New Drug Overview

Ekterly (sebetralstat)

PDL Category: Hereditary Angioedema Agents- Acute

Introduction

Disease Background:

- Hereditary angioedema is a rare but possibly life-threatening disease if the upper airway is affected (*Riedl et al 2024*) that is described by repeated episodes of angioedema (ie, swelling), without urticaria or pruritus (*Zuraw and Farkas 2025*).
  - Generally the extremities, abdomen, genitourinary tract, face, oropharynx, and larynx are involved in angioedema attacks (*Prasad and Fedorowicz 2025*).
- The angioedema associated with HAE due to a deficiency in C1 inhibitor (C1 INH) occurs due to too much production of bradykinin, which is a potent vasodilatory mediator (*Zuraw and Farkas 2025*).
  - There are two types of HAE that results including from either C1 INH deficiency (HAE Type 1) or C1 INH dysfunction (HAE Type II).
  - While the prevalence of HAE in the general population is approximately 0.001%-0.003%, Type 1 accounts for around 85% and Type 2 accounts for around 15% (*Prasad and Fedorowicz 2025*).
- Prior to HAE attacks, being several hours or a day before the attack, prodromal symptoms may occur, such as erythematous nonurticarial rash, localized tingling, sense of skin tightness, fatigue, flu-like symptoms, mood changes, hyperactivity, thirst, or nausea (*Prasad and Fedorowicz 2025*).
- A general time course pattern is likely in angioedema due to C1 INH deficiency, with the swelling worsening over 24 hours, which then levels off and gradually resolves over the next 48-72 hours. However, attacks may last longer (*Prasad and Fedorowicz 2025*).
  - While swelling is self-limited and typically settles in 2-5 days with no treatment, if there is laryngeal involvement it may cause fatal asphyxiation (*Zuraw and Farkas 2025*).
- Management involves treatment for acute attacks and prevention of recurrent attacks (*Prasad and Fedorowicz 2025*).
- Ekterly (sebetralstat) was FDA approved in 2025.

Pharmacology/Usage

- Ekterly (sebetralstat) is a plasma kallikrein inhibitor.
  - It is a competitive, reversible inhibitor of plasma kallikrein. Plasma kallikrein is a serine protease that cleaves high molecular weight kininogen (HK) releasing bradykinin which increases vascular permeability through activation of bradykinin receptors causing edema. Sebetralstat inhibits the cleavage of HK and reduces production of bradykinin, thus treating the clinical symptoms of an acute, episodic attack of HAE.
  - Sebetralstat also inhibits the positive feedback mechanism of the kallikrein kinin system by plasma kallikrein, thus reducing factor XIIa and additional plasma kallikrein generation.

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Ekterly (sebetralstat)
• For the treatment of acute attacks of hereditary angioedema (HAE) in adult and pediatric patients aged 12 years and older.	✔

(Prescribing information: Ekterly 2025)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ekterly (sebetralstat)	Film-Coated Tablets	Oral	One dose of 600mg at the earliest recognition of an acute HAE attack ○ A second dose of 600mg may be taken at least 3 hours after the first dose if response is inadequate, or if symptoms worsen or recur. ○ Maximum recommended dosage is 1,200mg in any 24-hour period.	• Avoid use of Ekterly in severe hepatic impairment. • For moderate hepatic impairment, the recommended dosage is one dose of 300mg at the earliest recognition of an acute HAE attack. A second dose of 300mg may be taken at least 3 hours after the first dose if response is inadequate, or if symptoms worsen or recur. • Dosage adjustment not required with mild hepatic impairment.

See the current prescribing information for full details.

Clinical Efficacy Summary

- The efficacy of Ekterly was assessed in a double-blind, randomized, placebo-controlled, multicenter crossover clinical trial (KONFIDENT), which employed a 3-way, complete crossover design comparing Ekterly 600mg and Ekterly 300mg to placebo. If needed (as determined by the patient) a second dose could be administered after 3 hours. The duration of the trial was about 25 weeks.
- Patients were required to treat an eligible HAE attack prior to crossover to the next treatment period. Note that severe laryngeal attacks were not treated in this study. In addition, while assessed in this study, Ekterly 300mg is not a recommended dose for treatment of acute HAE attacks.
- The baseline characteristics of the patients enrolled (N=110) included a mean age of 38 years, with 88% who were ≥18 years. In addition, 60% were female, 84% were White, 92% had HAE Type I, and 22% were on background HAE prophylaxis.
- Patients (N=110) were randomized and experienced at least one HAE attack. Of the 264 treated HAE attacks, 142 (54%) had peripheral symptoms only, 85 (32%) had abdominal symptoms only, 27 (10%) had abdominal and peripheral symptoms, 8 (3%) had mild to moderate laryngeal symptoms, and 2 (1%) had missing attack location.

- The primary endpoint was the 'time to beginning of symptom relief', defined as at least "a little better" at two consecutive time points within 12 hours of first dose administration, assessed using a seven-point scale Patient Reported Global Impression of Change (PGI-C) ranging from "much worse" to "much better".
  - Results suggested that there was a statistically significant faster time to the beginning of symptom relief for Ekterly 600mg compared to placebo. A total of 71 out of 93 patients (76%) administered Ekterly 600mg and 41 out of 84 patients (49%) administered placebo achieved the primary endpoint (NNT 4).
  - The median time to beginning of symptom relief within 12 hours of first dose was 2hrs in patients administered Ekterly 600mg.
  - Less than 50% of placebo patients reached beginning of symptom relief within 12 hours; thus, the median time could not be estimated.
  - Note that in the Ekterly 600mg group, 38% of patients administered a second dose within 12 hours.
- Patients who did not achieve the endpoint, received alternate on-demand therapy, or lacked at least 2 consecutive post-baseline assessments were right-censored at 12 hours.
- The first key secondary endpoint was the 'time to first incidence of reduction in severity' at two consecutive time points within 12 hours of first dose administration, assessed using a five-point scale Patient Global Impression of Severity (PGI-S) ranging from 'none' to 'severe'.
  - The 'time to first incidence of reduction in severity' was statistically significantly faster for Ekterly 600mg as compared to placebo. A total of 49 out of 93 patients (53%) administered Ekterly 600mg and 26 out of 84 patients (31%) administered placebo achieved reduction in severity within 12 hours.
  - The median time to achieve this endpoint was 9.1 hours in patients administered Ekterly 600mg.
  - Less than 50% of placebo patients reached beginning of reduction in severity within 12 hours; thus, the median time could not be estimated.
  - Note that in the Ekterly 600mg group, 38% of patients administered a second dose within 12 hours.
- Patients who did not achieve the endpoint, received alternate on-demand therapy, or lacked at least 2 consecutive post-baseline assessments were right-censored at 12 hours.
- The second key secondary endpoint was 'time to attack resolution' defined as PGI-S of "none" within 24 hours of first dose administration.
  - The 'time to attack resolution' was statistically significantly faster for Ekterly 600mg compared to placebo. A total of 46 out of 93 patients (49%) administered Ekterly 600mg and 23 out of 84 patients (27%) administered placebo achieved attack resolution within 24 hours.
  - Less than 50% of Ekterly 600mg and placebo patients had attack resolution within 24 hours; thus, the median time could not be estimated.
  - Note that in the Ekterly 600mg group, 39% of patients administered a second dose within 24 hours.
- Patients who did not achieve the endpoint, received alternate on-demand therapy, or lacked post-baseline assessments were right-censored at 24 hours.
- The time to beginning of at least "better" at two consecutive time points on the PGI-C within 12 hours of the first dose administration was assessed. A total of 54 out of 93 patients (58%) administered Ekterly 600mg and 21 out of 84 patients (25%) administered placebo achieved this endpoint. The median time was 4.6 hours in patients administered Ekterly 600mg.

Clinical guidelines

- It should be noted that guidelines do not currently include Ekterly (sebetralstat) as the guidelines were published prior to its FDA approval.
- **US Hereditary Angioedema Association (HAEA) Medical Advisory Board 2020 Guidelines for the management of hereditary angioedema** (*Busse et al 2021*).

- Patients must have available an effective on-demand medication to utilize at the onset of an HAE attack. An FDA-approved on-demand HAE treatment (ecallantide, icatibant, pd C1-INH or rh C1-INH) should be used as first-line for attacks if possible.
- On-demand treatment of HAE attacks should be self-administered (or given by a caregiver) if possible except when treating with ecallantide. This needs to be administered by a healthcare provider.
- All HAE attacks are eligible for treatment regardless of the swelling location or the attack severity.
- Short-term prophylaxis is indicated when patients are at increased risk of an attack that is associated with known triggers
- The choice on when to use long-term prophylactic treatment should consider the needs of each patient.
- Long-term prophylactic treatment of HAE C1-INH should include first-line medications (IV C1-INH, SC C1-INH, or lanadelumab-flyo).

- **The International World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) guideline for the management of hereditary angioedema- the 2021 revision and update** (*Maurer 2022*):
  - It is recommended to consider on-demand treatment for all attacks and that any attack that affects or potentially affects the upper airway is treated. In addition, attacks should be treated as soon as possible.
  - Guidelines recommend that attacks be treated with IV C1 inhibitor, ecallantide, or icatibant. Patients should have enough medications for on-demand treatment of at least two attacks.
  - It is recommended to consider short-term prophylaxis prior to medical, surgical, or dental procedures, as well as exposure to other angioedema attack-inducing events.
    - IV plasma-derived C1 INH is recommended as first-line short-term prophylaxis.
  - For long-term prophylaxis, guidelines recommend to utilize plasma-derived CI inhibitor, lanadelumab, or berotralstat as first-line long-term prophylaxis.
  - The guidelines recommend C1 inhibitor or icatibant therapy for treating attacks in children under the age of 12 years.

Safety summary

- **Contraindications:** None.

- **Box Warning:** None.

- **Warnings and precautions:** None.

- **Common adverse drug reactions**: Listed % incidence for adverse drug reactions= reported % incidence for drug (Ekterly) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.
  - The most frequently reported adverse event included headache (2%).

- **Drug interactions:**
  - Sebetralstat is a substrate of CYP3A4.
    - Avoid concomitant use of Ekterly with strong CYP3A4 inhibitors.
    - Reduce the dose of Ekterly to one dose of 300mg at the earliest recognition of an HAE attack when used concomitantly with moderate CYP3A4 inhibitors. A second dose of 300mg may be taken at least 3 hours after the first dose if response is inadequate, or if symptoms worsen or recur.
    - Dose modification is not recommended when Ekterly is used concomitantly with a weak CYP3A4 inhibitor
    - Use of Ekterly with strong or moderate CYP3A4 inducers is not recommended.
    - Dose modification is not recommended when Ekterly is used concomitantly with weak CYP3A4 inducers.

- **Special populations:**
  - There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.
  - The safety and efficacy of use in the pediatric population younger than 12 years of age have not been established.

Conclusion

- Hereditary angioedema is a rare but possibly life-threatening disease if the upper airway is affected (*Riedl et al 2024*) that is described by repeated episodes of angioedema (ie, swelling), without urticaria or pruritus (*Zuraw and Farkas 2025*).
- Ekterly is a plasma kallikrein inhibitor indicated for the treatment of acute attacks of HAE in adult and pediatric patients aged 12 years and older.
- Its efficacy was assessed in a double-blind, randomized, placebo-controlled, multicenter crossover clinical trial that compared Ekterly 600mg and 300mg with placebo. A second dose could be administered after 3 hours if needed.
  - The primary endpoint was the 'time to beginning of symptom relief', defined as at least 'a little better' at two consecutive time points within 12 hours of first dose administration.
  - Results suggested that there was a statistically significant faster time to the beginning of symptom relief for Ekterly 600mg as compared with placebo.
- Guidelines have yet to be updated to include Ekterly as they were published prior to the FDA approval of Ekterly, but they do discuss treatments for acute treatment of HAE.
- Comparator treatments may include CI-INH, Firazyr (icatibant), and Kalbitor (ecallantide).

- There is no evidence to suggest that Ekterly is safer or more effective than other currently preferred, more cost-effective medications. It is therefore recommended that Ekterly remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

- **PDL Placement:**
  - ☐ Preferred
  - ☒ Non-Preferred

References

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