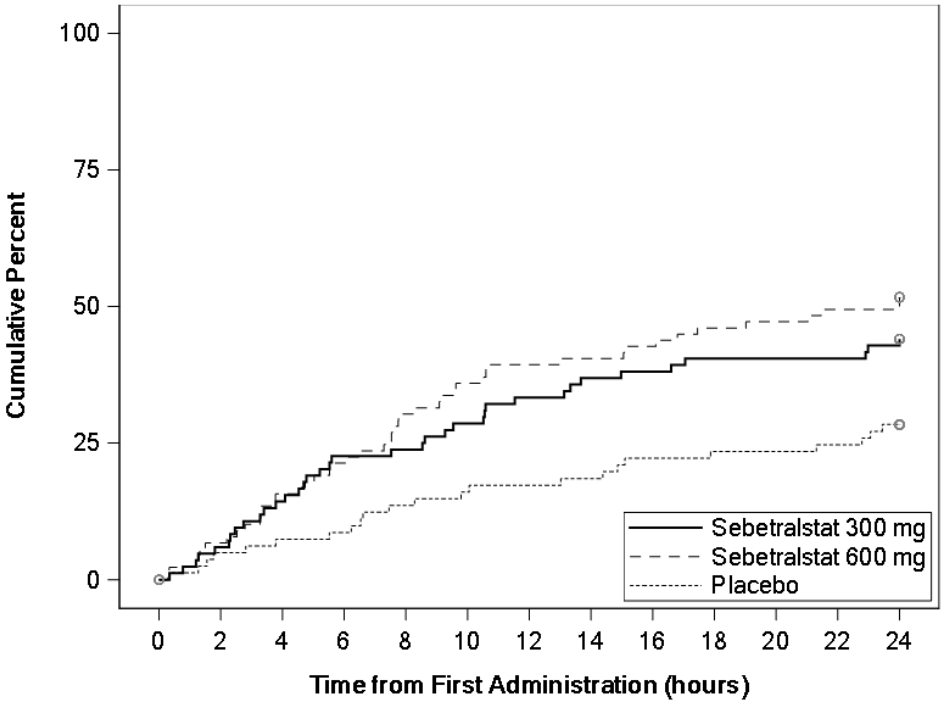
Figure 2. KONFIDENT trial - Kaplan-Meier plot for time to reduction in severity within 12 hours of dosing



The second key secondary endpoint was time to complete attack resolution defined on the PGI-S within 24 hours of dosing. To achieve the second key secondary endpoint, a patient had to report "none" on PGI-S within 24 hours.

There was a statistically significant faster time to complete attack resolution for 300 mg sebetralstat (Bonferroni adjusted p = 0.0022) and 600 mg sebetralstat (Bonferroni 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



Assessment of primary and key secondary efficacy endpoint results in the KONFIDENT trial in all predefined subgroups, including use of on-demand treatment only or long-term prophylactic treatment were consistent with the results in the overall population.

KONFIDENT-S trial

In the open-label KONFIDENT-S trial, patients treated multiple attacks with 600 mg sebetralstat for up to 2 years. A total of 134 patients (including 23 adolescents) have treated 1706 attacks. The median number of attacks treated by patients was 8 and ranged from 1-61 attacks. The median number of attacks treated ranged from 0 to 2 attacks per month. 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. Efficacy was maintained with repeated treatments.

Laryngeal HAE attacks

A total of 36 laryngeal attacks have been treated in clinical trials.
In the KONFIDENT trial, 4 laryngeal HAE attacks were treated (2 with 300 mg sebetralstat and 2 with 600 mg sebetralstat). In the open label KONFIDENT-S trial, 32 laryngeal attacks were treated with 600 mg sebetralstat. 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.

Normal C1-INH HAE population

There are no data available on the use of Ekterly in HAE patients with nC1-INH (see sections 4.2 and 4.4).

Cardiac Electrophysiology

In the clinical trial dedicated to the assessment of cardiac electrophysiology, a potential of sebetralstat to extend the QT interval was detected but only at high concentrations that are not expected to be reached with the recommended dose. The largest mean increase in QTc interval was 10.4 ms (upper confidence interval = 15.3 ms) after administration of Ekterly (5 times the maximum recommended

dose) in healthy subjects. The increase in the QTc interval was concentration dependent (see section 4.4).

Paediatric population

The European Medicines 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 with a high-fat meal. There was an approximately 29% reduction in C_{max}, and median T_{max} was delayed by 2 hours. Ekterly was administered without regard to food in clinical safety and efficacy trials, and 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 *in vitro*. Sebetralstat is an *in vitro* substrate of P-glycoprotein and BCRP. 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.

Sebetralstat is an *in vitro* inhibitor of CYPs 3A4 and 2C9, and of the transporters OAT3, OCT2, MATE1, MATE2-K, OATP1B1 and OATP1B3.

Sebetralstat is an *in vitro* inducer of CYP3A4. Given its intermittent use and its rapid absorption and elimination, the risk of CYP3A4 induction is considered not to be clinically significant.

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%. 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 (see sections 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 (see section 4.2).

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 (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship(s)

Concentration-dependent inhibition of plasma kallikrein, measured as a reduction from baseline of specific enzyme activity, was demonstrated to be rapid, with near complete (≥ 95%) suppression of plasma kallikrein as early as 15 minutes after dosing with 300 mg Ekterly in patients with HAE.

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.

In a fertility study conducted in rats, there was no effect on mating or fertility at any dose level while an increase in preimplantation loss was observed at the high dose level of 600 mg/kg/day (7.7 times human exposure at the MRHD based on unbound AUC levels). Embryofetal development studies were conducted in rats and rabbits. In rats, sebetralstat and/or its metabolites was shown to cross the placenta; malformations (cleft palate, ventricular septal defect) and embryofetal lethality were reported at 600 mg/kg/day (12 times human exposure at the MRHD based on unbound AUC levels); the no observed adverse effect level for embryofetal development was 300 mg/kg/day (3.0-times human exposure at the MRHD based on unbound AUC levels). In rabbits, no malformations or embryo-fetal lethality were observed at doses up to 300 mg/kg/day (6.8-times human exposure at the MRHD based on unbound AUC levels); potential developmental effects associated with PKa inhibition may not have been fully captured in rabbits due to interspecies difference in pharmacological activity of sebetralstat. There were no adverse developmental effects in a rat pre- and-post natal development study at doses up to 450 mg/kg/day.

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.

Environmental risk assessment studies have shown that sebetralstat has the potential to accumulate and may persist in some aquatic sediment systems.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Povidone K30 (E1201)
Magnesium stearate (E470b)

Film-coatings

Macrogol poly(vinyl alcohol) grafted copolymer (E1209)
Talc (E553b)
Titanium dioxide (E171)
Glycerol monocaprylocaprate (Type 1) (E471)
Poly(vinyl alcohol) (E1203)
Iron oxide yellow (E172)
Iron oxide black (E172)
Maltodextrin (E1400)
Guar galactomannan (E412)
Hypromellose (E464)
Triglycerides, medium-chain

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

oPA/Al/PVC with aluminium lidding blisters (1 film-coated tablet per blister).

The film-coated tablets are packed in a blister encased in a child-resistant cardboard wallet. The wallets are contained in a cardboard box.

Pack size: 4 or 6 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

KalVista Pharmaceuticals (Ireland) Ltd.
Magennis Place,
Block C,
Dublin 2,
D02 FK76,
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1975/001
EU/1/25/1975/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Almac Pharma Services Limited
Seagoe Industrial Estate
Portadown
Craigavon
Northern Ireland
BT63 5UA
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ekterly 300 mg film-coated tablets
sebetralstat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg sebetralstat.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

4 film-coated tablets
6 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KalVista Pharmaceuticals (Ireland) Ltd.
Magennis Place,
Block C,
Dublin 2,
D02 FK76
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

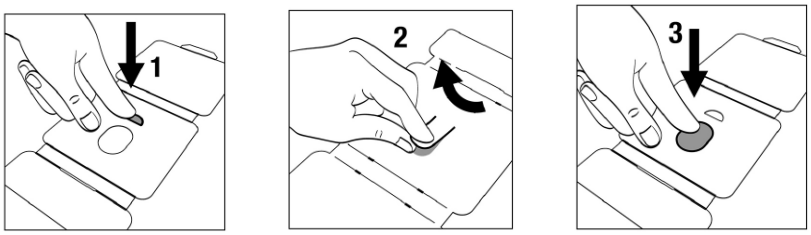
EU/1/25/1975/001 4 film-coated tablets
EU/1/25/1975/002 6 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE



1. Push through half circle.
2. Flip over and peel back tab.
3. Push pill through foil.

16. INFORMATION IN BRAILLE

Ekterly

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CHILD RESISTANT WALLET

1. NAME OF THE MEDICINAL PRODUCT

Ekterly 300 mg film-coated tablets
sebetralstat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg sebetralstat.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KalVista Pharmaceuticals [Logo]

12. MARKETING AUTHORISATION NUMBER(S)

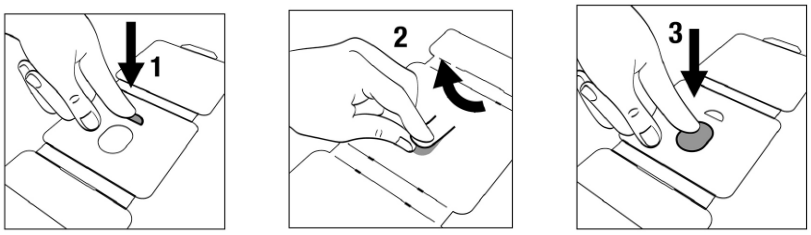
EU/1/25/1975/001 4 film-coated tablets
EU/1/25/1975/002 6 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE



1. Push through half circle.
2. Flip over and peel back tab.
3. Push pill through foil.

16. INFORMATION IN BRAILLE

[Braille will appear on the outer carton]

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ekterly 300 mg film-coated tablets
sebetralstat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KalVista Pharmaceuticals [Logo]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ekterly 300 mg film-coated tablets
sebetralstat

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ekterly is and what it is used for

Ekterly is a medicine that contains the active substance sebetralstat.

Ekterly is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.

HAE often runs in families, but some people may not have a family history. Three types of HAE are known, based on the type of genetic defect and its effect on a protein that circulates in your blood, named C1 esterase inhibitor (C1-INH). A person can have low levels of C1-INH in the body (type 1 HAE), poorly functioning C1-INH (type 2 HAE), or HAE with normal C1 esterase inhibitor (HAE nC1-INH). The last type is extremely rare. All three types can cause attacks and produce the same clinical symptoms of localized swelling and pain in different parts of the body including:
- hands and feet
- face, eyelids, lips or tongue
- voice-box (larynx), which may make breathing difficult
- genitals

When C1-INH does not work properly this leads to too much quantity of the enzyme ‘plasma kallikrein’, which in turn increases the levels of ‘bradykinin’ in your bloodstream. Overproduction of bradykinin causes swelling and inflammation.

The active substance in Ekterly, sebetralstat, works by blocking the activity of plasma kallikrein and helps reduce the levels of bradykinin. When taken at the start of or during an attack, this will keep the attack from progressing and stop the swelling and pain.

2. What you need to know before you take Ekterly

Do not take Ekterly
- if you are allergic to sebetralstat or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Ekterly if you:
- have moderate or severely reduced liver function which could increase blood levels of sebetralstat
- are at risk of a certain heartbeat abnormality, known as QT prolongation, or take a medication known to prolong the QT interval.

After taking Ekterly for a laryngeal attack (affecting the voice box) it is important **to seek immediate medical attention particularly if laryngeal attack symptoms worsen after treatment.**

Hereditary angiodema with normal C1 inhibitor may not respond to treatment with Ekterly.
Talk to your doctor if you have any concerns about this medicine.

Children
Ekterly is not recommended in children less than 12 years. This is because it has not been studied in this age group.

Other medicines and Ekterly
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because some other medicines can affect the way Ekterly works.

In particular, tell your doctor or pharmacist if you are taking the following medicines.
- These medicines may increase the levels of Ekterly in the blood and therefore increase the risk of side effects:
    - antibiotic medicines (e.g. erythromycin, clarithromycin)
    - some medicines for fungal infections (e.g. itraconazole, ketoconazole)
    - antiviral medicines (e.g. ritonavir)
- These medicines may decrease the levels of Ekterly in the blood and therefore may need a dose adjustment:
    - antibiotic medicines (e.g. rifampicin)
    - antiviral medicines (e.g. efavirenz)
    - some medicines used for epilepsy (e.g. carbamazepine, phenytoin, phenobarbital).

If you are not sure, talk to your doctor or pharmacist before taking Ekterly.

Ekterly with food and drink
This medicine can be taken with or without food (see section 3).

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. There is limited information on the safety of Ekterly used during pregnancy and breast-feeding. As a precautionary measure, it is preferable to avoid the use of Ekterly during pregnancy and to avoid breast-feeding for 24 hours after taking Ekterly. Your doctor will discuss the benefits and risks of taking Ekterly during pregnancy and breast-feeding with you.

Driving and using machines
Do not drive or use machines if you feel dizzy as a result of your HAE attack or after using Ekterly.

Ekterly contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Ekterly

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one 300 mg tablet of Ekterly which must be taken at the earliest sign that you are having an attack. An additional dose of one 300 mg tablet of Ekterly may be taken 3 hours after the first dose if symptoms persist. No more than two 300 mg tablets of Ekterly should be taken in 24 hours.

Swallow the tablet whole with some water, if required. The tablet can be taken with or without food.

Your doctor will prescribe only taking a single 300 mg tablet of Ekterly when treating an attack if you have problems with your liver (moderately reduced liver function) **and are also** taking medicines known as strong CYP3A4 inhibitors such as itraconazole which is used to treat fungal infections.

If you are taking medicines known as strong or moderate CYP3A4 inducers such as phenytoin (used to treat epilepsy) or efavirenz (an anti-viral medicine) your doctor will prescribe three 300 mg tablets of Ekterly to be taken together at the same time when treating an attack.

If you take more Ekterly than you should
Tell your doctor immediately if you have taken too many Ekterly tablets.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common side effects (may affect up to 1 in 10 people):
- Headache
- Vomiting
- Feeling sick (nausea)
- Abdominal pain
- Dizziness
- Back pain
- Hot flush
- Diarrhoea

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ekterly

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister wallet after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ekterly contains
- The active substance is sebetralstat.
- The other ingredients are:
  Tablet core: microcrystalline cellulose; croscarmellose sodium; povidone K30; magnesium stearate (see section 2 “Ekterly contains sodium”).
  Film-coatings: macrogol poly(vinyl alcohol) grafted copolymer, talc; titanium dioxide (E171), glycerol monocaprylocaprate (Type 1), poly(vinyl alcohol), iron oxide yellow (E172), iron oxide black (E172), maltodextrin, guar galactomannan, hypromellose, triglycerides, medium chain.

What Ekterly looks like and contents of the pack
Ekterly 300 mg film-coated tablets are yellow, oval (approximately 15 mm x 9 mm), biconvex tablets debossed with KalVista logo “K” on one side and “300” on the other side. The film-coated tablets are packed in a blister encased in a child-resistant cardboard wallet. The wallets are contained in a cardboard box. Please see the pack for opening instructions. The pack contains 4 or 6 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
KalVista Pharmaceuticals (Ireland) Ltd.,
Magennis Place,
Block C,
Dublin 2,
D02 FK76,
Ireland

Manufacturer:
Almac Pharma Services Limited
Seagoe Industrial Estate
Portadown
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BT63 5UA
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.