Therapeutic Class Overview
Hereditary Angioedema Agents

INTRODUCTION

- Hereditary angioedema (HAE) is a rare disease which affects 1 in 10,000 to 50,000 people worldwide and approximately 6,000 to 10,000 patients in the United States (U.S.). It is characterized by recurrent episodes of localized subcutaneous or submucosal edema lasting for 2 to 5 days that can be disabling and, in the case of laryngeal attacks, life-threatening (*Busse et al 2021, Craig et al 2018, Zuraw 2018, Zuraw and Christiansen 2016).*
  - All ethnicities and races are affected by HAE. The literature reports a female predominance, as women tend to be more symptomatic than men due to hormonal factors related to puberty, contraception, and pregnancy (*Food and Drug [FDA] FDA Multi-discipline Review [Takhzyro] 2018).* HAE is an autosomal dominant disease, and most patients with HAE have a positive family history of angioedema. However, approximately 25% of cases result from *de novo* mutations (*Zuraw 2018*).
  - For the majority of patients, HAE first presents in childhood between 8 to 12 years of age, worsens around puberty, and persists throughout life with fluctuating severity of disease over time (*Busse et al 2021, Farkas et al 2017, Zuraw and Christiansen 2016*).
  - The mortality rate for patients with HAE, despite effective therapies, has been estimated to be as high as 13%. In undiagnosed laryngeal edema cases, mortality can be as high as 30 to 40%. Almost 80% of patients with HAE will experience an abdominal attack, which can be debilitating (*FDA Summary Basis for Regulatory Action [Cinryze] 2018, Zuraw and Farkas 2020a*).
  - HAE is predominantly facilitated by an excessive production of bradykinin, a potent vasodilatory peptide which mediates swelling in HAE through vasodilation and vascular leakage and is thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. Component 1 esterase inhibitor (C1-INH) controls bradykinin production through inhibition of key steps in the coagulation system (*Banerji et al 2017, Busse et al 2021, Lumry 2018, Zuraw 2018*).
    - HAE due to C1-INH deficiency (HAE-C1INH) accounts for the majority of HAE cases and includes 2 subtypes that are clinically indistinguishable: type I HAE (85% of HAE cases) with low C1-INH antigenic and functional levels, and type II HAE (15% of HAE cases) with normal C1-INH antigenic levels but decreased C1-INH functional levels (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw 2018, Zuraw et al 2013a*).
- The frequency and severity of HAE attacks are highly variable and unpredictable, but attacks typically follow a predictable course: swelling that increases slowly and continuously for 24 hours and then gradually subsides over the next 48 to 72 hours (*Craig et al 2018, Zuraw 2018, Zuraw and Christiansen 2016)*.
  - Mild trauma, including dental work, is a common trigger for angioedema episodes in many patients, while tooth extraction and oral surgery are common triggers for laryngeal attacks. Other reported triggers include angiotensin-converting enzyme (ACE) inhibitors, estrogen-containing medications, febrile illness, stress (either mental or physical), menstruation, and possibly *Helicobacter pylori* infection, excitement, sleep deprivation, cold exposure, prolonged sitting or standing, and ingestion of certain foods (*Busse et al 2021, Maurer et al 2018, Zuraw and Farkas 2020a*).
- This monograph describes the agents used to treat HAE (types I and II), including Berinert (C1 esterase inhibitor [human]), Cinryze (C1 esterase inhibitor [human]), danazol, Firazyr (icatibant), Haegarda (C1 esterase inhibitor [human]), Kalbitor (ecallantide), Orladeyo (berotralstat), Ruconest (C1 esterase inhibitor [recombinant]), and Takhzyro (lanadelumab-flyo).
  - The various HAE agents act on different targets to reduce bradykinin production or its effects, decrease angioedema, and improve outcomes in patients with HAE (*Busse et al 2021, Lumry 2018*).
  - The C1-INH agents (ie, Berinert, Cinryze, Haegarda, and Ruconest) replace the missing or malfunctioning C1-INH protein in patients.
  - Danazol is an anabolic androgen which corrects, partially or completely, the primary biochemical abnormality of HAE by increasing the levels of the deficient C1-INH.
  - Firazyr is a bradykinin B2 receptor antagonist and inhibits bradykinin from binding to the bradykinin B2 receptor.
  - Kalbitor and Orladeyo are plasma kallikrein inhibitors that inhibit the production of bradykinin.

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- Takhzyro is a monoclonal antibody and kallikrein inhibitor which decreases plasma kallikrein activity to control excess bradykinin generation in patients with HAE.

- Effective HAE management includes acute treatment to arrest an ongoing attack and prophylactic treatment to prevent or minimize attacks (*Busse et al 2021*, *Farkas et al 2017, Maurer et al 2018*).
  - Berinert, Ruconest, Kalbitor, and Firazyr are indicated for the treatment of acute HAE attacks, and guidelines recommend early treatment with either of these 4 agents for on-demand treatment of acute HAE attacks (*Busse et al 2021*, *Maurer et al 2018*).
  - Cinryze, Haegarda, Orladeyo, Takhzyro, and danazol are indicated for routine prophylaxis against HAE attacks.
    - Cinryze, Haegarda, and Takhzyro are preferred prophylactic therapy options in most circumstances. Decisions regarding use of prophylaxis should be individualized, based on the patient's quality of life and treatment preferences in the context of attack frequency, attack severity, comorbid conditions, and access to emergent treatment (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw et al 2013a*).
    - Long-term prophylaxis with androgen therapy (ie, danazol) is not preferred, due to numerous safety concerns including androgenic, anabolic, and hepatic adverse events (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw et al 2013a*).
    - Orladeyo is the newest agent available for the prophylaxis of HAE attacks and was FDA-approved after the most recent HAE guidelines were published.
- Medispan classes: Androgens-Anabolic; Bradykinin B2 Receptor Antagonists; C1 Esterase Inhibitors; Plasma Kallikrein Inhibitors; Plasma Kallikrein Inhibitors - Monoclonal Antibodies

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Berinert (C1 esterase inhibitor [human])	-
Cinryze (C1 esterase inhibitor [human])	-
danazol	✔
Firazyr (icatibant)	✔
Haegarda (C1 esterase inhibitor [human])	-
Kalbitor (ecallantide)	-
Orladeyo (berotralstat)	-
Ruconest (C1 esterase inhibitor [recombinant])	-
Takhzyro (lanadelumab-flyo)	-

(*Drugs@FDA 2021*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*, *Purple Book 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Routine prophylaxis against HAE attacks	Treatment of acute HAE attacks
Berinert (C1-INH [human])		✔ *
Cinryze (C1-INH [human])	✔ †	
danazol	✔ ¶	
Firazyr (icatibant)		✔ ‡
Haegarda (C1-INH [human])	✔ †	
Kalbitor (ecallantide)		✔ ‖
Orladeyo (berotralstat)	✔ ‖	
Ruconest (C1-INH [recombinant])		✔ §
Takhzyro (lanadelumab-flyo)	✔ ‖	

* In pediatric and adult patients; the safety and efficacy of Berinert for prophylactic therapy have not been established. Berinert is indicated for the treatment of acute abdominal, facial, or laryngeal HAE attacks in pediatric and adult patients.
† In patients ≥ 6 years of age

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‡ In adults ≥ 18 years of age
§ In adolescent and adult patients; Ruconest limitation of use: effectiveness was not established in HAE patients with laryngeal attacks.

|| In patients ≥ 12 years of age
¶ Danazol is also indicated for the treatment of endometriosis amenable to hormonal management and for fibrocystic breast disease.

(*Prescribing information: Berinert 2020, Cinryze 2021, danazol 2020, Firazyr 2020, Haegarda 2020, Kalbitor 2020, Orladeyo 2020, Ruconest 2020, Takhzyro 2018*)

Off-label uses of HAE agents:

- Cinryze has been used off-label for treatment of acute HAE attacks (*Zuraw and Farkas 2020b, Zuraw et al 2013a*). However, results from an acute-attack trial for Cinryze were not robust enough for FDA approval (*Zuraw et al 2010a, ViroPharma Press Release 2009*).
- Some experts consider Berinert to be an additional option for long-term prophylaxis due to its long half-life, but data are lacking (*Xu et al 2013*).

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

CLINICAL EFFICACY SUMMARY

Agents for the on-demand treatment of acute HAE attacks

Berinert

- The efficacy and safety of Berinert were evaluated in a double-blind, placebo-controlled randomized-controlled trial (I.M.P.A.C.T.1) in 125 patients with HAE (*Craig et al 2009, FDA Summary Basis for Regulatory Action [Berinert] 2009*). The trial demonstrated that Berinert was effective in treating acute abdominal and facial HAE attacks. The time to onset of symptom relief was significantly shorter with Berinert 20 units (U)/kg vs placebo (48 minutes vs > 4 hours; p = 0.0016).
  - An open-label extension study of I.M.P.A.C.T.1 (I.M.P.A.C.T.2) concluded that Berinert provided reliable efficacy for successive HAE attacks at any anatomical location in 57 patients (*Craig et al 2011, FDA Summary Basis for Regulatory Action [Berinert] 2009*). The median time to symptom relief was 0.46 hours in the per-subject analysis (range, 0.39 to 0.48 hours) and 0.37 hours in the per-attack analysis (range, 0.25 to 0.50 hours). The median time to complete resolution of all HAE symptoms was 15.48 hours in the per-subject analysis (range, 5.79 to 26.63 hours) and 14.28 hours in the per-attack analysis (range, 8.38 to 28.33 hours).

Firazyr

- Firazyr was evaluated for the treatment of acute HAE attacks in 2 Phase 3, double-blind, multi-center, randomized-controlled trials (FAST-1, n = 56; FAST-2, n = 74) (*Cicardi et al 2010b*). FAST-1 compared Firazyr with placebo while FAST-2 compared Firazyr with tranexamic acid.
  - The primary endpoint was not met in FAST-1, and the FDA questioned the validity of using tranexamic acid as an active control in FAST-2 since its efficacy for treatment of acute HAE attacks has not been established. Consequently, the FDA issued a Complete Response Letter requesting a third controlled study (*ViroPharma Press Release 2009*).
- The FAST-3 Phase 3, double-blind, placebo-controlled randomized-controlled trial evaluated the efficacy of Firazyr for the treatment of acute HAE attacks in 98 patients (*Lumry et al 2011*). The study demonstrated that the median time to 50% reduction in symptom severity was significantly shorter with Firazyr (2.0 hours) vs placebo (19.8 hours; p < 0.001) in patients with cutaneous and/or abdominal attacks. In patients with laryngeal attacks, the median time to 50% reduction in symptom severity was 2.5 hours (95% confidence interval [CI], 1.3 to 3.0) with Firazyr vs 3.2 hours (95% CI, 1.0 to 5.4) with placebo.

Kalbitor

- Kalbitor was evaluated for the treatment of acute HAE attacks in 2 Phase 3, double-blind, placebo-controlled randomized trials (EDEMA3, n = 72; EDEMA4, n = 96) (*Cicardi et al 2010a, Levy et al 2010*). The mean change from baseline in the mean symptom complex severity (MSCS) score 4 hours after treatment was -1.1 (95% CI, -1.4 to -0.8) with Kalbitor vs -0.6 (95% CI, -0.8 to -0.4) with placebo (p = 0.041) in EDEMA3, and -0.8 with Kalbitor vs -0.4 with placebo (p = 0.01) in EDEMA4. A -0.3 change in the MSCS score indicated a minimally important difference in symptom improvement.

Ruconest

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- The efficacy of Ruconest for acute HAE attacks was evaluated in 2 similar double-blind, placebo-controlled, randomized trials (Study 1205, n = 38; Study 1304, n = 32) (*Zuraw et al 2010b*). The studies found that the median time to onset of symptom relief was 66 minutes (95% CI, 61 to 122) with Ruconest 100 international units (IU)/kg and 122 minutes (95% CI, 72 to 136) with Ruconest 50 IU/kg, vs 495 minutes (95% CI, 245 to 520) with placebo ($p < 0.001$ and $p = 0.013$, respectively).
  - Open-label extension studies of Studies 1205 (n = 62) and 1304 (n = 57) determined that Ruconest provided reliable efficacy for successive HAE attacks (*Moldovan et al 2012, Riedl et al 2013*). In 1205, the median times to beginning of symptom relief for the first 5 attacks were 37 to 67 minutes, and median times to minimal symptoms for the first 5 attacks were 120 to 244 minutes. In 1304, the median times to the beginning of relief of symptoms for attacks 1 through 5 were 60, 65, 120, 60, and 61 minutes, respectively, and overall sustained relief of symptoms was achieved in 87% of Ruconest-treated patients within 4 hours of treatment.
- Treatment with Ruconest for acute HAE attacks was evaluated in a third double-blind, placebo-controlled, randomized-controlled trial (Study 1310) in 75 patients (*Riedl et al 2014*). The median time to the beginning of symptom relief was 90 minutes (95% CI, 61 to 150) in patients treated with Ruconest vs 152 minutes (95% CI, 93 to "not estimable") in placebo-treated patients ($p = 0.031$).
  - An open-label extension study of Study 1310 in 44 patients concluded that Ruconest was effective in improving symptoms of repeat HAE attacks (*Li et al 2015*). The median time to symptom relief ranged from 75 to 90 minutes, and the median time to minimal symptoms for the first 3 attacks ranged from 243 to 303 minutes.

Comparative Review

- A systematic review compared the efficacy of the treatment of 881 acute laryngeal HAE attacks in 12 studies with various HAE agents, including plasma-derived and recombinant C1-INHs, Firazyr, and Kalbitor (*Bork et al 2016*). Onset of symptom relief was generally achieved with all treatment options within 1 hour after the start of treatment for 60 to 100% of laryngeal attacks. Treatment with the body-weight-adjusted dose of Berinert 20 U/kg provided the shortest median time to onset of symptom relief of 15 minutes, followed by approximately 30 to 45 minutes with fixed doses of Berinert or Firazyr, approximately 1.5 hours with Kalbitor, and 2 hours with Ruconest. The proportion of laryngeal attacks that required re-dosing ranged from 0 to 72%. For the 48 attacks treated with Berinert 20 U/kg, no re-dosing was needed after treatment. The comparative review included mostly open-label prospective studies with various protocols and the differences in endpoint definitions between studies made comparisons difficult; therefore, these results should be considered with caution.

Agents for routine prophylaxis against HAE attacks

Cinryze

- The efficacy of Cinryze for prophylaxis of HAE attacks was evaluated in a 24-week double-blind, placebo-controlled, crossover randomized-controlled trial in 22 patients with HAE (*Zuraw et al 2010a*). Treatment with Cinryze 1000 U every 3 to 4 days reduced the rate of attacks by 50% vs placebo (6.26 vs 12.73, respectively; $p < 0.001$). Treatment with Cinryze also significantly reduced the severity and duration of HAE attacks compared with placebo.
  - A 12-week, open-label, single-arm study evaluated the safety of escalating the dose of Cinryze up to 2500 U. Of 20 patients who initiated treatment with 1500 U of Cinryze in the trial, 13 escalated to 2000 U and 12 escalated to 2500 U based on treatment response. Overall, Cinryze was well-tolerated at all dose levels, and the majority of identified adverse events were mild to moderate (*Bernstein et al 2014*).
  - An open-label extension study of 2.6 years duration evaluated the efficacy of treatment with Cinryze 1000 U every 3 to 7 days for prophylaxis in 146 patients with HAE (*Zuraw et al 2012*). The mean frequency of HAE attacks during the study was 0.47 ± 0.83, a 90.0% reduction from the historical mean frequency of 4.7 ± 5.2 attacks/month. A total of 34.9% of patients had 0 attacks during the study.
- The efficacy of Cinryze for the prophylaxis of HAE attacks in pediatrics was established in an unpublished, dose-ranging, 24-week, Phase 3, multi-center, single-blind, crossover randomized-controlled trial in 12 children 7 to 11 years of age (*Aygören-Pürsün et al 2018, Clinicaltrials.gov Web site, FDA Summary Basis for Regulatory Action [Cinryze] 2018*). Compared to the baseline observational period, treatment with both Cinryze 500 U and 1000 U twice weekly decreased the mean number of HAE attacks per month by 2.6 and 3.0, respectively, with a mean reduction in HAE attacks of 71.1% and 84.5%, respectively. Treatment with both doses of Cinryze over a 3-month period also lessened the severity of attacks and reduced the requirement for acute treatment compared with baseline.

Danazol

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- Danazol was evaluated for the prevention of HAE attacks in a double-blind, placebo-controlled study in 9 patients with a total of 93 courses of treatment (*Gelfand et al 1976*). Patients treated with danazol were attack-free 93.6% of the time during a 28-day period vs 2.2% of the time in placebo-treated patients ($p < 0.001$). While treated with danazol, C1-INH levels in patients increased 3- to 4-fold, while complement component 4 (C4) levels rose 15-fold.
  - A systematic review of 43 reports evaluated the effectiveness and safety of the use of androgens for HAE prophylaxis in > 1600 patients. Two small placebo-controlled randomized-controlled trials and various long term open-label trials, most commonly with danazol, demonstrated that treatment with androgens reduced the HAE attack rate and were associated with reduced frequency and severity of acute HAE attacks (*Riedl 2015*).

Haegarda

- The efficacy of Haegarda for prophylaxis of HAE attacks was evaluated in COMPACT, a 32-week Phase 3, double-blind, placebo-controlled, crossover randomized trial in 90 patients with HAE (*Longhurst et al 2017*). Treatment with Haegarda 60 IU/kg subcutaneous (SC) injection twice weekly reduced the rate of attacks by 84%, with a mean difference of -3.51 attacks per month vs placebo (95% CI, -4.21 to -2.81; $p < 0.001$). Treatment with Haegarda also significantly reduced the severity and duration of HAE attacks compared with placebo.
  - Haegarda was also assessed in an open-label, parallel-arm extension of COMPACT, including patients ≥ 6 years of age who had either completed the trial or who were study treatment-naïve (*Craig et al 2019)*. The incidence of adverse events was similar in both Haegarda dose groups (11.3 and 8.5 events per patient-year for 40 and 60 IU/kg, respectively). Median annualized attack rates were 1.3 and 1.0, respectively, and median rescue medication use was 0.2 and 0.0 times per year, for 40 and 60 IU/kg groups.

Orladeyo

- The efficacy and safety of orally administered Orladeyo for prophylaxis of HAE attacks were evaluated in a 24-week Phase 3, double-blind, placebo-controlled, parallel-group, multi-center randomized-controlled trial in 121 patients ≥ 12 years of age with HAE (*FDA Multi-discipline Review [Orladeyo] 2020, Zuraw et al 2020*). Treatment with Orladeyo resulted in a significant reduction in the 28-day HAE attack rate relative to placebo; Orladeyo 150 mg demonstrated a 44.2% reduction (1.31 attacks/28 days; $p < 0.001$) and Orladeyo 110 mg demonstrated a 30.0% reduction (1.65 attacks/28 days; $p = 0.024$) compared to 2.35 attacks/28 days with placebo.
  - The proportion of responders with ≥ 50% reduction in HAE attack rates compared to baseline was statistically significant with Orladeyo vs placebo, at 58% with Orladeyo 150 mg ($p = 0.005$) and 51% with Orladeyo 110 mg ($p = 0.021$). In post-hoc analyses, 50% of patients treated with Orladeyo 150 mg achieved ≥ 70% reduction in HAE attacks from baseline, with a significant benefit vs placebo.

Takhzyro

- The efficacy and safety of Takhzyro for prophylaxis of HAE attacks were evaluated in a 26-week Phase 3, double-blind, placebo-controlled, parallel-group, multi-center randomized-controlled trial in 125 patients ≥ 12 years of age with type I or II HAE (*Banerji et al 2018; FDA Multi-discipline Review [Takhzyro] 2018*). There was a significant reduction in HAE attack rates with Takhzyro vs placebo; the mean number of HAE attacks per month with placebo was 1.97 vs 0.48, 0.53, and 0.26 with Takhzyro 150 mg every 4 weeks, 300 mg every 4 weeks, and 300 mg every 2 weeks, respectively ($p < 0.001$ for all treatment groups). There was also statistically significant improvement in the reduction of the number of HAE attacks requiring acute treatment and the number of moderate or severe HAE attacks with all 3 doses of Takhzyro vs placebo ($p < 0.001$ for all treatment groups).

Comparative Review

- An Institute for Clinical and Economic Review (ICER) and California Technology Assessment Forum (CTAF) final evidence report for Takhzyro in HAE included a comparative clinical effectiveness review of 3 clinical trials to evaluate the comparative safety and efficacy of prophylaxis with Takhzyro, Cinryze, and Haegarda in patients with type I and II HAE (*CTAF 2018*). The review determined that the data for Cinryze and Haegarda demonstrated a high certainty of substantial net health benefit vs no prophylaxis (“A” rating). Due to lack of long-term safety data for Takhzyro, evidence for Takhzyro was rated as promising but inconclusive, demonstrating a moderate certainty of a comparable or substantial net health benefit, and a small (but non-zero) likelihood of a negative net health benefit (“promising but inconclusive [P/I]” rating).

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CLINICAL GUIDELINES

- There are various organizations that have published guidelines for the treatment of HAE, including the International World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI), Hereditary Angioedema International Working Group (HAWK), U.S. Hereditary Angioedema Association (HAEA), and Joint Task Force on Practice Parameters (JTFPP) (representing the American Academy of Allergy, Asthma & Immunology [AAAAI]; the American College of Allergy, Asthma & Immunology [ACAAI]; and the Joint Council of Allergy, Asthma and Immunology) (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw et al 2013a*).
- Recent guidelines emphasize that the goals of HAE management are to "normalize" life as much as possible and improve quality of life, and ensure patients are able to engage in all work, school, family, and leisure activities as desired without limitation from angioedema symptoms (*Busse et al 2021, Maurer et al 2018*).
- For acute attacks, there is guideline consensus that patients with HAE should have on-demand access to at least 2 standard doses of an effective HAE-specific agent to treat an attack, including Berinert, Firazyr, Kalbitor, or Ruconest, at all times. All 4 of these on-demand medications are considered very effective and generally safe (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw et al 2013a*).
  - All attacks, irrespective of the location of the swelling or the severity of the attack, should be considered for on-demand treatment and treated as early as possible, as earlier treatment shortens attack duration and improves treatment outcomes (*Busse et al 2021, Maurer et al 2018*).
  - Self-administration of on-demand treatment is strongly recommended whenever feasible, except for Kalbitor, which requires administration by a healthcare provider (*Busse et al 2021, Maurer et al 2018*).
- Short-term (or pre-procedural) prophylaxis is indicated when patients are at increased risk of having an HAE attack associated with known triggers such as invasive dental or medical procedures or stressful life events. C1-INH and anabolic androgens are appropriate therapy options for short-term prophylaxis (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw et al 2013a*).
- The 2020 HAEA guidelines specify the C1-INHs, Cinryze and Haegarda, and Takhzyro as preferred prophylactic therapy options in most circumstances (*Busse et al 2021*).
  - Decisions regarding the use of long-term prophylactic treatment should be individualized, based on the patient's quality of life and treatment preferences in the context of attack frequency, attack severity, comorbid conditions, and access to emergent treatment (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw et al 2013a*).
  - While Cinryze has been shown to be both safe and effective against HAE attacks, repeated intravenous (IV) administration can result in loss of readily accessible veins unless great care is taken to preserve the veins. Indwelling ports are discouraged due to the risk of thrombosis and infection, unless deemed medically necessary (*Busse et al 2021*).
  - Long-term prophylaxis with androgen therapy (ie, danazol) is not preferred, due to numerous safety concerns including androgenic, anabolic, and hepatic adverse events (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018*).
- Orladeyo is the newest agent to be approved by the FDA for the prophylaxis of HAE attacks and is not included in current HAE guideline recommendations. However, the availability of new first-line oral prophylactic medications (eg, Orladeyo) may influence the choice of long-term prophylaxis (*Busse et al 2021*).

SAFETY SUMMARY

C1-INH agents (Berinert, Cinryze, Haegarda, and Ruconest):

- Contraindications:
  - Patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to C1-INH preparations.
  - Ruconest: patients with known or suspected allergy to rabbits and rabbit-derived products.
- Key warnings and precautions:
  - Hypersensitivity: severe hypersensitivity reactions may occur. Epinephrine should be immediately available for treatment of any acute severe hypersensitivity reaction following discontinuation of administration.
  - Thromboembolic events: serious arterial and venous thromboembolic events have been reported at the recommended dose of these products in patients with HAE.
  - Plasma-derived C1-INH agents (Berinert, Cinryze, and Haegarda): Transmissible infectious agents: as these agents are made from human plasma, they may contain infectious agents (eg, viruses, and, theoretically, the Creutzfeldt-Jakob agent).

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- Berinert: laryngeal HAE attacks; following treatment of laryngeal HAE attacks, patients should be advised to immediately seek medical attention.

- Adverse reactions:
  - Berinert: the most serious reported adverse reaction was an increase in the severity of pain associated with HAE. The most common adverse reaction (> 4%) was dysgeusia.
  - Cinryze: the most common adverse reactions (≥ 5%) included headache, nausea, rash, vomiting, and fever.
  - Haegarda: the most common adverse reactions (> 4%) included injection site reaction, hypersensitivity, nasopharyngitis, and dizziness.
  - Ruconest: the serious adverse reaction reported in clinical trials was anaphylactic reaction, while the most common adverse reactions (≥ 2%) included headache, nausea, and diarrhea.

Danazol:

- Contraindications: undiagnosed abnormal genital bleeding; markedly impaired hepatic, renal, or cardiac function; pregnancy; breast-feeding; porphyria; androgen-dependent tumor; active thrombosis or thromboembolic disease and history of such events; and hypersensitivity.
- Boxed warnings:
  - Use of danazol in pregnancy is contraindicated.
  - Thromboembolism, thrombotic and thrombophlebitic events including sagittal sinus thrombosis and life-threatening or fatal strokes have been reported.
  - Peliosis hepatis and benign hepatic adenoma have been observed with long-term use. Peliosis hepatis and hepatic adenoma may be silent until complicated by acute, potentially life-threatening intra-abdominal hemorrhage.
  - Danazol has been associated with several cases of benign intracranial hypertension (also known as pseudotumor cerebri).
- Key warnings and precautions: lipoprotein alterations, androgenic effects, porphyria, fluid retention, and hepatic dysfunction.
- Adverse reactions:
  - Androgen-like effects including weight gain, acne, and seborrhea.
  - Possible endocrine effects including menstrual disturbances.
  - Flushing, sweating, vaginal dryness and irritation, and reduction in breast size due to estrogen lowering.
  - Hepatic dysfunction; serious hepatic toxicities including cholestatic jaundice, peliosis hepatis, and hepatic adenoma have been reported.
  - Abnormalities in laboratory tests including creatine phosphokinase, glucose tolerance, glucagon, thyroid binding globulin, sex hormone binding globulin, other plasma proteins, lipids, and lipoproteins.
- Drug interactions:
  - Prolongation of prothrombin time may occur in patients stabilized on warfarin.
  - Increased in levels of carbamazepine, cyclosporine, and tacrolimus.
  - Insulin resistance; caution is advised when administered with antidiabetic drugs.
  - Increased calcemic response to synthetic vitamin D analogs in primary hypoparathyroidism.
  - Myopathy and rhabdomyolysis risk is increased by concomitant administration of danazol with statin agents.

Firazyr:

- Warnings/precautions: laryngeal HAE attacks; following treatment of laryngeal HAE attacks, patients should be advised to immediately seek medical attention.
- Injection site reaction was the most commonly reported adverse reaction and occurred in almost all patients (97%) in clinical trials. Other common adverse reactions (> 1%) included pyrexia, transaminase increase, dizziness, and rash.
- Drug interactions: Firazyr may attenuate the antihypertensive effect of ACE inhibitors. Clinical trials to date have excluded subjects taking ACE inhibitors.
- Firazyr is Pregnancy Category C.

Kalbitor:

- Contraindication: patients with known hypersensitivity to Kalbitor.
- Boxed warning: anaphylaxis has been reported after administration of Kalbitor. Due to this risk, Kalbitor should only be administered by a health care professional with appropriate medical support to manage anaphylaxis and HAE.
- The most common adverse reactions (≥ 3%) included headache, nausea, diarrhea, pyrexia, injection site reactions, and nasopharyngitis.
- Kalbitor is Pregnancy Category C.

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Orladeyo:

- Warnings/precaution: additional doses or dosages > 150 mg once daily may increase risk of QT prolongation.
- The most common adverse reactions (≥ 10%) included abdominal pain, vomiting, diarrhea, back pain, and gastroesophageal reflux disease.
- Drug interactions: Dose reductions are recommended in patients with chronic administration of inhibitors of P-glycoprotein or breast cancer resistance protein. P-glycoprotein inducers may decrease Orladeyo plasma concentration. Orladeyo at a dose of 150 mg is a moderate inhibitor of cytochrome P450 (CYP) 2D6 and CYP3A4; concomitant medications with a narrow therapeutic index that are predominantly metabolized by these enzymes should be appropriately monitored.
- In accordance with the FDA's Pregnancy and Lactation Labeling Rule, Orladeyo is not currently assigned a Pregnancy Category. The product prescribing information should be consulted for details.

Takhzyro:

- Warnings/precautions: hypersensitivity reactions have been observed.
- The most common adverse reactions (≥ 5%) included injection site reactions, upper respiratory infections, headache, rash, myalgia, dizziness, and diarrhea.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Berinert (C1 esterase inhibitor [human])	Injection	IV	One dose as needed to treat an acute HAE attack	• May be self-administered
Cinryze (C1 esterase inhibitor [human])	Injection	IV	Every 3 or 4 days	• May be self-administered
Danazol	Capsules	oral	Two or 3 times daily	• May be self-administered • Daily doses > 200 mg are not recommended for long-term use due to risk of adverse reactions (*Zuraw and Farkas 2021*).
Firazyr (icatibant)	Injection	SC	One dose as needed to treat an acute HAE attack; additional doses may be administered at intervals of at least 6 hours with no more than 3 doses in a 24-hour period	• May be self-administered
Haegarda (C1 esterase inhibitor [human])	Injection	SC	Every 3 or 4 days	• May be self-administered
Kalbitor (ecallantide)	Injection	SC	One dose as needed to treat an acute HAE attack; if an attack persists, 1 additional dose may be administered within a 24-hour period	• Should only be administered by a health care professional with appropriate medical support to manage anaphylaxis and HAE.
Orladeyo (berotralstat)	Capsules	oral	Once daily with food	• Dose reductions are recommended in patients with moderate or severe hepatic impairment, patients with chronic administration of P-glycoprotein or breast cancer resistance protein inhibitors,

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				and patients with persistent gastrointestinal reactions. • Should not be used in patients with end-stage renal disease.
Ruconest (C1 esterase inhibitor [recombinant])	Injection	IV	One dose as needed to treat an acute HAE attack; if an attack persists, 1 additional dose may be administered within a 24-hour period	• May be self-administered
Takhzyro (lanadelumab-flyo)	Injection	SC	Every 2 weeks; 4-week dosing may be considered if the patient is well-controlled (eg, attack free) > 6 months	• May be self-administered

See the current prescribing information for full details.

CONCLUSION

- HAE is a rare condition characterized by recurrent episodes of angioedema that may be disabling and, in the case of laryngeal attacks, life-threatening. Various agents are indicated for on-demand and prophylactic treatment of HAE, with a range of pathophysiological approaches. Head-to-head trials between the agents are lacking. Patient- and medication-specific factors should be considered when designing individualized treatment plans for patients with HAE.
- The plasma-derived (human) C1-INH Berinert, recombinant C1-INH Ruconest, the plasma kallikrein inhibitor Kalbitor (ecallantide), and the bradykinin B2 receptor antagonist Firazyr (icatibant), are indicated for acute treatment of HAE attacks and have been shown to be effective in placebo-controlled randomized-controlled trials.
  - Consensus guidelines recommend that patients should have access to an on-demand HAE-specific agent at all times. All 4 FDA-approved on-demand medications are considered very effective and generally safe.
  - Berinert is the only on-demand agent indicated for the treatment of acute abdominal, facial, or laryngeal HAE attacks, as well as the only on-demand agent indicated in pediatric and adult patients.
  - Berinert and Ruconest may be self-administered, via IV injection.
  - Firazyr may be self-administered via SC injection and has a high risk of injection site reactions.
  - Kalbitor has a boxed warning for anaphylaxis and requires administration by a health care professional.
- The plasma-derived (human) C1-INH agents Cinryze and Haegarda, the monoclonal antibody Takhzyro (lanadelumab-flyo), the plasma kallikrein inhibitor Orladeyo (berotralstat), and the anabolic androgen danazol are indicated for routine prophylaxis against HAE attacks.
  - Guidelines recommend Cinryze, Haegarda, and Takhzyro as the preferred prophylactic therapy options in most circumstances.
    - Orladeyo is the newest HAE agent approved by the FDA and is not included in current HAE guideline recommendations.
  - In clinical trials, Takhzyro, Haegarda, and Orladeyo reduced HAE attacks rates up to 87%, 84% and 44%, respectively, compared with placebo; Cinryze reduced rates by 90% compared with historical mean.
  - Cinryze and Haegarda are both indicated in children ≥ 6 years of age; Orladeyo and Takhzyro are indicated in patients ≥ 12 years of age.
  - Haegarda is self-administered via SC injection every 3 to 4 days, while Takhzyro is self-administered via SC injection every 2 to 4 weeks. Cinryze is self-administered via IV injection. Orladeyo capsules are orally administered once daily with food.
  - Orladeyo has a warning and precaution for an increase in QT prolongation at dosages greater than the recommended daily dose; common adverse reactions include gastrointestinal effects. Orladeyo is associated with various drug-drug interactions.
  - Long-term prophylaxis with oral androgen therapy (ie, danazol) is not recommended, due to numerous safety concerns including androgenic, anabolic, and hepatic adverse events.

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