swissmedic

Date: 25 November 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Ekterly

International non-proprietary name: sebetralstat

Pharmaceutical form:	film-coated tablets
Dosage strength(s):	300 mg
Route(s) of administration:	oral
Marketing authorisation holder:	KalVista Pharmaceuticals
Marketing authorisation no.:	69540
Decision and decision date:	approved on 17 September 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, definitions, abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HAE	Hereditary angioedema
HC	Health Canada
HPLC	High-performance liquid chromatography
HSA	Health Sciences Authority (Singapore)
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
MHRA	UK Medicines & Healthcare products Regulatory Agency
Min	Minimum
MRHD	Maximum recommended human dose
NAS	New active substance
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SMC	Swissmedic (Switzerland)
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration (Australia)
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for sebetralstat in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 13 November 2023.

Work-sharing procedure
The applicant requested a work-sharing procedure with Switzerland, the UK, Singapore, and Australia (SMC, MHRA, HSA, and TGA).
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), and Swissmedic – and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

Treatment of attacks of hereditary angioedema in adult and adolescent patients (aged 12 years and older).

2.2.2 Approved indication

Ekterly is approved for the treatment of acute attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

2.2.3 Requested dosage

Summary of the requested standard dosage:
300 mg, at the first sign of an attack. If necessary, another dose can be taken.

Can be taken with or without food.

Patients with liver impairment

Mild to moderate liver dysfunction (Child-Pugh class A or B): no dose adjustment required

Severe liver dysfunction (Child-Pugh class C): use not recommended.

Patients with renal impairment

Patients with renal impairment: no dose adjustment required.

Elderly patients

Patients over 65 years of age: no dose adjustment required.

Children and adolescents

Safety and efficacy in children under 12 years of age have not been established. No data available.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	26 September 2024
Formal objection	1 October 2024
Response to formal objection	9 October 2024
Formal control completed	30 October 2024
List of Questions (LoQ)	28 February 2025
Response to LoQ	23 April 2025
2nd List of Questions (LoQ)	12 June 2025
Response to 2nd LoQ	26 June 2025
Preliminary decision	24 July 2025
Response to preliminary decision	25 August 2025
Final decision	17 September 2025
Decision	approval

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority UK Medicines & Healthcare products Regulatory Agency (MHRA) (see section 2.1 Applicant's request / Work-sharing procedure).

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority UK Medicines & Healthcare products Regulatory Agency (MHRA) (see section 2.1 Applicant's request / Work-sharing procedure).

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority UK Medicines & Healthcare products Regulatory Agency (MHRA) (see section 2.1 Applicant's request / Work-sharing procedure).

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Ekterly, film-coated tablets was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼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. For information on reporting side effects, see "Undesirable effects" section.

Ekterly

Composition

Active substances

Sebetralstat

Excipients

Tablet core: Microcrystalline cellulose, Croscarmellose sodium (equivalent to 2.3 mg sodium), Povidone K30, Magnesium stearate.

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.

Pharmaceutical form and active substance quantity per unit

Film-coated tablet.

Each film-coated tablet contains 300 mg sebetralstat.

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

Indications/Uses

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

Dosage/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 dosage instructions

Patients with hepatic disorders

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 (see Pharmacokinetics Section).

Patients with renal disorders

No dose adjustment is required for patients with renal impairment (see Pharmacokinetics Section).

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 a strong or moderate CYP3A4 inducer a single dose of 900 mg (3 x 300 mg tablets) is recommended when treating an HAE attack.

Elderly patients

Only limited data from a total of 10 participants 65 years and older are available (2 treated with sebetralstat 300 mg and 8 treated with sebetralstat 600 mg). These data suggests no dose adjustment is necessary in this population (see section “Pharmacokinetics”).

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 on an empty stomach or with food.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section “Composition’ under “Excipients”.

Warnings and precautions

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

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say it is 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 (see Interactions Section).

Interactions

Effects of other medicinal products on the pharmacokinetics of sebetralstat

Sebetralstat is mainly metabolized by CYP3A4 (see section "Pharmacokinetics").

Clinical interaction studies were conducted to assess the effect of strong, moderate and weak CYP3A4 inhibitors and CYP3A4 inducers on the pharmacokinetics of sebetralstat. The results of these studies are described below and presented in Table 1, which shows the geometric mean ratios (GMR) for the pharmacokinetic parameters during administration with/without concomitant medication with 90% confidence intervals (CI).

CYP3A4 inhibitors

Itraconazole, a strong CYP3A4 inhibitor, increased the C_{max} of a dose of 600 mg sebetralstat by 135% and the AUC by 420%. The moderate CYP3A inhibitor verapamil increased the C_{max} of a dose of 600 mg sebetralstat by 76% and the AUC by 102%. Concomitant use with the weak CYP3A4 inhibitor cimetidine did not cause an increase in the C_{max} or AUC of a dose of 600 mg sebetralstat.

In patients using a strong CYP3A4 inhibitor (e.g., clarithromycin, itraconazole, ketoconazole, ritonavir), a single dose of 300 mg is recommended to treat an HAE attack. No dose adjustment is required when taking weak or moderate CYP3A4 inhibitors.

CYP3A4 inducers

Phenytoin, a strong CYP3A4 inducer, decreased the C_{max} of a dose of 600 mg sebetralstat by 66% and the AUC by 83%. The moderate CYP3A4 inducer efavirenz reduced the C_{max} of a dose of 600 mg sebetralstat by 63% and the AUC by 79%. Concomitant use with modafinil, which is a weak CYP3A4 inducer, reduced the C_{max} of a dose of 600 mg sebetralstat by 11% and the AUC by 21%.

In patients using strong or moderate CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz), it is recommended that an HAE attack be treated with a single dose of 900 mg (3 x 300 mg tablets). No dose adjustment is required when weak CYP3A4 inducers are used concomitantly.

Table 1. Interactions between sebetralstat and other medicinal products (CYP3A4-mediated)

Active substance (dosage regimen)	Effect on sebetralstat concentration GMR (90%-CI) (Possible interaction mechanism)	Recommendation on concomitant use
Itraconazole (200 mg q.d. for 6 days) Sebetralstat (600 mg single dose)	AUC_{0-t}: 521.07 (455.27-596.37) AUC_{0-inf}: 520.13 (455.82-593.53) C_{max}: 235.37 (193.18-286.78) (Inhibition of CYP3A4)	A single dose of 300 mg of sebetralstat in patients taking a strong CYP3A4 inhibitor
Verapamil (240 mg q.d. for 6 days) Sebetralstat (600 mg single dose)	AUC_{0-t}: 203.62 (183.20-226.32) AUC_{0-inf}: 202.15 (182.53-223.88) C_{max}: 176.37 (147.00-211.60) (Inhibition of CYP3A4)	No dose adjustment in patients taking a moderate CYP3A4 inhibitor
Cimetidine (800 mg single dose) Sebetralstat (600 mg single dose)	AUC_{0-t}: 88.68 (74.28-105.86) AUC_{0-inf}: 87.78 (73.41-104.96) C_{max}: 77.93 (63.47-95.67) (No effect observed)	No dose adjustment in patients taking a weak CYP3A4 inhibitor
Phenytoin (100 mg t.i.d. for 15 days) Sebetralstat (600 mg single dose)	AUC_{0-t}: 20.89 (16.86-25.87) AUC_{0-inf}: 20.82 (16.81-25.78) C_{max}: 36.66 (28.15-47.75) (Induction of CYP3A4)	A single dose of 900 mg of sebetralstat in patients taking a strong CYP3A4 inducer
Efavirenz (600 mg q.d. for 14 days) Sebetralstat (600 mg single dose)	AUC_{0-t}: 16.44 (13.65-19.81) AUC_{0-inf}: 17.28 (14.43-20.68) C_{max}: 33.64 (24.48-46.24) (Induction of CYP3A4)	A single dose of 900 mg of sebetralstat in patients taking a moderate CYP3A4 inducer
Modafinil (200 mg q.d. for 15 days) Sebetralstat (600 mg single dose)	AUC_{0-t}: 78.79 (64.90-95.67) AUC_{0-inf}: 78.58 (64.76-95.35) C_{max}: 88.96 (63.87-123.90) (Induction of CYP3A4)	No dose adjustment in patients taking a weak CYP3A4 inducer

Sebetralstat is an in vitro substrate of P-glycoprotein (P-gp) and the Breast Cancer Resistance Protein (BCRP). Sebetralstat is not an in vitro substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT2 and MATE1. It is a borderline substrate of MATE2-K, but this is not considered clinically relevant.

A clinical interaction study was conducted to investigate the effect of P-gp and BCRP inhibitors on the pharmacokinetics of sebetralstat. The results of this study are described below and presented in Table 2, which shows the geometric mean ratios (GMR) for the pharmacokinetic parameters during administration with/without concomitant medication with 90% confidence intervals (CI).

P-gp inhibitors

The P-gp inhibitor quinidine increased the C_{max} of a dose of 600 mg sebetralstat by 18% and the AUC of sebetralstat by 14%. Exposure to sebetralstat may be increased with concomitant use of P-gp inhibitors, but no dose adjustment is required.

BCRP inhibitors

The BCRP inhibitor eltrombopag increased the C_{max} of a dose of 600 mg sebetralstat by 12%, while the AUC of sebetralstat remained unchanged. The peak concentration of sebetralstat may be increased with concomitant use of BCRP inhibitors, but no dose adjustment is required.

Table 2. Interactions between sebetralstat and other medicinal products (transporter-mediated)

Active substance (dosage regimen)	Effect on sebetralstat concentration GMR (90%-CI) (Possible interaction mechanism)	Recommendation on concomitant use
Quinidine (300 mg 1 hour before and 3 hours after sebetralstat dosing) Sebetralstat (600 mg single dose)	AUC_{0-t}: 114.52 (97.09-135.06) AUC_{0-inf}: 114.18 (97.07-134.31) C_{max}: 235.37 117.75 (88.23-157.14) (Inhibition of P-gp)	No dose adjustment in patients taking a P-gp inhibitor
Eltrombopag (75 mg q.d. for 8 days) Sebetralstat (600 mg single dose)	AUC_{0-t}: 103.16 (88.32-120.50) AUC_{0-inf}: 102.61 (88.15-119.45) C_{max}: 111.56 (85.98-144.77) (Inhibition of BCRP)	No dose adjustment in patients taking a BCRP inhibitor

Effects of sebetralstat on the pharmacokinetics of 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 Ekterly to be a precipitant of CYP- and transporter-mediated DDIs is low.

In vitro studies indicate that sebetralstat inhibits CYPs 2C9 and 3A4 (IC_{50} of 30.1 and 120 µM respectively), and also inhibits the transporters BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1 and MATE2-K (IC_{50} of 82.3, 86.3, 51.3, 19.2, 5.28, 8.05 and 7.76 µM respectively). 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.

In vitro studies indicate that sebetralstat inhibits UGTs 1A4 and 1A9 (IC_{50} of 57.5 and 31.1 µM respectively). No or weak inhibition of UGT1A6, UGT2B7, UGT1A1, and UGT1A3 (IC50 of >100 µM, >100 µM, 87.9 µM, and 90.1 µM) by sebetralstat was observed. Clinical interaction data are not available. Sebetralstat is not an in vitro inhibitor of CYP1A2, 2B6, 2C8, 2C19 and 2D6, or of the transporters P-gp or OAT1. No time-dependent inhibition of CYP enzymes was observed. *In vitro* induction of CYP3A4 was seen at concentrations of ≥10 µM; there was no or minimal *in vitro* induction of CYP1A2, 2B6, 2C8, 2C9 and 2C19 at 100 µM. Given the intermittent use of sebetralstat, in vitro induction of CYP3A4 is not considered clinically relevant.

Pregnancy, 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 toxicity at exposures higher than clinical exposures. A study in rabbits had equivocal results (see “Preclinical data”).

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 data in animals have shown excretion of sebetralstat and/or its metabolites in milk (see “Preclinical data”).

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 “Preclinical data”).

Effects on ability to drive and use machines

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

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, 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, not serious and resolved without 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 3. Summary of adverse reactions by system organ class and frequency

System Organ Class	Adverse Reaction	Frequency
Nervous System Disorder	Headache	Common

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No case of overdose has been reported in clinical trials.

Properties/Effects

ATC code

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.

Pharmacodynamics

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.

Cardiac Electrophysiology

In a tQT study, the largest mean increase in QTc interval was 10.4 msec (upper 90% confidence interval = 15.3 msec) after administration of 3000 mg Ekterly (5 times the maximum recommended dose) in healthy subjects. The increase in the QTc interval was concentration dependent.

Clinical efficacy

The efficacy of Ekterly for the treatment of acute attacks in adult and adolescent patients aged 12 years and older with hereditary angioedema (HAE) was investigated in a randomized, double-blind, placebo-controlled study using a three-way crossover design (KONFIDENT).

Of the 136 patients randomized in the study, 110 patients treated at least one acute attack, resulting in a cumulative total of 264 attacks (87 with 300 mg Ekterly, 93 with 600 mg Ekterly, and 84 with placebo). The attacks ranged in severity from mild to very severe and involved all anatomical 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 scale within 12 hours.

There was a statistically significant faster time to the beginning of symptom relief for 300 mg Ekterly (Bonferroni adjusted $p < 0.0001$) compared to placebo (Table 4, Figure 1).

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

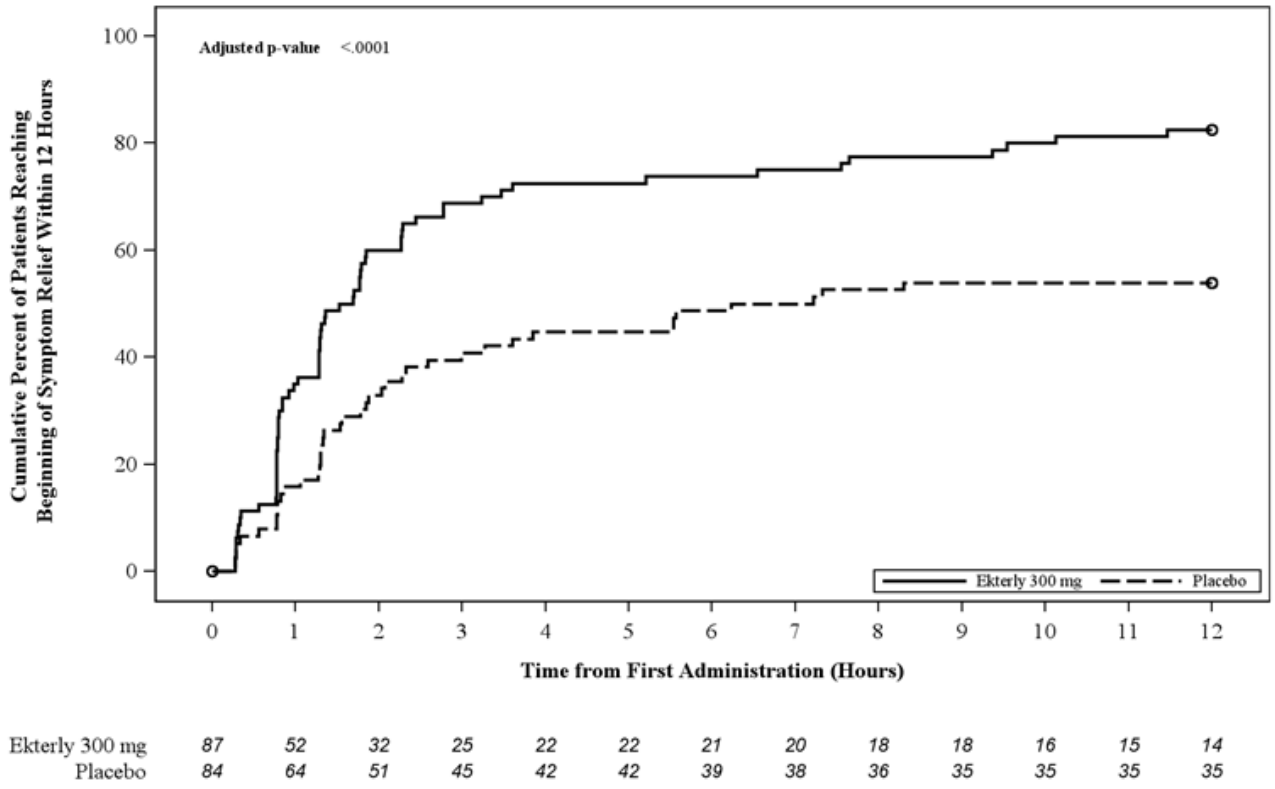


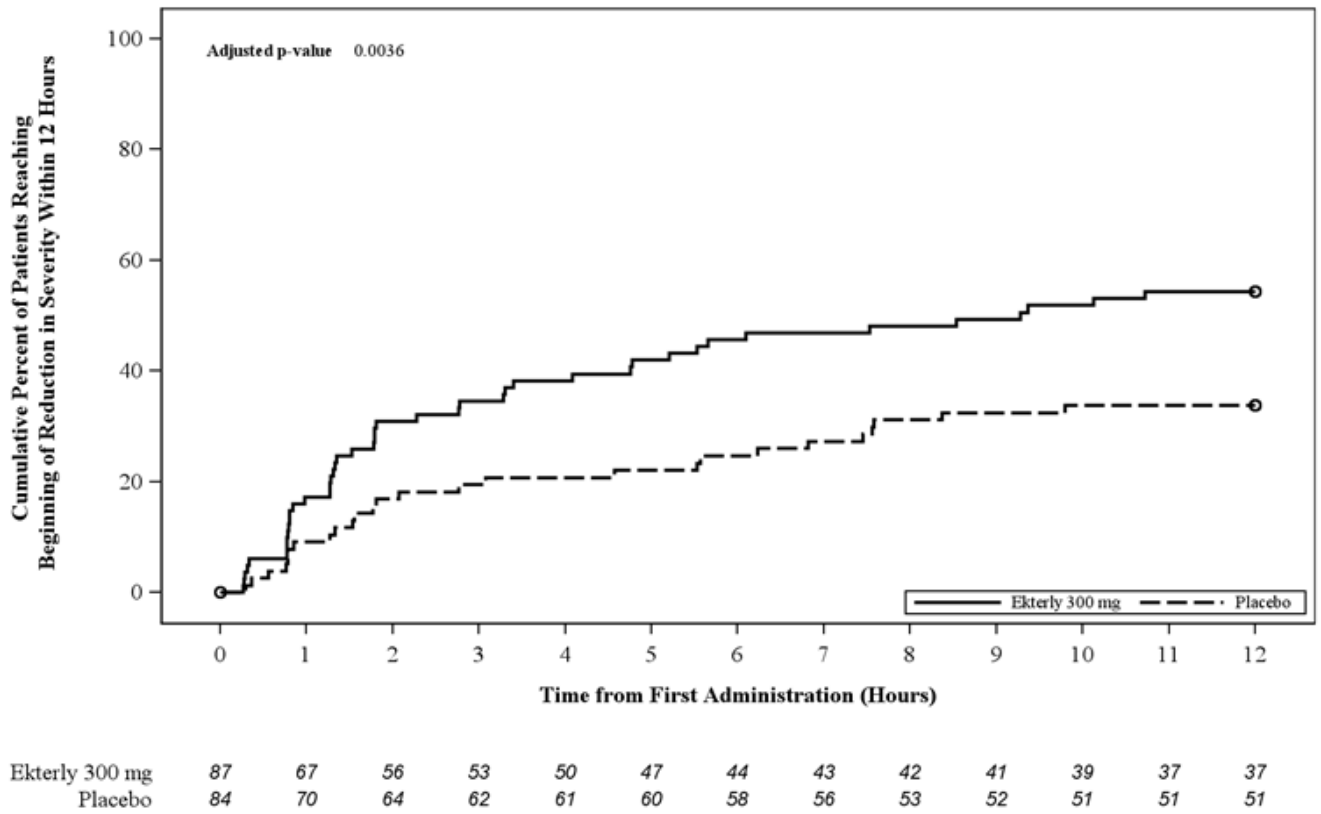
Table 4. KONFIDENT Trial - Time to beginning of symptom relief within 12 hours of dosing

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

NE = not evaluable at 12 hours

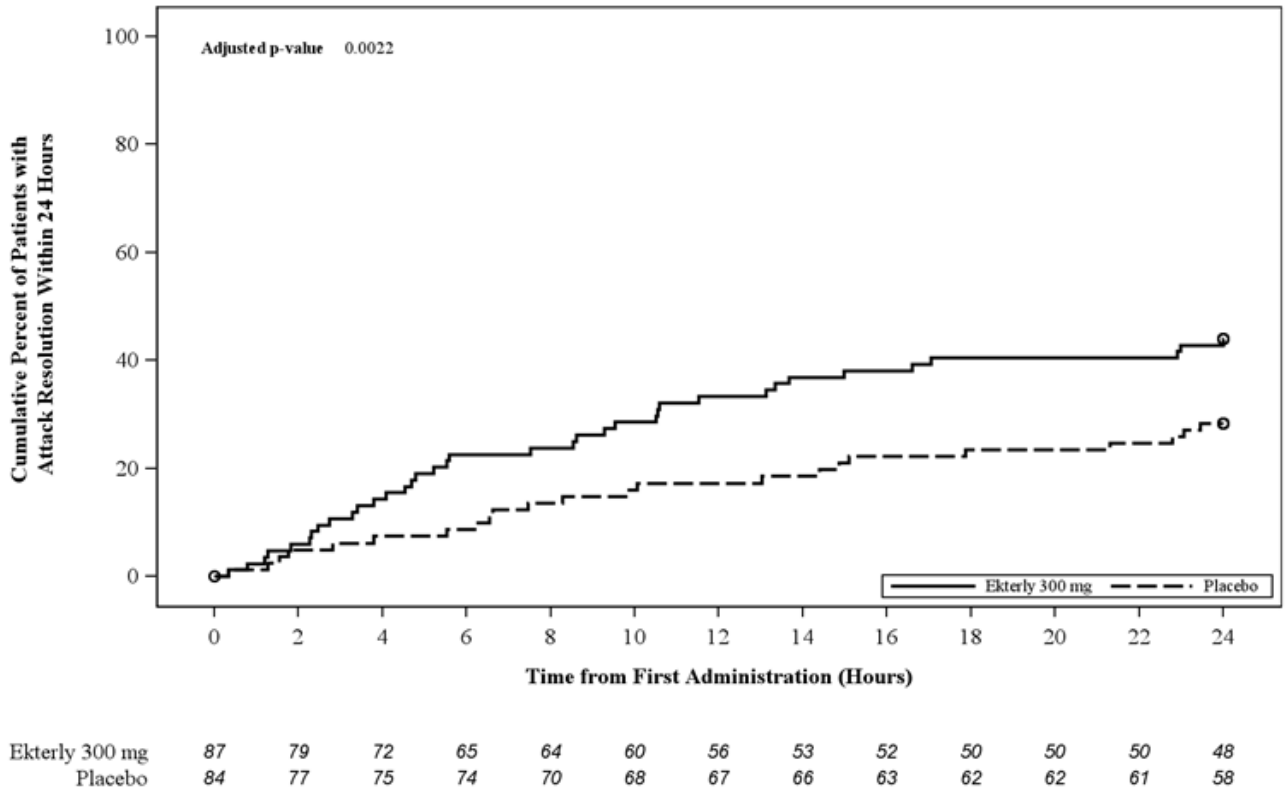
The first key secondary endpoint was time to reduction in severity on the Patient Global Impression of Severity (PGI-S). There was a statistically significant faster time to reduction in severity for 300 mg Ekterly (adjusted p=0.0036) compared to placebo (Figure 2).

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) 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 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 treated multiple attacks with Ekterly for up to 2 years. A total of 134 patients (including 23 adolescents) have treated 1706 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 4). 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 adolescent patients aged 12 to <18 years of age. The safety and efficacy in adolescent patients 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.

Pharmacokinetics

Absorption

After administration of a 300 mg dose in the fasting state, peak plasma concentrations were reached after approximately 1 hour.

Food effect

No difference in the AUC of sebetralstat was observed following administration of a 600 mg dose of sebetralstat with a high-fat meal, but a 29% reduction in C_{max}, and a 2-hour delay in median T_{max} were observed.

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.

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.

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.

Excretion

After a dose of 600 mg radiolabelled sebetralstat administered 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.

Kinetics in specific patient groups

In population pharmacokinetic analysis, no influence of gender, age (12 to 68 years); weight (44.0 kg to 135 kg), or ethnicity was apparent on clearance or volume of distribution of sebetralstat.

Patients with hepatic disorders

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%.

The pharmacokinetics of sebetralstat have not been studied in patients with severe hepatic impairment.

Patients with renal disorders

The pharmacokinetics of sebetralstat have not been studied in patients with renal impairment. Because sebetralstat is not primarily eliminated by the kidneys and is not used as long-term therapy, no clinically relevant effects of impaired renal function on the pharmacokinetics of sebetralstat are expected.

Elderly

Only limited data from a total of 10 participants 65 years and older are available (2 treated with sebetralstat 300 mg and 8 treated with sebetralstat 600 mg). These data suggests no dose adjustment is necessary in this population.

Preclinical data

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

The carcinogenic potential of sebetralstat was investigated in a 26-week study in transgenic rasH2 mice and in a 104-week study in rats. There was not found to be an increased incidence of malignant tumours and there was no evidence of a carcinogenic effect at any dosage in either of the two animal species. Exposure at the highest doses (in relation to the AUC of unbound plasma sebetralstat) in male and female mice were 0.2 and 0.4 times, respectively, the exposure in humans at the maximum recommended human dose (MRHD) and 5.7 times 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 a higher exposure (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 relationship and all malformations were within the 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.

Other information

Incompatibilities

Not applicable.

Shelf life

The medicine must only be used up to the date marked "EXP" on the package.

Special precautions for storage

Do not store above 30°C

Keep out of the reach of children

Instructions for handling

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

Authorisation number

69540 (Swissmedic)

Packs

Packs of 4 tablets [B] (currently not commercially available)

Packs of 6 tablets [B]

Tablets are packed in oPA/Al/PVC with aluminium lidding blisters (1 tablet per blister).

Marketing authorisation holder

KalVista Pharmaceuticals Switzerland GmbH

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