Summary Report of Benefit-Risk Assessment

EKTERLY FILM-COATED TABLETS 300 MG

NEW DRUG APPLICATION

Active Ingredient(s)	Sebetralstat
Product Registrant	PHARMA TO MARKET PTE. LTD.
Product Registration Number	SIN17392P
Application Route	Full evaluation
Date of Approval	12 November 2025

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A INTRODUCTION

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

The active substance, 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.

Ekterly is available as film-coated tablets containing 300 mg of sebetralstat. Other ingredients in the tablet core are microcrystalline cellulose, croscarmellose sodium, povidone K30 and magnesium stearate. Ingredients in the film coating include macrogol poly (vinyl alcohol) grafted copolymer, talc, titanium dioxide, glycerol monocaprylocaprate (type 1), polyvinyl alcohol, iron oxide yellow (E172), iron oxide black (E172), maltodextrin, guar galactomannan, hypromellose, and medium-chain triglycerides.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, sebetralstat, is manufactured at [redacted]. The drug product, Ekterly film-coated tablets 300 mg, is manufactured at Catalent Nottingham Limited, Nottingham, United Kingdom.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates, and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP).

The characterisation of the drug substance and its impurities have been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guideline and the impurity limits were appropriately qualified. The analytical procedures used were adequately described and non-compendial procedures have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at or below 25°C with a re-test period of 60 months. The packaging is double low-density polyethylene (LDPE) sealed bags. The LDPE bags are placed into a high-density polyethylene (HDPE) container.

Drug product:

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The tablets are manufactured using a dry granulation approach followed by compression and film-coating which is considered a standard manufacturing process.

The manufacturing site is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A guideline and impurity limits were adequately qualified. The analytical procedures used were adequately described and non-compendial procedures have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 48 months when stored at or below 30°C. The container closure system is an oPA/Al/PVC-Alu blister containing 1 tablet per blister.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of sebetralstat in the treatment of HAE attacks was based primarily on one pivotal Phase III study (KVD900-301), referred to as the KONFIDENT trial. This was a double-blind, randomised, placebo-controlled, multicentre, three-way crossover trial that evaluated the efficacy and safety of two dose levels of sebetralstat (300 mg and 600 mg) for on-demand treatment in patients 12 years and older with HAE Type I or II. The crossover design is considered appropriate for this acute treatment setting, allowing within-patient comparisons that reduce variability and increase statistical power. Supporting evidence of clinical efficacy was derived from a Phase II, randomised, double-blind, placebo-controlled crossover trial (KVD900-201; efficacy assessed in Part 2) evaluating sebetralstat 600 mg against placebo, and an ongoing Phase III, open-label, extension study (KVD900-302) assessing long-term safety and providing supportive efficacy data with repeated sebetralstat administration.

In study KVD900-301, adult and paediatric patients aged 12 years and older with confirmed HAE Type I or II were enrolled. Patients were randomly assigned to 1 of 6 treatment sequences (in a 1:1:1:1:1:1 ratio) to receive three treatments in a crossover fashion to treat three separate eligible HAE attacks: sebetralstat 300 mg, sebetralstat 600 mg, or placebo. The study included both patients on conventional on-demand treatment only and those on stable long-term prophylactic treatment. Patients with severe laryngeal attacks were not eligible for treatment. At the earliest recognition of an HAE attack, patients self-administered a single oral dose of the assigned treatment. If needed, as determined by the patient, a second administration of the same assigned treatment could be taken at least 3 hours after the first administration. At least 48 hours was required to have elapsed since use of conventional on-demand treatment or investigational product for a previous attack for an attack to be considered eligible. Conventional on-demand treatment was permitted at the patient's discretion if HAE attack symptoms were judged adequately severe. The use of placebo as comparator is considered acceptable given the study design allowed rescue medication use, ensuring patient safety while enabling clear demonstration of treatment effect in this acute setting where attacks may resolve spontaneously.

The primary efficacy endpoint was time to beginning of symptom relief defined by the Patient Global Impression of Change (PGI-C) as at least "a little better" for 2 time points in a row within

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12 hours of the first treatment administration. Attacks were treated as right-censored at 12 hours if they did not achieve beginning of symptom relief or if patients received conventional on-demand treatment prior to the time-to-event. Key secondary endpoints were time to reduction in severity (defined as first incidence of decrease from baseline for 2 time points in a row in Patient Global Impression of Severity [PGI-S]) within 12 hours, and time to complete attack resolution (defined as "none" on PGI-S) within 24 hours. Patients assessed their symptoms using electronic diaries at specific time points after dosing. The statistical analysis plan included appropriate multiplicity adjustments using Bonferroni correction with a loop-back feature for multiple dose levels and a fixed-sequence, closed testing procedure for primary and key secondary endpoints.

A total of 136 patients were randomised in the study, of whom 110 patients (including 13 adolescent patients aged 13–17 years) treated at least 1 attack and were included in the Full Analysis Set (FAS). A total of 264 HAE attacks were treated, comprising 87 attacks treated with sebetralstat 300 mg, 93 attacks treated with sebetralstat 600 mg, and 84 attacks treated with placebo. Demographics and baseline characteristics were well-balanced across treatment groups. The mean (SD) age was 37.7 (14.96) years (range: 13 to 74 years), with more females (60.0%) than males (40.0%). The majority of patients were White (83.6%) and had HAE Type I (91.8%).

Most treated attacks were of mild (42.8%) or moderate (38.6%) severity at time of treatment, with a smaller proportion being severe (14.4%) or very severe (2.7%). The predominant attack locations were subcutaneous only (53.8%) and abdominal only (32.2%), with laryngeal swelling occurring in 3.0% of attacks. The overall median time from symptom onset to first treatment administration was 41.0 minutes (range: 6.0 to 140.0 minutes), with the 300 mg group at 35 minutes, the 600 mg group at 41 minutes, and the placebo group at 51 minutes. Most attacks were treated with a single dose, with a higher proportion in the sebetralstat treatment groups (61.6% for 300 mg, 58.9% for 600 mg) compared to placebo group (44.6%). For attacks requiring a second dose, the median time between doses was 3.858 hours for 300 mg group, 3.783 hours for 600 mg group, and 3.500 hours for placebo group.

Of the participants, 86 patients (78.2%) were taking on-demand treatment only, while 24 patients (21.8%) were on long-term prophylaxis prior to trial initiation. The most common prior medications included icatibant (77.3%), C1 esterase inhibitor (34.5%), conestat alfa (14.5%), and berotralstat (10.0%).

Summary of key efficacy results (Study KVD900-301)

	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo
Primary endpoint			
Time to beginning of symptom relief (hours)[a]			
25th percentile (95% CI)	0.78 (0.77, 0.98)	1.02 (0.78, 1.30)	1.34 (0.85, 2.07)
Median (95% CI)	1.61 (1.28, 2.27)	1.79 (1.33, 2.27)	6.72 (2.33, NE)
75th percentile (95% CI)	7.04 (2.28, NE)	3.79 (2.78, NE)	NE (NE, NE)
Gehan score LS means (SD)[b]	-29.44 (13.82)	-11.32 (13.65)	51.59 (14.51)
LS means difference from Placebo (95% CI)	-81.03 (-117.38, -44.68)	-62.91 (-98.61, -27.21)	-
Adjusted p-value (active versus placebo)[c]	<0.0001	0.0013	-
Key secondary endpoints			
Time to reduction in severity (hours)[d]			
25th percentile (95% CI)	1.53	2.19	6.23

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	(0.85, 2.78)	(1.30, 2.79)	(1.76, NE)
Median (95% CI)	9.27 (4.08, NE)	7.75 (3.27, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Gehan score LS means (SD)[e]	-38.01 (12.45)	-37.44 (12.08)	13.21 (12.93)
LS means difference from Placebo (95% CI)	-51.22 (-83.13, -19.31)	-50.65 (-81.82, -19.48)	-
Adjusted p-value (active versus placebo)[c]	0.0036	0.0032	-
Time to HAE attack resolution (hours)[f]			
25th percentile (95% CI)	8.58 (4.08, 13.13)	7.54 (3.78, 9.55)	22.78 (9.79, NE)
Median (95% CI)	NE (16.60, NE)	24.00 (10.60, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Gehan score LS means (SD)[g]	1.62 (13.98)	-17.46 (13.62)	56.25 (14.43)
LS means difference from Placebo (95% CI)	-54.62 (-87.05, -22.19)	-73.71 (-105.35, -42.08)	-
Adjusted p-value (active versus placebo)[c]	0.0022	<0.0001	-

NE = not evaluable
[a] Kaplan-Meier estimates for the time to the beginning of symptom relief within 12 hours.
[b] Least square (LS) means, LS means differences, p-values, and adjusted p-values from the linear mixed model used to analyse Gehan score transformation of time to beginning of symptom relief within 12 hours including terms for sequence, period, and treatment in the model as fixed effects and patient nested within the sequence as a random effect.
[c] Adjusted p-value came from Bonferroni adjustment allowing 2-way alpha passing.
[d] Kaplan-Meier estimates for time to reduction in severity within 12 hours.
[e] LS means, LS means differences, p-values, and adjusted p-values from linear mixed model used to analysze Gehan score transformation of time to first incidence of decrease within 12 hours including terms for sequence, period, treatment, and baseline PGI-S category (none or mild, moderate, and severe or very severe) in the model as fixed effects and patient nested within the sequence as a random effect.
[f] Kaplan-Meier estimates for time to HAE attack resolution within 24 hours.
[g] LS means, LS means differences, p-values, and adjusted p-values from linear mixed model used to analyse Gehan score transformation of time to HAE attack resolution within 24 hours including terms for sequence, period, treatment, and baseline PGI-S category (none or mild, moderate, and severe or very severe) in the model as fixed effects and patient nested within the sequence as a random effect.

The primary analysis demonstrated a statistically significant improvement for both sebetralstat doses compared to placebo. The median time to beginning of symptom relief was 1.61 hours (95% CI: 1.28, 2.27) for 300 mg and 1.79 hours (95% CI: 1.33, 2.27) for 600 mg, compared to 6.72 hours (95% CI: 2.33, NE [i.e. >12 hours]) for placebo (adjusted p<0.0001 for 300 mg, p=0.0013 for 600 mg vs placebo). A higher proportion of attacks reached beginning of symptom relief within 12 hours in the sebetralstat groups (75.9% for 300 mg, 76.3% for 600 mg) compared to placebo (48.8%). These findings indicate a clinically meaningful and consistent treatment effect across both dose levels.

Both key secondary endpoints were also met with statistical significance. For the first key secondary endpoint, time to reduction in severity was significantly faster for both sebetralstat doses versus placebo (adjusted p=0.0036 for 300 mg, p=0.0032 for 600 mg), with median times of 9.27 hours (95% CI: 4.08, NE) for 300 mg, 7.75 hours (95% CI: 3.27, NE) for 600 mg, and >12 hours for placebo. More attacks achieved reduction in severity within 12 hours after sebetralstat (50.6% for 300 mg, 52.7% for 600 mg) compared to placebo (31.0%). These findings were consistent across both dose levels and support a treatment effect on reduction in attack severity.

For the second key secondary endpoint, time to complete attack resolution within 24 hours, both sebetralstat doses showed significant improvement versus placebo (adjusted p=0.0022 for 300 mg, p<0.0001 for 600 mg). The median time to complete resolution was not estimable for the 300 mg (95% CI: 16.60, NE) and placebo (95% CI: NE, NE) groups, while the median was 24.00 hours (95% CI: 10.60, NE) for the 600 mg group. For the 300 mg and placebo groups, the 25th percentile times to complete resolution were 8.58 and 22.78 hours,

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respectively. In addition, a higher proportion of attacks achieved complete resolution within 24 hours with sebetralstat (42.5% for 300 mg, 49.5% for 600 mg) compared with placebo (27.4%). These findings support a treatment effect on complete attack resolution with both sebetralstat doses.

The efficacy findings from the pivotal KONFIDENT trial were supported by both the earlier Phase II study (KVD900-201) and the ongoing Phase III, open-label, extension study (KVD900-302). The Phase II trial KVD900-201 was a randomised, double-blind, placebo-controlled, crossover study that evaluated sebetralstat 600 mg versus placebo in 53 adults with HAE Type I or II. Only mild to moderate attacks were eligible for treatment in this study. The primary endpoint demonstrated a statistically significant difference between sebetralstat and placebo groups in time to use of conventional on-demand treatment within 12 hours, with fewer patients requiring conventional on-demand treatment in the sebetralstat group compared to placebo (15.1% vs 30.2%; p=0.0010). Supporting this, the median time to beginning of symptom relief was shorter with sebetralstat (1.6 hours) compared with placebo (9.0 hours) (p<0.0001). Time to complete attack resolution within 24 hours was also faster with sebetralstat (median 18 hours vs not evaluable for placebo, p=0.0021). The median time from attack onset to treatment was 30 minutes.

An open-label extension study (KVD900-302) was initiated to evaluate long-term safety, with supportive efficacy as a secondary objective. This trial is ongoing and has enrolled 84 patients (including 12 adolescent patients) who have treated a median of 5 attacks (range: 1 to 37) with sebetralstat 600 mg. As of January 2024, analysis of 639 treated attacks demonstrated consistent efficacy across repeated treatments. The overall median times remained stable throughout the study: 1.8 hours for beginning of symptom relief, 6.57 hours for reduction in severity, and 21.02 hours for complete attack resolution. No clear trends in efficacy were observed across sequential attacks, and efficacy was maintained through the highest observed attack number (up to 37 attacks per patient).

Overall, the efficacy of sebetralstat was demonstrated in the pivotal Phase III study, with both 300 mg and 600 mg doses showed statistically significant improvements compared to placebo in time to beginning of symptom relief, reduction in severity, and complete attack resolution. These findings were supported by positive results from the Phase II study and further supported by the ongoing open-label extension study, in which efficacy was maintained with repeated treatment across multiple attacks.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of sebetralstat was primarily based on the Phase II trial (KVD900-201) and the pivotal Phase III KONFIDENT trial (KVD900-301), supported by interim data from the ongoing Phase III, open-label, extension study (KVD900-302).

A total of 213 patients participated in the Phase II-III trials, with 208 receiving at least one administration of sebetralstat. Of these, 198 patients treated 879 HAE attacks with sebetralstat, including 21 paediatric patients (aged ≥12 to <18 years) who treated 159 attacks and 5 geriatric patients (aged ≥65 years) who treated 27 attacks.

Overview of safety profile (Phase II-III Double-blind Safety Population)

Adverse Event (AE)	Sebetralstat 300 mg (N=86)	Sebetralstat 600 mg (N=151)	Placebo (N=138)
Any AE	17 (19.8%)	28 (18.5%)	24 (17.4%)

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Treatment-related AE	2 (2.3%)	6 (4.0%)	6 (4.3%)
SAE	1 (1.2%)	2 (1.3%)	0 (0%)
Treatment-related SAE	0 (0%)	0 (0%)	0 (0%)
Discontinuations due to AE	0 (0%)	0 (0%)	0 (0%)
Deaths due to AE	0 (0%)	0 (0%)	0 (0%)

In the Phase II-III double-blind safety population, the overall type and incidence of adverse event (AEs) in the pooled clinical studies were similar between sebetralstat and placebo. The most frequently reported AE (≥2%) in any treatment group was headache, occurring in 1 patient (1.2%) in the 300 mg group, 7 patients (4.6%) in the 600 mg group, and 4 patients (2.9%) in the placebo group. Similarly, the most frequently reported on-treatment AE (≥2%) (occurring within 3 days after treatment administration) in any treatment group was also headache, occurring in 6 patients (4.0%) in the 600 mg group and 3 patients (2.2%) in the placebo group. The majority of AEs were mild or moderate in severity, with only one severe (Grade 3) event of intervertebral disc protrusion reported in the 300 mg group, which was not considered related to treatment. Results from the ongoing open-label study KVD900-302 were consistent with these findings, with headache being the most frequently reported AE (11.9% of patients), followed by nasopharyngitis and upper respiratory tract infection (8.3% each). Among on-treatment AEs (occurring within 3 days of administration), headache remained the most frequent (7.1%).

Treatment-related AEs were reported for 2 patients (2.3%) who received 300 mg, 6 patients (4.0%) who received 600 mg, and 6 patients (4.3%) who received placebo in the Phase II-III double-blind safety population. The only treatment-related AE reported by more than a single patient in any treatment group was headache (2 patients [1.3%] who received 600 mg and 2 patients [1.4%] who received placebo). All other treatment-related AEs, including nausea, dyspepsia, upper abdominal pain, fatigue, back pain and hot flushes, were each experienced by a single patient. Adverse reactions identified in the pivotal study included dyspepsia and fatigue (each in 1 patient). In the ongoing KVD900-302 study, 8 (9.5%) patients reported treatment-related AEs, with headache being the most common (3.6% of patients).

The incidence of serious AEs (SAEs) was low. In the pivotal Phase III study KVD900-301, three SAEs were reported in 3 (2.7%) patients: intervertebral disc protrusion in 1 patient in the 300 mg group; and anisocoria and HAE in 1 patient each in the 600 mg group. None of the SAEs were considered treatment-related. In the ongoing KVD900-302 study, 3 (3.6%) patients receiving sebetralstat 600 mg reported 5 SAEs including hyperthermia, headache, intracranial mass, meningitis viral, and Waldenstrom's macroglobulinaemia. None of these SAEs were considered treatment-related. No deaths occurred during the clinical program.

Discontinuations due to AEs were infrequent. In the Phase II-III double-blind safety population, there were no AEs that led to premature discontinuation. In the open-label Phase III study KVD900-302, 4 (4.8%) patients receiving sebetralstat 600 mg discontinued due to AEs including alanine aminotransferase increased, intracranial mass, skin burning sensation, and nausea. The AEs of nausea and skin burning sensation occurred within 3 days of sebetralstat 600 mg administration and were considered treatment-related. Both events resolved without intervention.

There were no AEs of special interest (AESIs). The safety profile of sebetralstat in both paediatric and geriatric populations was consistent with that observed in the general adult population. In paediatric patients, one AE was reported per treatment group: blood urine present in the 300 mg group, vomiting in the 600 mg group, and influenza in the placebo group. Similarly, in geriatric patients, only two AEs were reported: seasonal allergy (300 mg) and

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COVID-19 (600 mg). None of these events in either age group were considered treatment-related, serious, or led to discontinuation.

Overall, the pooled Phase II-III data, including longer-term safety data from the ongoing KVD900-302 study, demonstrated a favourable safety profile for sebetralstat in the acute treatment of HAE attacks, with predominantly mild to moderate AEs and no major safety signals identified. The most common AE was headache, with low and comparable rates of treatment-related events and SAEs.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The management of HAE attacks currently has limited treatment options. Existing first-line treatments require either intravenous or subcutaneous administration, which may delay early treatment and limit ease of self-administration.

The pivotal Phase III KONFIDENT trial (KVD900-301) demonstrated a statistically significant improvement in time to beginning of symptom relief for both sebetralstat doses compared to placebo (1.61 hours for 300 mg and 1.79 hours for 600 mg versus 6.72 hours; adjusted $p<0.0001$ and $p=0.0013$, respectively). A higher proportion of attacks achieved symptom relief within 12 hours with sebetralstat (75.9% for 300 mg, 76.3% for 600 mg) compared to placebo (48.8%).

These results were supported by both key secondary endpoints. Time to reduction in severity was significantly faster for both sebetralstat doses versus placebo (adjusted $p=0.0036$ for 300 mg, $p=0.0032$ for 600 mg), with more attacks achieving severity reduction within 12 hours (50.6% for 300 mg, 52.7% for 600 mg vs 31.0% for placebo). Time to complete attack resolution also showed significant improvement for both doses versus placebo (adjusted $p=0.0022$ for 300 mg, $p<0.0001$ for 600 mg).

The Phase II study and ongoing open-label extension study provided supporting evidence of efficacy. The Phase II study demonstrated consistent results with the pivotal trial. The extension study, with analysis of 639 treated attacks, showed sustained efficacy with repeated use, with median times remaining stable throughout the study period (1.8 hours for symptom relief, 6.57 hours for severity reduction, and 21.02 hours for attack resolution).

The safety profile was consistent across studies, with no major safety concerns identified. The most common AE was headache (1.2% with 300 mg and 4.6% with 600 mg vs 2.9% with placebo). Treatment-related AEs occurred at low rates across treatment groups (2.3%–4.3%) and were all mild to moderate in severity. The incidence of SAEs was low (1.2–1.3%) with no treatment-related cases. No deaths occurred during the clinical program, and discontinuations due to AEs were rare.

Overall, the benefit-risk profile of sebetralstat for the treatment of HAE attacks in adults and adolescents aged 12 years and older was considered favourable, with efficacy demonstrated across multiple endpoints, and the safety profile was well-characterised and manageable. Furthermore, the oral route of administration offers an important clinical advantage by enabling earlier treatment.

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F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Ekterly for the treatment of HAE attacks in adult and adolescents aged 12 years and older was deemed favourable and approval of the product registration was granted on 12 November 2025.

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▼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. Use of an additional dose is not recommended.

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".

The potential for interaction should be considered when sebetralstat is administered to patients taking substrates of CYPs 2C9 and 3A4, and the transporters BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1 and MATE2-K (see section 4.5).

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. No dose adjustment is required when taking weak or moderate CYP3A4 inhibitors. In patients who are taking a strong CYP3A4 inhibitor a single dose of 300 mg is recommended when treating an HAE attack. Use of an additional dose is not recommended.

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.

In vitro studies indicate that sebetralstat inhibits UGTs 1A4 and 1A9. Clinical interaction data are not available.

Paediatric population

Interaction studies have only been performed in adults.

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 (during treatment with Ekterly and for a period of 24 hours after the last dose).

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

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, 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
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 at https://www.hsa.gov.sg/adverse-events.

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. 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)). Attacks ranged in severity from mild to very severe and occurred in all anatomic locations. Patients with severe laryngeal attacks were not included in the KONFIDENT trial. 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.

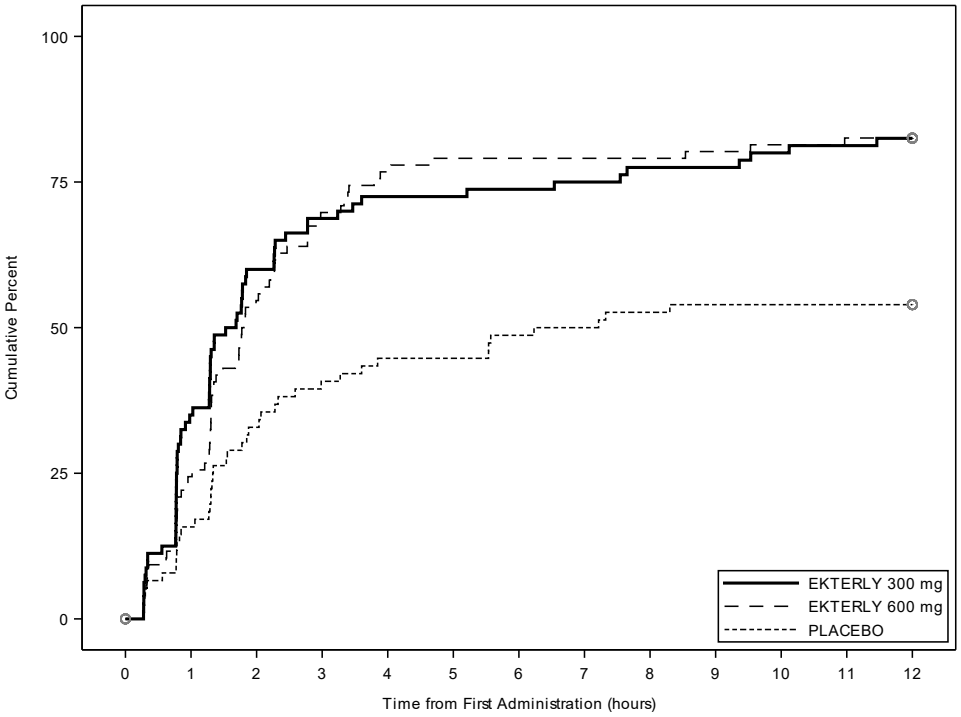
There was a statistically significant faster time to the beginning of symptom relief for 300 mg Ekterly (Bonferroni adjusted $p < 0.0001$) and 600 mg Ekterly (Bonferroni adjusted $p < 0.0013$) compared to placebo (Table 2, Figure 1).

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)

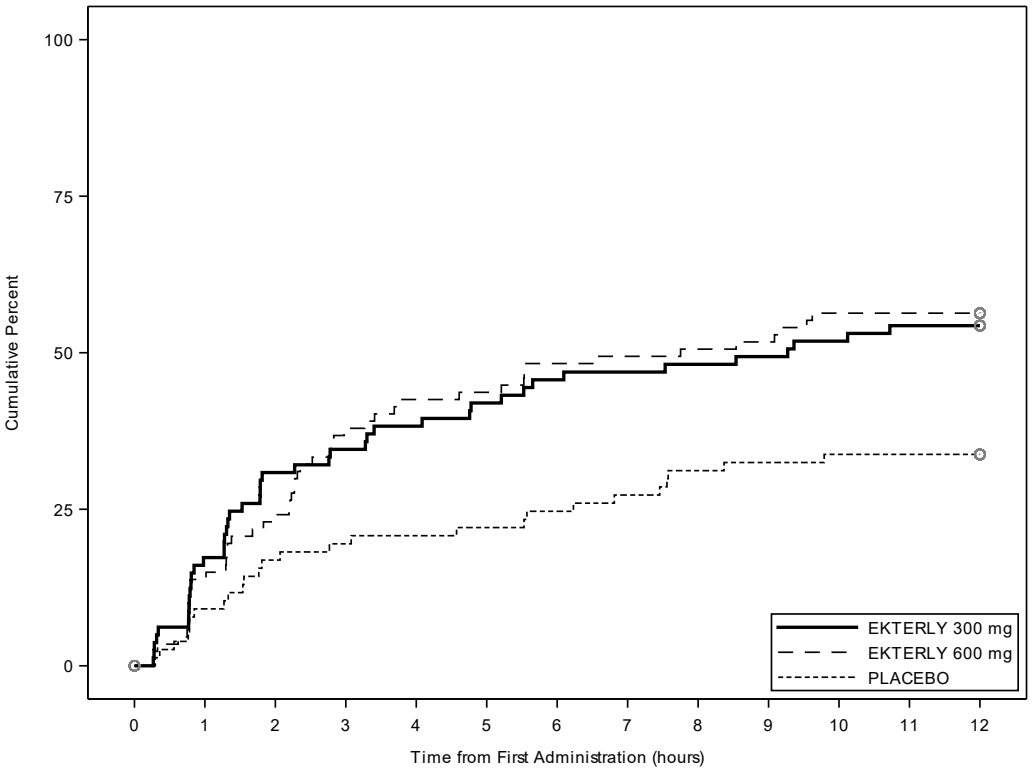
NE = not evaluable at 12 hours

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



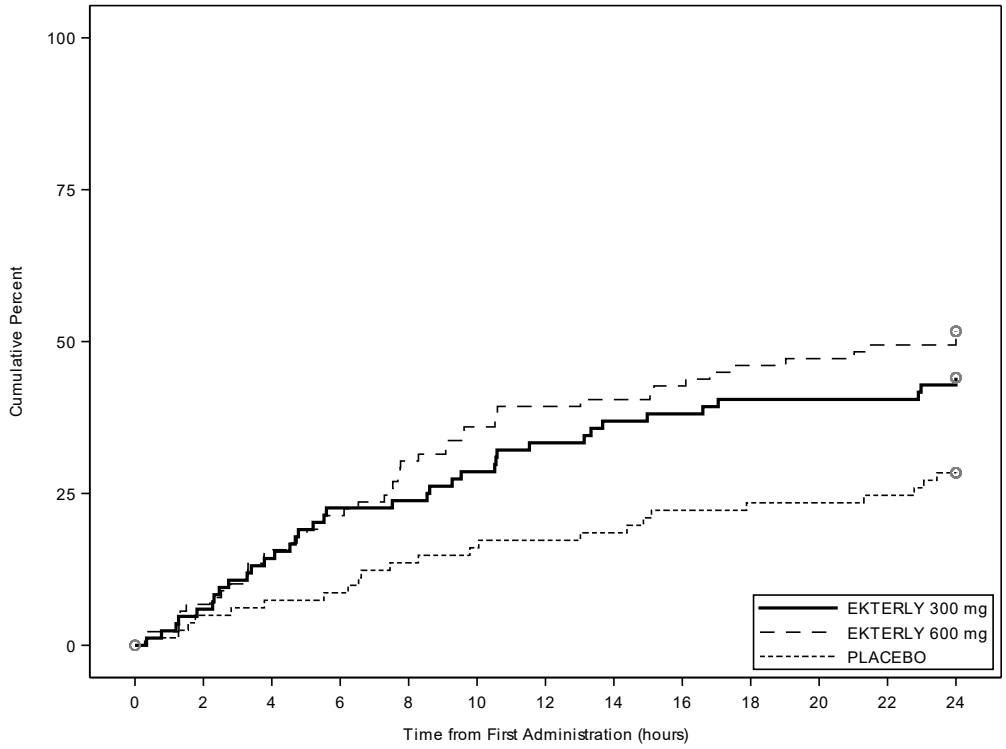
The first key secondary endpoint was time to reduction in severity on the Patient Global Impression of Severity (PGI-S) within 12 hours of dosing. There was a statistically significant faster time to reduction in severity for 300 mg Ekterly (adjusted p=0.0036) and 600 mg Ekterly (adjusted p=0.0032) compared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

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%.

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).

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

4 years.

6.4 Special precautions for storage

Store below 30°C.

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. PRODUCT OWNER

KalVista Pharmaceuticals Ltd
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Wiltshire,
SP4 0BF, United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

SINXXXXXP

9. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>