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FDA-APPROVED PROPHYLACTIC AND RESCUE AGENTS FOR HEREDITARY ANGIOEDEMA

C1 Esterase Inhibitor [Human]/pdC1INH (CINRYZE, HAEGARDA, BERINERT)
C1 Esterase Inhibitor [Recombinant]/rhC1INH (RUCONEST)
Berotralstat (ORLADEYO)
Lanadelumab-flyo (TAKHZYRO)
Icatibant (FIRAZYR, SAJAZIR)
Ecallantide (KALBITOR)
Danazol

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CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

ACE	angiotensin-converting enzyme inhibitors
ADAs	anti-drug antibodies
AEs	adverse events
C1INH	C1 esterase inhibitor
CHAEN	Canadian Hereditary Angioedema Network
CHAEN/IE	Canadian Hereditary Angioedema Network and International Expert joint guideline
CYP	cytochrome
EAACI	European Academy of Allergy and Clinical Immunology
EU	European Union
FDA	Food and Drug Administration
FFP	fresh frozen plasma
GI	gastrointestinal
HAE	hereditary angioedema
HAEA	US Hereditary Angioedema Association
HAE-C1INH	hereditary angioedema due to C1 inhibitor deficiency
HAE-nl-C1INH	hereditary angioedema with normal levels of C1 inhibitor
IU	international units
IV	intravenous
LDL	low-density lipoprotein
LTP	long-term prophylaxis
pdC1INH	plasma derived C1 esterase inhibitor
PDL	preferred drug list
PO	oral
RCT	randomized controlled trial
rhC1INH	recombinant C1 esterase inhibitor
SC	subcutaneous
SDP	solvent detergent-treated plasma
STP	short-term prophylaxis
WAO	International World Allergy Organization

EXECUTIVE SUMMARY

BACKGROUND

Hereditary angioedema (HAE) is a rare disorder of recurrent severe swelling episodes (ie, HAE attacks) within submucosal or subcutaneous layers typically affecting the skin, gastrointestinal tract, upper airway, face, and/or throat.[1] HAE-induced laryngeal swelling is life-threatening and necessitates immediate rescue therapy.[1,2] Attacks can be spontaneous and unpredictable, while some episodes may be foreseeable upon common triggers such as physical trauma (especially dental procedures), emotional stress, fatigue, infections, or certain medications such as estrogens.[1] Approximately 1 in 50,000 persons worldwide are affected by HAE.[1]

Most HAE cases are attributed to genetic mutations in a key protein (C1 esterase inhibitor [C1INH]) that regulates the production of bradykinin,[3] a potent vasodilator (ie, key mediator of laryngeal edema).[4] Such cases are classified as HAE-C1INH type 1 or type 2, depending on the quality/quantity of C1INH produced. Rarer HAE cases have normal C1INH levels/function, encompassing heterogenous subtypes with different causative genetic mutations, and are classified as HAE-nl-C1INH.

HAE attacks and swelling are unresponsive to common agents used for inflammation or airway constrictive reactions (eg, antihistamines, glucocorticoids, or epinephrine); thus, HAE-specific treatments must be used for the management of this disease. Treatment strategies include providing an on-demand, rescue agent for the event of an HAE attack, as well as pharmacotherapy either for short-term prophylaxis (STP) of an anticipated attack, or for long-term prophylaxis (LTP) to decrease the frequency and severity of unpredictable attacks.[5]

APPROVED HAE MEDICATIONS

Currently approved medications for HAE therapeutically function by either (a) replenishing deficient C1INH plasma levels (C1INH concentrate products), (b) inhibiting production of bradykinin activation through the enzyme, kallikrein (kallikrein inhibitors), or (c) targeting bradykinin receptors to halt or prevent HAE symptoms (bradykinin B2 receptor antagonists). HAE medications are approved for either acute treatment of attacks or for prophylaxis therapy to prevent attacks. Additional key differences among HAE medications include their approved age for use and characteristics relevant to the ease of use, such as the route of administration, potential need for reconstitution (for injectables), self-administrability, or dosing frequency (for prophylaxis agents).

On-demand (rescue) medications approved in the US include the kallikrein inhibitor, **ecallantide**; the bradykinin B2 receptor antagonist, **icatibant**; the plasma-derived C1INH (pdC1INH) concentrate, **Berinert**; and the recombinant C1INH (rhC1INH) concentrate, **Ruconest**. The C1INH concentrates are intravenously administered, require reconstitution, and can be self-administered by trained patients or caregivers. They are approved for adults and either pediatric (Berinert) or adolescent (Ruconest) patients.[6,7] Ecallantide (Kalbitor) is a subcutaneous solution approved for patients 12 years and older. Its usability outside of the clinic is limited due to the labeled requirement for administration by a healthcare professional who can respond to a potential anaphylactic reaction.[8] Icatibant, approved for adults only, is available as subcutaneous solutions (Firazyr, Sajazir) which do not require reconstitution

and are self-administered.[9,10] Icatibant may be the most convenient on-demand product for self-administration, given that the others require intravenous administration (ie, Berinert and Ruconest) or must be administered by a healthcare provider (ie, ecallantide).

Approved **routine (ie, LTP) prophylaxis agents** include the attenuated androgen, **danazol**; the pdC1INH concentrates**, Cinryze** and **Haegarda**; and the kallikrein inhibitors, **lanadelumab**-flyo (Takhyzro) and **berotralstat** (Orladeyo). The two pdC1INH concentrates are indicated for the youngest age, of at least 6 years old, and are administered twice weekly but by different routes—Cinryze intravenously and Haegarda subcutaneously. These products require reconstitution before use and can be self-administered.[5,11-14] In other countries (not in the US), Cinryze also has approval for pre-procedural prophylaxis (ie, STP) and for on-demand treatment of attacks, as it is intravenously administered/rapidly bioavailable. Newer prophylactic kallikrein inhibitors include the subcutaneously administered monoclonal antibody, lanadelumab and the first oral medication for LTP, berotralstat; both are indicated for patients 12 years or older.[15,16] Lanadelumab is administered least frequently of the prophylactic agents (every 2 or 4 weeks), does not require reconstitution, and is self-administered. Oral berotralstat is administered daily.[15] Danazol is an older oral agent, generally indicated for prevention of HAE attacks with daily dosing/use.

Overall, there is a lack of head-to-head comparative trials among approved agents for HAE. Thus, clinical guidelines typically recommend either several agents or a particular drug class for a particular use (eg, first-line LTP), rather than a single preferred agent.

GUIDELINE RECOMMENDATIONS

Clinical treatment guidelines recommend considering on-demand, rescue therapy for all patients with HAE, to be used at the onset of any HAE attack, to reduce the duration and severity of the attack.[1,5,13,17] The approved agents for on-demand, rescue therapy are all considered first-line options for HAE attacks in patients with HAE-C1INH; they can also be used for HAE-nl-C1INH.[5] Additionally, European guidelines include Cinryze as an on-demand option (Cinryze is approved in several other countries but not in the US for on-demand treatment). Providing readily accessible, on-demand medication to patients with HAE is a strong recommendation by guidelines since HAE attacks can be unpredictable and life-threatening.[1,5,13] Thus, it is inferred that for ambulatory patients, a self-administrable, on-demand product is generally preferrable versus relying on modalities limited to clinic use (ecallantide) or hospital use (fresh frozen plasma). Guidelines emphasize the importance of early treatment of attacks, since early versus later treatment is associated with better outcomes.[1,5,13] The US guideline describes that because HAE is rare, HAE-specific medications may not be readily available in hospitals or emergency departments, so prescribing the rescue (on-demand) therapy to patients is important.[5] The WAO/EAACI recommends that patients carry sufficient on-demand medication supply to treat at least two attacks, at all times.[1]

Guidelines recommend STP before any known trigger or potential stressful event that could trigger an attack (eg, medical, surgical, or dental procedures)[1,5,13] for all patients with HAE, including HAE-nl-C1INH.[5] Intravenous pdC1INH products are generally the treatment of choice for STP, and guidelines note positive but limited evidence for STP with the rhC1INH product, Ruconest, as well.[1,5,13,17]

The decision of whether to start LTP is personalized and should take into consideration patient preferences, disease activity (eg, attack frequency and severity), disease burden/quality of life, and

practical factors such as the patient's ability to access emergency care for attacks and ability to self-administer on-demand medication.[1,5,13] **For HAE type 1 or 2, pdC1INH, lanadelumab, or berotralstat** (ie, FDA-approved prophylactic therapies, with the exception of danazol) are recommended first line options for LTP, based on randomized controlled trial evidence supporting their efficacy.[1] Danazol, with a high adverse event burden and/or anabolic effects in most patients, many drug interactions, and contraindications, is reserved as a second-line LTP option in the event first-line options cannot be used.[1] The US guideline also describes that rhC1INH (Ruconest), which so far is approved in the US for on-demand treatment of HAE attacks, has phase II supportive evidence for use as LTP and could serve as a potential option during pdC1INH shortages that occasionally occur.[5]

With respect to on-demand treatment for children, the US guideline suggests that **pdC1INH** is preferred (but not specified at the level of a formal recommendation) and describes other options with positive evidence (with or without FDA approval; refer to section 7.1.1). Similarly, pdC1INH is generally recognized as the treatment of choice for STP and LTP in children, as it has the most evidence for use in pediatric HAE.[1,5,17] The US guideline also recognized lanadelumab as an option for LTP, with approval in the US for children of age 12 or older.[5] Long-term use of attenuated androgens (eg, danazol) is generally reserved as a last-line option after reaching Tanner developmental stage 5 (and/or after the age 16) due to the risk of adverse developmental effects on growth and sexual maturation.[1,5,13,17] Regarding other subpopulations, refer to section 7.2 for pregnancy; and, section 6.2.2 for LTP in HAE-nl-C1INH.

SAFETY

All C1INH concentrates, ecallantide, and danazol have contraindications regarding hypersensitivity to the product. Furthermore, the labeling of pdC1INH products highlights that epinephrine should be made immediately available to patients (ie, dispensed for take home use) to be able to respond to a hypersensitivity (allergic) reaction. Ecallantide, in particular, requires administration in a clinic due to the risk of anaphylaxis. All C1INH products and danazol have a warning for serious arterial and venous thromboembolic events; this is a black box warning for danazol. Danazol is also contraindicated in many other subpopulations including patients with cardiac, hepatic, or renal dysfunction, and in pregnancy, among others. Refer to section 9.1.2 for additional warnings regarding danazol.

Notable common side effects include injection site reactions with several of the injectable products (lanadelumab, Haegarda, icatibant, and ecallantide)[18,19] and GI-related adverse events with berotralstat.[20] Common AEs associated with androgens such as danazol when used for ongoing prophylaxis include weight gain, virilization, myalgias, hypertension, mood changes, and laboratory parameter abnormalities for creatine phosphokinase, liver enzymes, and LDL (low-density lipoprotein).[21]

CONCLUSION

No available direct, head-to-head clinical trials that compare the reviewed on-demand or prophylactic HAE medications were identified. However, differences in the agents' ease of use which could influence response time in an active HAE attack (for on-demand agents) or the burden of treatment (for LTP) could be considered in the decision of preferential status for the Utah Medicaid Preferred Drug List (PDL).

With respect to the Utah Medicaid PDL, at least one agent *that can be self-administered* for on-demand treatment of HAE attacks could be considered for preference for both children and adults (ie, as the same agent or different agents approved for the respective age group). A self-administrable product would allow the patient to have the medication on hand in the event of a potentially life-threatening attack. Moreover, some emergency departments may not carry HAE medications, making it necessary for patients to have personal access to rescue therapy. Currently, of the products approved for on-demand treatment, only ecallantide should not be self-administered; others are self-administrable.

At least one guideline-recommended, *first-line prophylaxis agent* could be included as preferred on the PDL; all agents FDA-approved for HAE prophylaxis meet this specification except for danazol. Considering the burden of IV administration for routine (ongoing) prophylaxis and the frequent dosing interval of IV products (twice weekly), the additional specification of a *non-IV product* for prophylaxis treatment may also be desirable for preference (or could be reserved for request/approval via prior authorization). Currently, there are 3 approved prophylactic agents that are self-administrable by non-IV routes, the subcutaneous products Haegarda (indicated for ≥6 years old) and lanadelumab (indicated for ≥2 years old); or the oral product, berotralstat (indicated for ≥ 12 years old). Notably, patients with HAE also require STP when undergoing medical procedures (especially those that affect the larynx/oral cavity) or in anticipation of other known attack triggers.[5] Though it may be considered off-label in the US (but approved in other countries), IV pdC1INH concentrates are guideline recommended and routinely used for STP[1,5]; thus, the PDL may also include an IV pdC1INH product as preferred, if not already selected to satisfy the on-demand or LTP options.

1.0 INTRODUCTION

Hereditary angioedema (HAE) is a rare disorder characterized by recurrent, unpredictable episodes of severe submucosal or subcutaneous swelling (ie, HAE attacks) that significantly impact patient quality of life.[5] [2] Laryngeal HAE attacks, in particular, are a life-threatening medical emergency.[5] The disease course of HAE is heterogenous, and even for the same patient, symptom severity may vary over time.[2] Most HAE cases are mediated by excess bradykinin,[3] pathologically induced by genetic mutations encoding C1 esterase inhibitor (C1INH); such cases are classified as HAE-C1INH. Much rarer cases, encompassing heterogenous subtypes with different causative genetic mutations but with normal levels of C1INH, are classified as HAE-nl-C1INH.

HAE-specific medications are imperative for disease management because HAE attacks and swelling are unresponsive to conventional anti-inflammatories such as epinephrine, antihistamines, or glucocorticoids.[2] Treatment strategies for HAE include providing an on-demand, rescue agent to have on hand in the event of an HAE attack; as well as prophylaxis therapy, either short-term prophylaxis (STP) for an anticipated attack trigger, or for ongoing, long-term prophylaxis (LTP) to decrease the frequency and severity of unanticipated attacks.[5]

Many approved medications for HAE target the endogenous bradykinin-production pathway (ie, the kallikrein-kinin cascade), either by replenishing deficient C1INH plasma levels or by inhibiting bradykinin activation through the enzyme, kallikrein. Other agents target bradykinin receptors to halt or prevent HAE symptoms. HAE medications are approved by the FDA (US Food and Drug Administration) for either immediate treatment of an HAE attack or for prophylaxis therapy to prevent attacks.

Approved agents for on-demand (rescue) treatment of HAE attacks include the kallikrein inhibitor, ecallantide (Kalbitor); the bradykinin B2 receptor antagonist, icatibant (Firazyr and Sajazir); and several types of C1INH replacement concentrates: the plasma-derived C1INH (pdC1INH) product, Berinert; and the recombinant human C1INH (rhC1INH) product, Ruconest.[5] Approved agents for prophylaxis therapy include the attenuated androgen, danazol; pdC1INH concentrates, Cinryze and Haegarda; and the kallikrein inhibitors, berotralstat (Orladeyo) and lanadelumab-flyo (Takhyzro).[11,12,15,16] **Table 1** summarizes the available formulations of these approved HAE agents. Other key differences among them include the approved age for use and characteristics that can affect their ease of use (eg, the route of administration, need for reconstitution, self-administrability, dosing frequency; refer to Section 4.0 for more details).

This review serves to inform the decision-making process regarding the Utah Medicaid Preferred Drug List (PDL). The scope covers the HAE-related product indications and guideline-recommended place-in-therapy of the reviewed products for the management of HAE, along with their labeled safety information. A literature search for direct-comparative randomized controlled trial (RCT) evidence was also conducted. While medications approved for HAE are not categorized on the Utah Medicaid PDL as preferred or non-preferred, submission/approval of the non-drug-specific prior authorization form is required for receipt of these rare-disease agents.

Table 1. Approved Medications for Hereditary Angioedema[6-12,15,16,22]

Active Ingredient	Formulations
Prophylaxis Agents	
Plasma-derived C1 Esterase Inhibitor	**Cinryze**, (IV): 500 IU powder for reconstitution, single-use vial **Haegarda** (SC): 2000 IU or 3000 IU powder for reconstitution, single use vials
Lanadelumab-flyo	**Takhzyro** (SC): 150 mg/mL or 300 mg/2 mL prefilled syringes; or 300 mg/2 mL read-to-use solution, single-use vial
Berotralstat	**Orladeyo** (PO): 110 mg or 150 mg capsules
Danazol[a]	Danazol generic (PO): 50 mg capsule
On-demand, Rescue Therapies for HAE Attacks	
Plasma-derived C1 Esterase Inhibitor, Human	**Berinert** (IV): 500 IU powder for reconstitution, single-use vial
Recombinant C1 Esterase Inhibitor	**Ruconest** (IV): 2100 U powder for reconstitution, single-use vial
Ecallantide	**Kalbitor** (SC): 10 mg/mL solution, single-use vial
Icatibant	**Firazyr** (SC): 30 mg/3 mL single-dose prefilled syringe **Sajazir** (SC): 30 mg/3 mL single-dose prefilled syringe

Abbreviations: HAE, hereditary angioedema; IV, intravenous; PO, oral; SC, subcutaneous

2.0 METHODS

Recent clinical practice guidelines (ie, within the previous 5 years) pertaining to the treatment of HAE were searched in the following websites:

- Asthma and Allergy Foundation of America: www.aafa.org
- American College of Allergy Asthma and Immunology: www.acaai.org
- American Academy of Allergy, Asthma, and Immunology: www.aaaai.org
- US Hereditary Edema Association, and Hereditary Angioedema International (HAEi): www.haei.org
- International World Allergy Organization (WAO): www.worldallergy.org
- European Academy of Allergy and Clinical Immunology (EAACI): www.eaaci.org
- Canadian Hereditary Angioedema Network (CHAEN): www.chaen-rcah.ca
- The Trip Database: www.tripdatabase.com

An additional search for guidelines was performed in Ovid-Medline. For prescribing information (ie, package inserts), we searched the respective drug sponsor's website or DailyMed (https://dailymed.nlm.nih.gov/dailymed/).

2.1 Literature Search for Comparative Evidence with Respect to Overlapping Approved Indications

Targeted search strategies were developed in a phased approach to identify systematic reviews (SRs) of randomized controlled trials (RCTs) for the reviewed agents for the management of HAE. The phased approach incorporated searching for and screening recently published SRs first (2022 onward), then performing supplemental searches for RCTs in Ovid-Medline and Embase, with searches dates tailored to those uncaptured in SRs.

Strategies in Ovid-Medline consisted of controlled vocabulary (ie, Medical Subject Headings [MeSH]) and keyword phrases for active ingredients and overlapping approved indications. Strategies in Epistemonikos consisted of keyword phrases with Boolean operators. A combination of independently derived filters was used to identify SRs in Ovid-Medline. Search filters for RCTs were applied using options referred to in the Cochrane Collaboration Handbook for SRs (Ovid-Medline[23] and Embase[24]). See **Appendix A** for search strategy details.

Potential non-indexed systematic reviews were also searched at the following websites:

- The Agency for Healthcare Research and Quality (AHRQ) website for evidence based reports (https://www.ahrq.gov/research/findings/evidence-based-reports/search.html),
- Institute for Clinical and Economic Review (ICER) website (https://icer.org/)

2.2 Screening

The lead author independently screened all search result records (titles/abstracts/full texts) for inclusion. **Appendix B** shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[25] flow chart for the literature screening process.

2.3 Inclusion and Exclusion Criteria for Comparative Evidence

Eligible reports were either SRs with RCTs of parallel study arms, or individual primary RCTs, directly comparing 2 different HAE products. Direct pair-wise meta-analysis statistical data were eligible for inclusion or result data from individual RCTs with direct comparisons. Conference abstracts (ie, non-peer-reviewed publications) were filtered out (excluded). Refer to **Appendix C** for a list of excluded studies during full-text screening.

3.0 DISEASE OVERVIEW

HAE is a rare swelling disorder, most often involving derailment in bradykinin production. The disorder affects approximately 1 in 50,000 persons, globally.[1] HAE-related swelling is non-allergen mediated and nonpruritic. Generally, affected persons experience unpredictable attacks, along with attacks precipitated by patient-specific or common triggers with some foreseeability. HAE swelling involves the subcutaneous and/or submucosal layers, and can occur anywhere in the body (ie, internally and/or visibly externally).[3,26,27] Common locations include the extremities and gastrointestinal system, which can be very painful. The face, upper respiratory tract, genitals, and other organs can also be affected.[27] Laryngeal attacks occur less often but are life-threatening;[28] many patients live in fear of when a laryngeal attack might occur.[29] It is estimated that more than 50% of patients with HAE will have an

attack that affects the airway during their life.[28] A review of observational studies involving various populations around the world found death rates from laryngeal edema averaged 1 per 20 HAE cases among the studies.[28]

HAE is a burdensome disorder that results in psychological distress, disruption of daily life and career goals, and reduced quality-of-life compared to the general population.[30,31] Patients with HAE typically present with symptoms related to the location of swelling (eg, abdominal pain, throat tightness or hoarseness).[27] Swelling typically worsens over several hours, and without effective treatment, may last as long as 5 days.[5] Bowel wall edema is common in children, causing abdominal pain, nausea, vomiting, and diarrhea.[17] Children with HAE frequently suffer from anxiety and may avoid common activities of childhood due to fear of triggering an attack. Furthermore, this heightened stress can worsen symptoms.[32] Some patients report "prodromal" symptoms prior to an attack such as a nonpruritic rash (erythema marginatum; often misdiagnosed as urticaria),[27] fatigue, nausea, or tingling.[29] HAE sequela are unresponsive to agents that modulate mast cell-mediated swelling (eg, epinephrine, antihistamines, glucocorticoids) because the underlaying pathology differs.

The age of HAE-symptom onset may vary according to the type of HAE, but many patients manifest symptoms during childhood or adolescence. The earliest age of onset has been observed at 4 weeks of age.[1] The mean age of onset is about 12 years old.[32] Generally, earlier onset of disease is associated with a more severe disease course over the lifetime. Perhaps due to the disease rarity, diagnosis can be challenging and elusive, with many patients reporting frustration due to a prolonged time to diagnosis.[29,30] Lack of diagnosis or mis-diagnosis increases the risk of death.[30]

The frequency of attacks among the HAE population and among any single patient over their lifetime is variable.[27] One study reported 12 attacks or less annually in the majority of HAE cases (70%); yet 30% of patients had an average of more than 1 attack per month.[33,34] Frequency of attacks does not necessarily indicate severity, as just one attack involving the airway could be fatal. Perhaps due to smaller airways, suffocation from airway edema can occur more rapidly in children.[5,35]

While attack triggers may not be entirely elucidated, common recognized triggers include infections, stress, physical damage (eg, medical/dental procedural trauma), and certain medications.[27] Patients with HAE should avoid use of angiotensin-converting enzyme (ACE) inhibitors and exogenous estrogens at a minimum,[5,13,35] along with dipeptidyl peptidase (DPP)-4 inhibitors and neprilysin inhibitors, advised by some experts.[13] For women, menses is associated with increased attacks; pregnancy may be associated with an increased or decreased attack frequency.[1,36] Dental procedures can trigger life-threatening laryngeal and oral cavity attacks; thus, pre-procedural prophylaxis should be considered.[2]

Given the diverse affected atomical locations of HAE disease and the serious nature of events, management often requires an interdisciplinary approach including a variety of specialists from fields of allergology, dermatology, emergency medicine, gastroenterology, hematology, immunology, internal medicine, otolaryngology, and pediatrics.[1]

3.1 Pathophysiology and Subtypes of HAE

Hereditary angioedema, in most cases, is caused by mutations in the gene encoding C1 esterase inhibitor (C1INH) and is inherited as an autosomal dominant trait. Most HAE cases without functional

C1INH have a positive family history (75% of cases), but about a quarter of the time, the disorder arises from a new mutation.[26]

C1INH is a key protein responsible for regulating the production of bradykinin by the kallikrein-kinin cascade. Bradykinin is a potent vasodilator and enhancer of vascular permeability. It is the key mediator of HAE-related edema (eg, laryngeal edema). Bradykinin also has direct bronchoconstrictive properties, particularly in asthmatic patients.[37-39] Loss of C1INH activity leads to unregulated kallikrein over-production of bradykinin. Over stimulation of the bradykinin B_2 receptor results in prolonged angioedema, and thus severe and sometimes life-threatening HAE attacks.

The kallikrein-kinin cascade, and thus C1INH, also play a role in regulating the activation of the intrinsic coagulation pathway (also known as the contact system) and the complement pathway. C1INH increases complement component 4 (C4) production; thus, patients with HAE typically have low activity levels of both C1INH and C4. C1INH covalently binds and inactivates plasma kallikrein and factor XIIa, preventing the downstream conversion of high molecular weight kininogen to bradykinin. C1INH is also responsible for inactivation of compliment component 1 (C1 esterase, also known as C1r/C1s or C1 convertase) of the complement system (part of immune system). Nonetheless, the pathogenic mechanism *triggering* an HAE attack is not entirely elucidated.

In rarer cases, HAE is caused by mutations in genes other than C1INH genes, in which cases the pathophysiology is not as well-characterized. In some of these rare HAE subtypes (eg, HAE-FXII, HAE-PLG), current knowledge suggests that causative mutations may also lead to excess bradykinin,[3] which is the theoretical basis for why some of these patients may benefit from treatments targeting C1INH-related pathways.

HAE cases are classified according to 3 main subtypes: HAE type 1, HAE type 2, and HAE with normal levels of C1INH (HAE-nl-C1INH). Both HAE type 1 and type 2 are, as a group, commonly referred to as HAE with deficient C1INH (abbreviated HAE-C1INH). In 2023, the US prevalence of each main type (HAE-C1INH or HAE-nl-C1INH) was estimated as follows: 4,529 to 5,158 patients with HAE-C1INH, and 1,230 to 1,331 patients with HAE-nl-C1INH. Further details regarding the HAE subtypes are described below:

- **HAE type 1** is the most common type of HAE, accounting for about **85%** of HAE-C1INH cases.[1] Patients with this disorder have a mutation in the *SERPING1* gene (on chromosome 11q) that manifests as reduced expression of the protein, C1INH[1]; thus the overall concentration of C1INH is low (ie, low C1INH antigenic level) and therefore the overall C1INH activity is low.[1]

- **HAE type 2** is less common than HAE type 1 (only about 15% of HAE-C1INH cases).[13] Patients have a mutation in the *SERPING1* gene that leads to production of *dysfunctional* C1INH.[1] Thus, while C1INH levels (ie, antigenic levels) are either normal or elevated, the overall activity of C1INH is low.

- **HAE-nl-C1INH** is more rare and the pathological mechanisms are less understood compared to HAE-C1INH.[5,30] Unlike HAE-C1INH, individuals with HAE-nl-C1INH produce normal functional levels of C1INH;[5] however, mutations in genes other than *SERPING1* are the pathologic cause. Several HAE-nl-C1INH variants have been identified that are due to mutations in genes encoding the following proteins: factor XII (HAE-FXII), angiopoietin 1 (HAE-ANGPT1), plasminogen (HAE-PLG), kininogen (HAE-KNG), myoferlin (HAE-MYOF), or heparan sulfate 3-O-sulfotransferase 6 (HAE-HS3ST6).[26] Yet, for some patients, the exact mutation remains unknown (HAE-unknown).[5,30] According to a 2021

international HAE treatment guideline, authors describe that over-production of bradykinin seems to play a major role in most types of HAE-nl-C1INH, particularly in HAE-FXII and HAE-PLG, whereas HAE-ANGPT1 and HAE-MYOF are subtypes with mutations in certain proteins of the vascular endothelium.

The presentation of HAE-nl-C1INH can differ slightly from HAE type 1 or type 2 (HAE-C1INH), with symptom onset at an older age[5] and facial swelling as the predominant affected location.[27,40]

For patients over 1 year of age, diagnosis of HAE type 1 and type 2 is based on symptoms of angioedema without urticaria, coupled with low C4 levels and low function of C1INH. C1INH laboratory parameters are typically normal in HAE-nl-C1INH; thus, diagnosis of this type is based on genetic testing or a positive family history, in addition to a lack of response to antihistamines.[5] Refer to **Appendix D** for additional elaboration regarding the diagnosis of HAE and laboratory features of each type.

4.0 THERAPEUTIC TARGETS OF HAE MEDICATIONS

Pharmacotherapeutics for HAE include (a) replacement C1INH products the serve to increase C1INH activity, (b) agents that directly affect downstream components of the kallikrein-kinin cascade, or (c) agents that inhibit the bradykinin B2 receptor to modulate vascular permeability effects of bradykinin:

- *Replacement C1INH products (Cinryze, Haegarda, Berinert, Ruconest)* increase concentrations of C1INH in the blood to help normalize the complement and intrinsic coagulation pathways (also affects the fibrinolytic system). C1INH inactivates plasma kallikrein and factor XIIa, among other proteases (eg, complement component 1 and 4 [C1, C4], factor XIa), lessening the production of bradykinin. Typically, "…one unit of C1INH concentrate corresponds to the mean quantity of C1INH present in 1 ml of fresh normal plasma" (Maurer et al, page 1969).[1]
- *C1INH production stimulator (danazol[*])* increases C1INH and C4 levels (though C4 is not considered to be directly correlated with the pathogenesis of HAE).
- *Kallikrein inhibitors (berotralstat, lanadelumab-flyo, ecallantide)* inhibit plasma kallikrein, which is the bradykinin-generating enzyme with increased activity in most patients with HAE, especially during attacks. Of these agents, lanadelumab is a monoclonal antibody.
- *The selective bradykinin B2 receptor antagonist (icatibant)* blocks bradykinin from interacting with its receptor, thus preventing the characteristic symptoms associated with an HAE attack.

5.0 INDICATIONS AND CHARACTERISTICS OF HAE MEDICATIONS

Replacement C1INH products, particularly as intravenous (IV) formulations, have been available since the early 2000s, with approval of a subcutaneous (SC) C1INH concentrate following about a decade later. The two C1INH concentrates approved for routine (ie, ongoing) *prophylaxis therapy* are both derived from human plasma: the IV product, Cinryze (2008 approval), and the subcutaneous product, Haegarda (2017 approval). Cinryze and Haegarda are indicated for patients at least 6 years of age with

[*] Other pharmacologic effects of danazol (useful for endometriosis indication) include suppression of the pituitary-ovarian axis and inhibition of gonadal steroids at target organ receptors.

HAE, for routine prophylaxis therapy.[11,12] Both medications are administered twice weekly (Cinryze by IV and Haegarda by SC route). Both products must be reconstituted before use and can be prepared and self-administered at home by patients or their caregiver, if the patient or caregiver has been trained and is willing/able.[5,11-14] Cinryze also has approval in other countries (not in the US) for pre-procedural prophylaxis (ie, STP) and for on-demand treatment of attacks being the it is intravenously administered/bioavailable for such uses.[13]

The two C1INH concentrates approved in the US for on-demand, rescue therapy of HAE attacks include the plasma-derived product, Berinert (2009 approval), and the recombinant product, Ruconest (2014 approval). Both are intravenously administered, require reconstitution, and can be prepared and self-administered at home by patients or caregivers. Indications for these on-demand therapies are without a precise age specification, but both are approved for adults and either pediatric (Berinert) or adolescent (Ruconest) patients.[6,7] Berinert can also be used off-label for STP— it has approval in the EU for pre-procedural prophylaxis (ie, STP) yet is not formally indicated for STP in the US.[13]

Of the kallikrein inhibitors, the on-demand agent, ecallantide, has been available the longest (approved in 2009). Ecallantide is a subcutaneous solution (Kalbitor) approved to treat HAE attacks in patients 12 years and older. Its usability outside of the clinic, however, is restricted because it is labeled for administration only by a healthcare professional who can promptly respond to a potential anaphylactic reaction. Newer kallikrein inhibitors are approved for routine *prophylactic therapy* including the subcutaneously administered monoclonal antibody, lanadelumab (approved in 2018) and the first-in-class *oral* option, berotralstat (Orladeyo; approved in December 2020).[15,16] Of the prophylactic agents for HAE, lanadelumab has the youngest approved age for use (for ≥2 years of age) and is administered the least frequent (every 2 to 4 weeks), compared to daily administration with berotralstat and danazol; or every 3-4 days with the injectable C1INH concentrates, Cinryze and Haegarda. Berotralstat is indicated for patients 12 years or older.[15,16] Uniquely, lanadelumab subcutaneous solution (Takhzyro) does not require reconstitution and can be self-administered; however, it does require storage under refrigeration.[16]

The selective bradykinin B2 receptor antagonist, icatibant has been approved since 2011. It is indicated for on-demand treatment of HAE attacks in adults.[9] Icatibant is available as subcutaneous solutions (Firazyr, Sajazir) which do not require reconstitution and can be self-administered (or by caregiver). These (Firazyr and Sajazir) may be the most convenient on-demand products for self-administered use, being that other on-demand options are intravenously administered (ie, C1INH replacement products, Berinert and Ruconest) or must be administered by a healthcare provider (ecallantide).

Danazol is an old, attenuated androgen that has been available since the 1970's, however, it is not clear when it gained approval for the treatment of HAE. Danazol is an oral agent, taken daily, approved for the prevention of HAE attacks in general. The labeled indication does not specify an age for use, but the labeling declares elsewhere that the safety and effectiveness have not been established in the pediatric population.[41]

Table 2 summarizes the approved indications for the reviewed HAE products, while **Table 3** provides the available preparations, recommended dosing, and key administration considerations.

Table 2. Indications for FDA Approved Hereditary Angioedema Medications[6-12,15,16,22]

Active Ingredient *Formulation* **(Brand)**	**Labeled Indication**	**Indicated Population**
Prophylaxis Agents		
C1 Esterase Inhibitor, Human *IV injection* **(Cinryze)** *Subcutaneous injection* **(Haegarda)**	For **routine prophylaxis** to prevent HAE attacks	Adult and pediatric patients ≥ 6 years old with HAE
Lanadelumab-flyo *Subcutaneous injection* **(Takhzyro)**		Adult and pediatric patients ≥ 2 years old with HAE
Berotralstat *Oral capsule* **(Orladeyo)**		Adult and pediatric patients ≥ 12 years old with HAE
Danazol[a] *Oral capsule, generic*	**To prevent** HAE attacks of all types	Non-specified age group in indication • Safety/effectiveness unestablished in pediatrics
On-demand, Rescue Therapies		
C1 Esterase Inhibitor, Human *IV injection* **(Berinert)**	For treatment of acute abdominal, facial, or laryngeal HAE attacks	Adult and pediatric patients with HAE
C1 Esterase Inhibitor, Recombinant *IV injection* **(Ruconest)**	For treatment of acute HAE attacks	Adult and adolescent patients with HAE • *Limitation*: effectiveness unestablished in patients with laryngeal attacks
Ecallantide *Subcutaneous injection* **(Kalbitor)**		Adult and adolescent patients ≥ 12 years old with HAE
Icatibant *Subcutaneous injection* **(Firazyr)** *Subcutaneous injection* **(Sjazir)**		Adults 18 years of age and older with HAE

[a] *Danazol is also approved for the treatment of endometriosis*

Abbreviations: FDA, Food and Drug Administration; HAE, hereditary angioedema; IV, intravenous

Table 3: Available Preparations, Recommended Dosing, and Administration Considerations for HAE Medications[6-12,15,16,22]

Active Ingredient (Brand) Preparations	Dosing and Administration
Prophylaxis Agents	
Danazol, for oral use 50 mg capsule	• 150 mg **orally** once **daily** with food • Dose-adjust for moderate-severe hepatic impairment, or for persistent gastrointestinal reactions
C1 esterase inhibitor, human, for IV injection **(Cinryze)** 500 IU, powder for reconstitution (single-use vial); packaged with Mix2Vial transfer device	• *Age ≥ 12 years old*: 1,000 units **IV every 3–4 days**; doses up to 2,000 units (and ≤ 80 units/kg) every 3–4 days can be used per patient response • *Age 6–11 years old*: 500 units **IV** every 3–4 days; doses up to 1,000 units every 3–4 days can be used per patient response • Can be reconstituted and self-administered after training • Administer within 3 hours of reconstitution at an infusion rate of 1 mL/min
C1 esterase inhibitor, human, for subcutaneous injection **(Haegarda)** 2000 IU or 3000 IU powder for reconstitution (single use vials); packaged with Mix2Vial transfer device	• 60 IU/kg **SC every 3–4 days** • For patient or caregiver administration after training • Administer within 8 hours of reconstitution
Lanadelumab-flyo, subcutaneous solution **(Takhzyro)** 150 mg/mL solution; single-dose prefilled syringes or vials	• *Age ≥ 12 years old*: 300 mg **SC every 2–4 weeks**[a] • *Age 6 to <12 years old*: 150 mg **SC** every 2–4 weeks[a] • *Age 2 to <6 years old*: 150 mg **SC** every 4 weeks • For patient or caregiver administration after training; administer SC to abdomen, thigh or upper arm • Requires storage under refrigeration
Berotralstat capsule **(Orladeyo)** 110 mg or 150 mg capsules	• 150 mg **orally** once **daily** with food • 110 mg daily for patients with moderate-severe hepatic impairment, or receiving P-gp or BCRP inhibitors, or for troublesome gastrointestinal side effects
On-demand, Rescue Therapies	
C1 esterase inhibitor, human, for IV injection **(Berinert)** 500 IU powder for reconstitution, single-use vial; packaged with Mix2Vial transfer device	• 20 IU/kg **IV** • Can be reconstituted and self-administered after training and upon recognition of an acute HAE attack • Administer within 8 hours of reconstitution at an infusion rate of 4 mL/min
C1 esterase inhibitor, recombinant, for IV injection **(Ruconest)**	• *For body weight <84 kg*: 50 U/kg **IV** • *For body weight ≥ 84 kg*: 4200 U (2 vials) **IV**

Table 3: Available Preparations, Recommended Dosing, and Administration Considerations for HAE Medications[6-12,15,16,22]

Active Ingredient (Brand) Preparations	Dosing and Administration
2100 U powder for reconstitution, (single-use vials); packages with transfer vial adapters	• Can be reconstituted and self-administered after training and upon recognition of an acute HAE attack • Administer immediately, or within 8 hours stored under refrigeration, after reconstitution • Infuse over approximately 5 minutes
Ecallantide, for subcutaneous injection **(Kalbitor)** 10 mg/mL solution (single use vials)	• 30 mg **SC** (as three 10 mg injections); may repeat dose within 24 hours if attack persists • ***Healthcare professional administration only***: due to risk of anaphylaxis and need for close monitoring
Icatibant, for subcutaneous injection **(Firazyr, Sajazir)** 30 mg/3 mL subcutaneous solution, single-use prefilled syringes	• 30 mg **SC** into abdominal area; may repeat dose at intervals of at least 6 hours If attack persists, but up to a maximum of 3 injections in a 24-hour period • Can be self-administered after training and upon recognition of an acute HAE attack

[a] *Start with 300 mg every 2 weeks. Every 4 weeks can be considered if the patient becomes HAE attack-free for >6 months.*

Abbreviations: BCRP, breast cancer resistance protein; IV, intravenous; P-gp, P-glycoprotein; SC, subcutaneous

5.1 Pharmacokinetics of HAE Medications

Of the on-demand rescue agents, the IV C1INH product, Berinert, has a considerably longer elimination half-life (around 20 hours) relative to other rescue products (<3 hours), thus, it is also used for short-term prophylaxis (STP) therapy. Though not formally indicated for STP in the US, Berinert has approval in the EU for pre-procedural prophylaxis (ie, STP).[13] The onset of action of Berinert also appears slightly faster (by indirect comparison) to other agents. **Tables 4 and 5** summarize select pharmacokinetic parameters for the on-demand (rescue) or prophylactic HAE agents, respectively.

Of the prophylaxis agents, lanadelumab has the longest half-life and thus the least frequent dosing interval. Because it takes a long time to reach steady state (70 days), it is not practical for short-term prophylaxis therapy, thus, it is reserved for routine, long-term prophylaxis use.

Table 4. Select Pharmacokinetic Information for HAE Rescue Agents [a,6-10,42]

Agent (Route) (Brand)	**Onset** (hours)	**Tmax** (hours)	**Half-life** (hours)	**Duration of action** (hours)
C1INH, human (IV) (Berinert)	Onset of symptom relief: 0.25 (15 minutes; median per attack)	Not reported	Adult population: • Unadjusted for baseline: 21.9 ± 1.7 • Adjusted for baseline: 18.4 ± 3.5 Pediatric population (6−13 years): • Unadjusted for baseline: 22.4 ± 1.6 • Adjusted for baseline: 16.7 ± 5.8 (following a 500 to 1500 IU dose)	Time to complete resolution of HAE symptoms: 8.4
C1INH, recombinant (IV) (Ruconest)	Onset of action: 1.5 (median)	approx. 0.3 (18 minutes)	approx. 2.5 (following a 6.25 to 100 U/kg dose)	Not reported
Icatibant (SC) (Firazyr; Sajazir)	Time to 50% reduction in symptoms: approx. 2	approx. 0.75 (45 minutes)	1.4 ± 0.4 (following a 30 mg SC dose)	approx. ≥6
Ecallantide (SC) (Kalbitor)	0.5−4	approx. 2−3	2.0 ± 0.5 (following a 30 mg SC dose)	Not reported

[a] *Information pertains to adults only, unless otherwise stated*

Abbreviations: approx., approximately; C1INH, C1 esterase inhibitor; HAE, hereditary angioedema; IU, international unit; IV, intravenous; SC, subcutaneous; Tmax, time to maximum concentration post-dose

Table 5. Select Pharmacokinetic Information for HAE Prophylactic Agents [a,11,12,15,16]

Agent (Brand)	**Tmax**	**Time to Steady State Concentration**	**Half-life** (hours)
C1INH, human (IV) (Cinryze)	4 ± 7 hours	Not reported in PI	Adults: 56 ± 36 hours Children (7-11): 34 hours
C1INH, human (SC) (Haegarda)	59 hours	Not reported in PI	69 hours
Lanadelumab (SC) (Takhzyro)	4-5 days	70 days	14-15 days
Berotralstat (PO) (Orladeyo)	5 hours	6-12 days	About 4 days (range 39 -152 hours)

[a] *Abbreviations: C1INH, C1 esterase inhibitor; HAE, hereditary angioedema; IV, intravenous; PI, package insert; SC, subcutaneous; Tmax, time to maximum concentration post-dose*

6.0 GUIDELINE RECOMMENDATIONS FOR THE GENERAL POPULATION WITH HAE

Guidelines reviewed in this section, published for the treatment of HAE in the last 5 years, include the following:

- 2021 International World Allergy Organization and European Academy of Allergy and Clinical Immunology (WAO/EAACI) guideline[1]
- 2020 US Hereditary Angioedema Association (HAEA) guideline[5]
- 2019 Canadian Hereditary Angioedema Network /International Expert (CHAEN/IE) guideline[13]

Guidelines address the treatment of HAE-C1INH, and a couple (HAEA and CHAEN/IE guidelines) include recommendations for the treatment of HAE-nl-C1INH. Any differences in recommended medications between guidelines are likely related to differences in drug indications among applicable countries along with differences in the year of drug regulatory approval or availability at the time of the guideline's composition.

Treatment modalities for HAE include acute, on-demand treatment to abort an HAE attack; short-term prophylaxis (STP) to prevent an anticipated attack due to *foreseeable* triggers (eg, dental or surgical operation); and long-term prevention of unforeseeable attacks. STP entails temporary administration of HAE medication prior to a trigger (and sometimes after depending on the medication), while LTP entails ongoing use of preventative HAE medication. The goal of prophylaxis (STP and LTP) is to reduce the overall attack burden (ie, attack frequency or severity), with the decision to employ LTP based on the patient's needs.[5] Training patients (and/or caregivers) to self-administer medications, and facilitating home administration, is strongly encouraged by guidelines because this allows for improved outcomes with earlier treatment of attacks (with on-demand therapy) and lessens treatment burdens (eg, transportation and time-demands) in the case of prophylaxis therapy.[1,5,13,35]

All HAE attacks are eligible for on-demand treatment. Decision-making regarding when to start or stop prophylaxis therapy (STP or LTP) should be delegated to the patient and HAE specialist to account for individualized considerations.[1,5,13] Overall treatment goals include minimizing morbidity, mortality and treatment burdens to normalize life as much as possible (ie, improve patient quality of life).[1,5] Disease activity and impact should be monitored, especially for those on LTP, using validated tools such as the angioedema activity score (AAS), the hereditary angioedema activity score (HAE-AS), the angioedema quality of life questionnaire (AE-QoL), the hereditary angioedema quality of life questionnaire (HAE-QoL), and/or the angioedema control test (AECT).[1,13]

6.1 Treatment of HAE Attacks

Agents recommended and considered effective for on-demand treatment of HAE attacks, including attacks experienced by patients with HAE-nl-HAE, include IV C1INH products, icatibant, and ecallantide.[1,5,13] While the non-US guidelines consider Cinryze an on-demand option (an IV C1INH approved in Europe but not in the US for on-demand treatment), the US HAEA recommends *FDA-approved* therapies for on-demand treatment. Last-line options include solvent detergent-treated

plasma (SDP) or fresh-frozen plasma (FFP), if available (ie, in the hospital or upon emergency services).[1,5,13]

Providing readily accessible, on-demand medication to patients is a strong recommendation by guidelines;[1,5,13] thus, self-administered options are inferred as preferrable. Of the US approved on-demand agents, ecallantide cannot be self-administered; it requires administration by a healthcare provider in a healthcare setting.[8]

On-demand treatment of HAE attacks should be considered for *all* patients with HAE regardless of attack location or severity.[1,5,13,17] Attacks that affect or that may affect the upper airway and/or tongue are considered as life-threatening and a medical emergency.[1,5] Treatment of upper airway attacks is generally regarded as mandatory due to the risk of death and poor outcomes from asphyxiation.[1,5] The WAO/EAACI recommends that patients carry sufficient on-demand medication supply to treat at least two attacks, at all times.[1]

All attacks are recommended to be treated according to the 2021 WAO/EAACI guideline.[1] The 2020 HAEA guideline uses softer language, stating that all HAE attacks are eligible for treatment.[5] Earlier (vs. later) on-demand treatment of an HAE attack is associated with shorter attack duration and better outcomes.[1,17] Thus, the WHO/EAACI recommends treating attacks as early as possible (inferring preferability of self-administered products).[1] Similarly, the HAEA recommends self-administered, on-demand treatment whenever feasible.[5] The CHAEN/IE guideline also emphasizes the importance of early treatment.[13] Furthermore, the US HAEA guideline describes that because HAE is rare, HAE-specific medications may not be readily available in hospitals or emergency departments, so rescue therapies (on-demand agents) are important to prescribe to patients as a readily accessible treatment source.[5]

Refer to **Appendix D,** Table D2, for recommendations consolidated per treatment guideline regarding the treatment of HAE attacks.

6.2 Prophylaxis Therapy: Short-term Prophylaxis (STP) and Long-term Prophylaxis (LTP) for Non-pregnant Adults and Possibly Adolescents

Guidelines recommend short-term prophylaxis (STP) before any known trigger or potential stressful event that could trigger an attack (eg, medical, surgical, or dental procedures),[1,5,13] including for patients with C1INH-nl-HAE.[5]

The 2021 WAO/EAACI guideline recommends considering long-term prophylaxis (LTP) for patients at every healthcare visit, if not already started.[1] Authors highlight that LTP provides the opportunity to reduce the burden of HAE attacks and allows some patients to achieve *complete control* of HAE (ie, absence of attacks).[1] The decision of whether to start LTP is personalized and should take into consideration patient preferences, disease activity (eg, attack frequency and severity), disease burden/quality of life, and practical factors such as the patient's ability to access emergency care for attacks and ability to self-administer on-demand medication.[1,5,13] The decision of stopping LTP should also be personalized.[13,17]

While receipt of LTP or STP may reduce the need for on-demand medication and can potentially reduce the frequency and severity of attacks,[18,19,43] prophylaxis may not completely prevent all attacks.[5,13,20,44] Thus, patients on STP or LTP should also have access to on-demand HAE medication at all times.[5] In particular, the CHAEN/IE guideline recommends having at least 2 doses of on-demand treatment on-hand whenever undergoing a potentially triggering event, whether or not the patient has received STP for that event.[13]

The following section provides recommendations from guidelines regarding which specific type of agent should be used for prophylaxis treatment, if such recommendation is specified.

6.2.1 STP

The WAO/EAACI guideline and CHAEN/IE guideline strongly recommend **intravenous pdC1INH for STP (eg, Cinryze or Berinert[†])** before an anticipated trigger (eg, within 1 hour before a surgical procedure).[1,13] The most recent guideline (WAO/EAACI) describes that although attenuated androgens (eg, danazol) may have been specified as an option in the past for preprocedural prophylaxis, intravenous pdC1INH concentrate is now considered the STP agent of choice.[1] Guidelines also mention some positive, though limited, evidence for **recombinant C1INH (Ruconest)** for STP.[1,5] Off-label agents such as tranexamic acid (an antifibrinolytic) are mentioned as potential last-in-line options by the CHAEN/IE guideline if the other therapies (IV pdC1INH or attenuated androgen) cannot be used or are unavailable.[13] Fresh-frozen plasma (FFP) is also a last-line option if the others are not available.[1,5,13,35] Because lanadelumab takes approximately 70 days to reach a steady state concentration it is not effective or recommended for STP.[13]

In general, STP can also be considered for HAE-nl-C1INH, with the same options as in C1INH-HAE, but there is less empirical evidence In this HAE subtype to guide selection of therapy.[5] The HAEA guideline weakly recommends STP for HAE-nl-C1INH[5], while the CHAEN/IE recommendations for STP seem to apply to both HAE-C1INH and HAE-nl-C1INH.[13]

6.2.2 LTP

For HAE type 1 or 2, the 2021 WAO/EAACI guideline strongly recommends **pdC1INH, lanadelumab, or berotralstat for first line-LTP**, based on RCT evidence supporting their safety and efficacy.[1] Because attenuated androgens including danazol have a high adverse event burden and/or anabolic effects in most patients, along with many drug interactions and contraindications, danazol is reserved as second-line.[1] The 2020 US HAEA and CHAEN/IE guideline recommendations for first-line LTP are similar, with the exception of berotralstat since it was not yet approved at the time of the guideline's composition. pdC1INH replacement products (ie, IV or SC pdC1INH [eg, Cinryze, Haegarda]), and SC lanadelumab (Takhyzro) were strongly recommended first-line options based on a high level of evidence; androgens and antifibrinolytics (off-label) were considered second-line options.[5,13] Antifibrinolytics are considered the least effective of the aforementioned drugs for LTP, according to the HAEA guideline. The HAEA guideline also describes that rhC1INH (Ruconest), which so far is approved in the US for on-demand

[†] In the US Berinert is indicated for on-demand treatment (not prophylaxis) however it is also approved in Europe for pre-procedural prophylaxis, as it has a longer half-life to accommodate such use.

treatment, has phase II supportive evidence for use as LTP and could serve as a potential option during pdC1INH shortages that occasionally occur.[5]

Although not a formal recommended preference, the CHAEN/IE guideline noted the lack of direct comparative trials for pdC1INH products, but also noted the *observation* of better outcomes with *subcutaneous* pdC1INH over IV pdC1INH based on indirect comparative observations (or pre-post comparisons[45]).[13] The difference observed is likely related to consistent therapeutic C1INH steady-state concentrations attainable with the SC C1INH product versus more variable plasma concentrations with IV C1INH products.[1] Moreover, the subcutaneous route circumvents the inconvenience, burdens, and potential for serious adverse events associated with IV administration (eg, potential infection, loss of vein patency). In a post-hoc assessment of a pivotal trial for SC pdC1INH (Haegarda), the small subgroup of patients that switched from prior IV C1INH LTP to the study drug (SC C1INH) were observed to experience improved outcomes (further reduction in attacks).[46]

For HAE-nl-C1INH, there is a paucity of RCT evidence to guide selection of the optimal LTP agent. Based on small open-label studies, the HAEA recommends progestin-only pills or antifibrinolytics. Attenuated androgens have been used, but the HAEA does not give a formal recommendation for their use in HAE-nl-C1-INH. Another option, only to be considered on a trial basis if other prophylactic treatments fail, is pdC1INH therapy since some subgroups seem to benefit, per case reports (ie, limited evidence). Lanadelumab is listed as a theoretical option based on mechanism of action; HAEA panelists favor its trial if progestins and tranexamic acid (an antifibrinolytic) fail.[5]

Refer to **Appendix D,** Table D3, for recommendations consolidated per treatment guideline regarding HAE prophylaxis therapy.

7.0 SPECIAL POPULATIONS

7.1 Pediatric

Generally, the same rationale and treatment approach for treating adults is used for children. Some agents however are not approved for children in the US, which may limit their use to later lines of therapy, for instance if there are availability or tolerability issues with on-label agents. Maintaining intravenous (IV) access can be difficult for children who require IV prophylaxis treatment, and may create an additional barrier to at-home self- (or caregiver-) treatment.[32] It is important that everyone in contact with the child is knowledgeable about the disease and how to respond to an attack (eg, at school, daycare, non-specialist providers, etc).[2,17]

7.1.1 On-demand Treatment for Children

Approved indications for the on-demand, C1INH agents (to rescue a patient from an active attack) are general with respect to the indicated age: Berinert (IV pdC1INH) is indicated for pediatric patients, and Ruconest (IV rhC1INH) is indicated for adolescent patients. Ecallantide, the subcutaneous product that must be administered by a healthcare professional, is indicated for patients ≥12 years of age, whereas icatibant is indicated for adults only in the US but has approval in other countries (Canada, European Union, and Australia) for as young as 2 years of age.[13]

The US HAEA guideline does not make a graded formal recommendation but suggests that **pdC1INH** is the preferred on-demand treatment in children and describes other options with pediatric evidence (with or without FDA approval):

- rhC1INH and ecallantide have US approval for adolescent patients
- authors described that although icatibant lacks US approval for pediatrics, it has positive evidence and approval in other countries for as young as the age of 2

For on-demand treatment, the 2 international guidelines (2021 WAO/EAACI and 2019 CHAEN/IE) recommended *intravenous* C1INH or icatibant for all children (including those below 12 years of age); or ecallantide for adolescents.[1,13]

7.1.2 Prophylaxis in Children

A similar treatment approach for STP and LTP as per adults is recommended; however the regulatory status of some drugs may affect use of some agents in certain age groups.[5] Of the FDA-approved prophylaxis agents, lanadelumab has the youngest approved age for use (≥2 years of age), followed by the C1INH products, Cinryze and Haegarda (both approved for ≥ 6 years of age), then berotralstat (for ≥12 years of age). According to the package insert, the safety and efficacy of danazol has not been formally established (eg, by RCT evidence submitted to the FDA) in pediatric patients.[41]

pdC1INH is generally recognized as the treatment of choice for prophylaxis in children (STP or LTP) since it has the most evidence for use in pediatric HAE.[1,5,17,35] Berinert, an IV pdC1INH that is FDA approved for acute treatment but approved in other countries for prophylaxis, is the primary pdC1INH STP option recommended by international pediatric experts.[17] The US HAEA guideline also recognized lanadelumab as an option for LTP, with approval in the US for children age 12 or older.[5] In the past, antifibrinolytics (that are off-label for HAE) were used more often while experience/evidence was developing for pdC1INH.[17]

Long-term use of attenuated androgens (eg, danazol) is generally reserved as a last-line option for adolescents who have reached Tanner developmental stage 5 (and/or after the age 16) due to the risk of adverse developmental effects on bones, growth, and sexual maturation.[5,13,17,35] Regular safety monitoring (every 6 months) of laboratory tests (liver function tests, lipids, urinalysis), blood pressure, liver ultrasound (every 12 months if on higher doses), and for side effects (eg, virilization) is recommended for HAE patients receiving long-term androgen therapy.[5]

Guidelines that address treatment of HAE-nl-C1-INH (ie, HAEA, CHAEN/IE), do not make separate recommendations for treatment of HAE type 1 or 2 versus HAE-nl-C1-INH in children.[5,13]

7.2 Pregnancy

HAE attack frequency may change during pregnancy. Some women may experience an increased attack frequency, particularly women with HAE-nl-C1INH. Breastfeeding may also increase the frequency of attacks.[5]

During pregnancy, C1INH concentrate is the recommended agent for the management of HAE (as on-demand and prophylactic treatment)[1,5,13,35] based on supportive descriptive or observational studies.[5,47] The international guidelines prefer pdC1INH in particular during pregnancy,[1,13] while the US HAEA

guideline is more general, stating C1INH for use with acknowledgement that rhC1INH has limited but reassuring evidence.[5] *For HAE-nl-C1INH*, case reports have demonstrated benefit from pdC1INH during pregnancy. There is a lack of information regarding the use of other agents (eg, lanadelumab, berotralstat, ecallantide) during pregnancy; icatibant has limited case reports, and attenuated androgens are contraindicated during pregnancy.[1,5]

During breastfeeding, either pdC1-INH,[5,35] or rhC1-INH are recommended for prophylactic treatment.[5] There is a lack of information regarding lanadelumab.[5] Use of attenuated androgens while breastfeeding is not recommended.[5]

Regarding the labeling of the reviewed agents, only danazol has a formal contraindication (and black box warning) for use during pregnancy. Animal models in rabbits showed impaired fetal development upon use of danazol dosages 2-4 times the expected human exposure on days 6-18 of gestation. **Table 6** summarizes pregnancy information from package inserts for the remaining HAE agents.

Table 6. Labeled Pregnancy Information for HAE Medications[6-12,15,16,22]

Agents	Prescribing Information
Prophylaxis Agents	
Danazol, for oral use	***Contraindicated (black box warning):*** animal models in rabbits showed impaired fetal development upon use of dosages 2-4 times the expected human exposure on days 6-18 of gestation
C1INH, human, for IV injection **(Cinryze)**	No formal human studies during pregnancy with Cinryze; no evidence of fetal harm at high doses in rats
C1INH, human, for subcutaneous injection **(Haegarda)**	Retrospective data of use of C1-INH (IV or SQ) during human pregnancy have not reported serious AEs; no animal data
Lanadelumab-flyo, subcutaneous solution **(Takhzyro)**	No formal human studies during pregnancy; no evidence of fetal harm at high doses in monkeys
Berotralstat capsule **(Orladeyo)**	No formal human studies during pregnancy; no evidence of fetal harm at high doses in rats/rabbits
On-demand, Rescue Therapies	
C1INH, human, for IV injection **(Berinert)**	Retrospective data of Berinert use during human pregnancy showed no serious AEs; no animal data provided
C1INH, recombinant, for IV injection **(Ruconest)**	No serious AEs related to embryofetal development have been observed in limited retrospective human data (pharmacovigilance data) or in animal data from rabbits
Ecallantide, for subcutaneous injection **(Kalbitor)**	No serious AEs related to embryofetal development have been observed in limited retrospective human study data or in animal data from rabbits and rats
Icatibant, for subcutaneous injection **(Firazyr, Sajazir)**	Retrospective data of icatibant use during human pregnancy showed serious AEs; however, animal studies have shown some issues (premature birth and decreased embryofetal survival in rabbits at an SC dose 13 times the expected human exposure; and fetal rat deaths at doses 2 times the expected human exposure

Abbreviations: C1INH, C1 esterase inhibitor concentrate; IV, intravenous

7.3 Renal or Hepatic Impairment

Danazol is contraindicated in patients with substantial renal or hepatic impairment. Otherwise, no *renal* dosage adjustments are required or recommended for any of the reviewed HAE agents, and only berotralstat has *hepatic* dosage adjustments (recommended for mild to severe impairment; see **Table 7**).

Table 7. Renal and Hepatic Impairment Information[6-12,15,16,22]

Renal dosage adjustments
No renal dosage adjustments are specified in the product labeling for C1INHs (ie Berinert, Cinryze, Haegarda, Ruconest), berotralstat (Orladeyo), lanadelumab-flyo (Takhzyro), icatibant (Firazyr; Sajazir), ecallantide (Kalbitor), or danazol[a] • *The following have not been studied in patients with renal impairment:* Berinert, Cinryze, Haegarda, Ruconest, ecallantide (Kalbitor) • *The following have not been studied in patients with ESRD (CrCl <15 mL/min or eGFR <15 mL/min/1.73 m^2) or hemodialysis*: berotralstat (Orladeyo)
Hepatic dosage adjustments
No hepatic dosage adjustments are required in the product labeling for C1INHs (ie Berinert, Cinryze, Haegarda, Ruconest), danazol[a], ecallantide (Kalbitor), icatibant (Firazyr, Sajazir), or for lanadelumab-flyo (Takhzyro) • *The following agents have not been studied in patients with hepatic impairment*: prophylaxis products, Cinryze, Haegarda; on-demand products, Berinert, Ruconest, ecallantide (Kalbitor)
For moderate hepatic impairment (Child-Pugh Class B): • Berotralstat (Orladeyo): reduce the recommended dosage to 110 mg once daily For severe hepatic impairment (Child-Pugh Class C): • Berotralstat (Orladeyo): reduce the recommended dosage to 100 mg once daily

[a] *Danazol is contraindicated in patients with substantial renal or hepatic impairment*

Abbreviations: C1INH concentrates, C1 esterase inhibitor concentrates; CrCl, renal creatinine clearance; ESRD, end-stage renal disease

8.0 LITERATURE SEARCH RESULTS FOR DIRECT COMPARATIVE RCTS

No head-to-head RCTs were identified for HAE agents. Several publications corroborate the lack of comparative studies for approved HAE agents in the setting of (a) routine prophylactic treatment, including a 2022 Cochrane SR[48], among other SRs and expert reviews;[48-53] or (b) for on-demand treatment of HAE attacks (reviews[54,55]).

Not only is there heterogeneity between patient populations of placebo-controlled studies, there are also differing outcome measures which hinders indirect comparisons versus placebo. Experts propose standardizing outcome measures in HAE-medication clinical trials. Moreover, efficacy outcomes have been largely based on patient-reported measures of acute improvement in symptoms (eg, symptom relief, discomfort, disability, and pain) or outcomes that relate to modification of attack frequency/severity (change in quality of life, or attack features). [56,57]

We are aware of results from a post-hoc observational assessment suggesting improvements in attack rates in patients switching from IV pdC1INH to SC pdC1INH.[45] This observation was drawn from a subset of patients (n=21) from an RCT whom were on IV prophylaxis therapy prior to entering the study, then randomized to SC pdC1INH (rather than placebo). The median attack rate dropped by about 74%, compared with the subgroup's prestudy rate while on intravenous C1-INH prophylaxis.[45] Nonetheless, additional studies are needed to confirm these observations and the potential benefits of SC C1INH over IV C1INH for routine prophylaxis.

9.0 SAFETY

9.1 Contraindications and Warnings[6-12,15,16,22]

9.1.1 Contraindications

The following bullet points summarize contraindications for the reviewed products for HAE. Icatibant, berotralstat, and lanadelumab-flyo *do not* have any labeled contraindications:

- The C1INH products (ie, Berinert, Ruconest, Cinryze, Haegarda), ecallantide, and danazol are contraindicated in patients with a history of hypersensitivity reactions, including anaphylaxis, to the active ingredient, product preparation, or excipients.
- In addition, the recombinant C1INH, Ruconest, is contraindicated in patients who previously experienced an allergic reaction to rabbits or rabbit-derived products.
- Of the reviewed agents, danazol has the most labeled contraindications. Danazol is contraindicated with/during any of the following:
    - undiagnosed abnormal genital bleeding or porphyria
    - substantial hepatic or renal impairment, or cardiac dysfunction
    - androgen-dependent tumor
    - pregnancy (also a black box warning) or breast feeding
    - active thrombosis or thromboembolic disease or documented history of such events

9.1.2 Warnings

Most products, including the C1INH replacement products, ecallantide, and lanadelumab, have a warning for potential hypersensitivity reactions, which can be life-threatening. As for ecallantide, the warning is a black box warning; thus, the agent is required to be administered in a healthcare setting by a provider equipped to respond to anaphylaxis. Anaphylaxis occurred in about 4% of ecallantide-treated patients in pivotal clinical trials. For pdC1INH products (ie, Berinert, Cinryze, Haegarda), labeling highlights that epinephrine should be made immediately available to patients (ie, dispensed for take home use) to be able to respond to a reaction— a prudent point that could also apply to other self-administered agents with a hypersensitivity warning.

All C1INH products and danazol have a warning for serious arterial and venous thromboembolic events[‡]; this is a black box warning for danazol. Although events were rare in clinical trials, the risk can be potentiated by underlying risk factors for thrombosis (eg, prior history of thrombosis, immobility, oral contraceptive use, significantly overweight, presence of atherosclerosis). Patients with risk factors should be monitored more closely.

Human, plasma-derived C1INHs have a warning for the potential transmission of infectious, pathogenic agents (eg, viruses, variant Creutzfeldt-Jakob disease agent). Although the potential for transmission has been minimized by screening plasma donors for certain viruses, testing for viral infections, and employing manufacturing processes to inactivate and/or remove certain viruses, these products may theoretically still harbor human pathogenic agents, and therefore, *complete* elimination of transmission risk cannot be guaranteed. Unlike the plasma-derived C1-INHs, rhC1-INH is absent of the risk of human blood-borne pathogen transmission because it is synthesized via the milk of transgenic rabbits.[7]

Warnings that are unique to a few reviewed agents include the following:

- QT prolongation with higher-than-recommended dosages: **berotralstat** (Orladeyo)
- Peliosis hepatis and benign hepatic adenoma (black box warning); benign intracranial hypertension (black box warning); transient changes in lipoproteins (eg, reductions in high density lipoproteins, elevations in low density lipoproteins); and androgenic effects (eg, acne, weight gain, edema, voice change; may be irreversible even after drug discontinuation): **danazol**
- Seek prompt medical attention following a laryngeal HAE attack, due to the potential risk for airway obstruction: **Berinert, icatibant** (Firazyr; Sajazir)
- Potential to cause fluid retention: **danazol**
    - Used cautiously in patients with diabetes mellitus, or conditions that can be affected by edema, such as hypertension, migraine, epilepsy, or polycythemia, or renal or cardiac impairment.

Table 8 provides an overview of the labeled warnings and precautions for the reviewed agents, according to their respective product labeling.

[‡] Thromboembolic events while using C1INHs has been reported, especially when at higher-than-recommended doses.

Table 8. Labeled Warnings for FDA-approved Agents for HAE[6-12,15,16,22]

Warning	C1-INH Concentrates				B_2Ri	Kallikrein Inhibitors			Androgen
	Rescue		Phx		Rescue	Rescue	Phx		Phx
	Berinert	**Ruconest**	**Cinryze**	**Haegarda**	**Icatibant**	**Ecallantide**	**Berotralstat**	**Lanadelumab**	**Danazol**
Hypersensitivity reactions	X	X	X	X		**X (BBW)**		X	
Thromboembolic events	X	X	X	X					**X (BBW)**
Transmission of infectious pathogens	X		X	X					
Medical attention following laryngeal HAE attacks	X				X				
QT prolongation (at higher-than-recommended dosages)							X		

Additional Warnings for Danazol

- Peliosis hepatis and benign hepatic adenoma **(BBW)**
- Benign intracranial hypertension **(BBW)**
- Avoid use during pregnancy **(BBW)**
- Hepatic dysfunction (increased liver transaminases reported with danazol): monitor liver function
- Transient changes in lipoproteins (eg, decreased high density lipoprotein and increased low density lipoprotein levels)
- Androgenic effects (may be irreversible)
- Use cautiously in patients with diabetes mellitus or conditions affected by edema because danazol can cause fluid retention

Abbreviations: BER, Berinert; BERO, berotralstat; BBW, black box warning; CIN, Cinryze; DAN, danazol; ECA, ecallantide; FDA, US Food and Drug Administration; HAE, hereditary angioedema; HAEG, Haegarda; ICA, icatibant; LAN, lanadelumab-flyo; Phx, approved for prophylaxis HAE therapy; Rescue, refers to agent approved for on-demand treatment of HAE attacks; RUC, Ruconest

9.2 Other Concerns: Theoretical Concerns with Long-term Kallikrein Inhibition

With long-term inhibition of plasma kallikrein there is a theoretical risk for dysregulation of fibrinolysis, and emergent cardiovascular dysfunction such as thrombotic events and hypertension. A 2020 systematic review assessed risks of cardiovascular, bleeding, or autoimmune events among patients with hereditary prekallikrein deficiency to estimate long-term risks due from kallikrein inhibition. Overall, their analysis did not suggest safety concerns; many of the patients with prekallikrein deficiency were generally asymptomatic.[58]

Published "long-term" data for the kallikrein inhibitor for LTP, lanadelumab, includes a median duration of exposure of 33 months,[59] and exposure to about 2 years for the other kallikrein inhibitor for LTP, berotralstat.[60] For lanadelumab, bleeding or thrombotic events were considered safety signals of special interest. Investigators reported a lack of these events that were considered drug-related.[59] In the berotralstat study, only 1 of the 81 patients experienced grade 3 or higher activated partial thromboplastin time (aPTT) elevation or a prothrombin laboratory abnormality.[60] Yet experts describe that the prothrombin time and aPTT …"reflect clotting times only and are not sensitive to fibrinolytic capacity at all," and overall there are no reliable markers for monitoring fibrinolysis in routine coagulation assessments.[61]

9.3 Adverse Events

The most common adverse events (AEs) occurring in clinical trials, as reported in the prescribing information for each product, are summarized below.

9.3.1 Prophylactic HAE agents[11,12,15,16]

- C1INH−human (Cinryze; AEs with incidence ≥5%): nausea, headache, rash, pyrexia, and vomiting
- C1INH−human (Haegarda; AEs with incidence >4% and greater than the incidence in the placebo arm): injection site reactions (eg, bruising, pain, erythema), nasopharyngitis, hypersensitivity, and dizziness
- Berotralstat (Orladeyo; AEs with incidence ≥10% and greater than the incidence in placebo arm): abdominal pain, back pain, vomiting, diarrhea, and gastroesophageal reflux disease
- Lanadelumab-flyo (Takhzyro; AEs with incidence ≥10% and greater than the incidence with placebo): injection site reactions, upper respiratory infections (for 300 mg every 2 week dosing only), dizziness, rash, and myalgia
- Danazol (incidence not reported): androgenic effects (eg, acne, sore throat, mild hirsutism, voice change, hair loss), menstrual disturbances (eg, amenorrhea), reproductive abnormalities (eg, vaginal dryness, breast size reduction, abnormal semen volume), signs of hepatic impairment (eg, transient increase in serum enzymes, jaundice) or toxicity (eg, peliosis hepatis, hepatic failure), and laboratory abnormalities (eg, glucose tolerance, lipoproteins, thyroid binding globulin)
    - According to a systematic review of prospective studies, common AEs among androgen (danazol or stanozolol) users with HAE were weight gain, virilization, menstrual irregularity,

myalgias, headache, and mood changes (anxiety or depression). Elevations in creatine phosphokinase and abnormal liver enzymes were also frequently reported.

9.3.2 Rescue HAE agents[6-10,22]

- C1INH, human (Berinert; AEs with incidence>4% and greater than the placebo arm incidence): dysgeusia
    - Serious adverse reaction (incidence not reported): increase in HAE-related pain
- C1INH, recombinant (Ruconest; AEs with incidence ≥2%): nausea, headache, and diarrhea
    - Serious adverse reaction (incidence not reported): anaphylaxis
- Icatibant (Firazyr; Sajazir; AEs with incidence ≥3% and at least twice that of the placebo arm): injection site reactions, pyrexia, transaminase elevation, and dizziness
- Ecallantide (Kalbitor; AEs with incidence ≥3% and at least twice that of the placebo arm): injection site reactions, nausea, pyrexia, and nasopharyngitis

9.4 Immunogenicity

With large molecule, therapeutic protein drugs, the development of anti-drug antibodies (ADAs), some potentially neutralizing is a theoretical possibility.

- In clinical studies with lanadelumab, ADAs were detected among about 12% to 15% of patients in clinical trials cited in the package insert. Nonetheless, the labeling describes that the development of ADAs, including neutralizing ADAs in 3 patients, did not appear to impact pharmacokinetics, pharmacodynamics, safety or clinical response.[16]
- Labeling for Ruconest (rhC1INH) describes that at least 10% of treated subjects expressed ADAs after five treated HAE attacks, but none were neutralizing, and ADAs did not impact clinical efficacy/safety.[7]
- Labeling for Berinert (pdC1INH) notes that no neutralizing ADAs were observed in a subset of patients treated post-marketing, although 28% had detectable non-inhibitory ADAs at some point during the study.[6]
- Labeling for Cinryze and Haegarda (both pdC1INH products) do not provide any details regarding the development of ADAs.[11,12]

9.5 Drug Interactions

Most of the reviewed agents for HAE lack drug-interaction studies or their product labeling does not provide information regarding potential drug-drug interactions (as with C1INH products, lanadelumab, and ecallantide). Caution is advised for use of berotralstat with p-glycoprotein inducers or narrow therapeutic index drugs that are p-glycoprotein, or cytochrome (CYP) 2D6 or 3A4 substrates.[15] Danazol also has various potential drug-drug interactions (eg, prolonging prothrombin time with warfarin, inducing insulin resistance with antidiabetic agents, increased risk of myopathy and rhabdomyolysis with statins).[22] Icatibant has the potential to reduce the antihypertensive effect of ACE inhibitors.[10] **Table 9** summarizes the drug-drug interactions for the FDA-approved agents for HAE, according to their respective product labeling.

Table 9. Drug-drug Interactions for HAE Agents[6-12,15,16,22]

Prophylactic Agents	
C1INH, human (Cinryze and Haegarda)	• None listed in product labeling; no drug-interaction studies performed noted in Haegarda package insert
Berotralstat (Orladeyo)	• Avoid use with P-glycoprotein inducers • If used with narrow therapeutic index drugs that are P-glycoprotein substrates, or primarily metabolized by CYP2D6 or CYP3A4, monitor or adjust the dose of the P-glycoprotein, CYP2D6, or CYP3A4 substrate accordingly • May elevate etonogestrel (metabolite) when used with desogestrel
Lanadelumab-flyo (Takhzyro)	• No studies investigating drug interactions have been performed
Danazol	• Concomitant use with warfarin may prolong prothrombin time • May elevate carbamazepine levels • May increase insulin resistance; consider dose-adjustment needs for anti-diabetic agents • May increase concentrations of cyclosporin or tacrolimus, thus, increasing risk of renal toxicity; monitor and consider potential dose adjustments • Combination use with synthetic vitamin D analogs may enhance calcemic response in patients with primary hypoparathyroidism • Concomitant use with statins increases the risk of myopathy and rhabdomyolysis; caution is advised, and product labeling for statins should be consulted for specific dose adjustments
Rescue Agents	
C1INH, human (Berinert)	• None listed in product labeling
C1INH, recombinant (Ruconest)	• None listed in product labeling
Icatibant (Firazyr; Sajazir)	• Has the potential to reduce the antihypertensive effect of ACE inhibitors
Ecallantide (Kalbitor)	• No drug-interactions studies performed

Abbreviations: ACE, angiotensin-converting enzyme; C1INH, C1 esterase inhibitor; CYP, cytochrome; HAE, hereditary angioedema

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APPENDIX A - LITERATURE SEARCHES

The phased literature search approach involved screening the most recently published SRs first, then refining the search to later publication years tailored to certain drugs/indications as needed (per the rationale described in Box 1). The search strategies for each literature search (A-C, in Box 1) are included in following.

Box 1. Phased Literature Search Approach for SRs or RCTs with Direct, Head-to-head Comparisons

A. SR Search in Epistemonikos

a. Searched for 2022-2024 SRs for the FDA-approved HAE medications: **18** results
   i. Located a 2022 Cochrane Review the prophylactic HAE medications; since recent SRs were lacking for the on-demand agents, the search was expanded to older years for these agents.

b. To capture additional/older SRs for the on-demand HAE agents, the search terms were narrowed to on-demand HAE drugs only and results limited 2000 to 2021: **26** results

B. Supplemental SR search in Ovid-Medline

a. Searched for 2022-2024 SRs for the FDA-approved HAE medications: **31** results

C. Supplemental RCT searches in Ovid-Medline and Embase

a. Searched for 2021-2024 comparative RCTs of the reviewed HAE medications: **25** results from Ovid-Medline and **40** results from Embase on 3/4/2024

b. Searched for older years (2010-current) for comparative RCTs of the reviewed on-demand HAE medications in Ovid-Medline: ***139*** *results (16 duplicative with search "C.a." since some later years overlap)*

A. SR Search Epistemonikos

Query date: July 3, 2024

Searched Title or Abstract and filtered to Systematic Reviews: hereditary-angioedema OR HAE OR C1-esterase-inhibitor OR C1-INH OR C1INH OR rhC1INH OR pdC1INH OR cinryze OR haegarda OR berinert OR ruconest OR lanadelumab OR berotralstat OR danazol OR ecallantide OR icatibant

- Limited from 2022 to 2025 publication year: **18 results**

Added additional years for on-demand drugs only (query date July 10, 2024):

Searched Title or Abstract and filtered to Systematic Reviews: C1-esterase-inhibitor or C1-INH or C1INH or berinert or ruconest or ecallantide or icatibant

- Limited from 2000 to 2021 publication year: **26 results**

B. SR Search Ovid-Medline

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to July 2, 2024		
#	**Searches**	**Results**
1	((angioedema* adj3 (hereditary or acquired)) or HAE).ti,ab,kw,kf. or exp Angioedemas, Hereditary/	4656
2	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw. or (Medline or Embase or Pubmed or literature-search).ab. or (systematic-review or meta-analysis).pt.	700518
3	1 and 2	119
4	limit 3 to yr="2022 -Current"	31

C. RCT Search Ovid-Medline

Database(s): Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to July 3, 2024		
#	**Searches**	**Results**
1	((angioedema* adj3 (hereditary or acquired)) or HAE).ti,ab,kw,kf. or exp Angioedemas, Hereditary/	4656
2	(C1-esterase-inhibitor or C1-INH or cinryze or haegarda or berinert or ruconest or lanadelumab or berotralstat or danazol or ecallantide or icatibant).ti,ab,kw,kf. or *Complement C1 Inhibitor Protein/	5533
3	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1483052
4	1 and 2 and 3	188
5	limit 4 to yr="2021 -Current"	25
6	(C1-esterase-inhibitor or C1-INH or berinert or ruconest or ecallantide or icatibant).ti,ab,kw,kf. or *Complement C1 Inhibitor Protein/	2973
7	1 and 3 and 6	169
8	limit 7 to yr="2010 -Current"	139
9	**5 or 8**	**148**

D. Embase RCT Search

	Search string, query date July 5, 2024	Result
#1	'angioneurotic edema'/exp OR 'angioneurotic edema'	26,343
#2	hereditary:ti,ab,kw AND angioedema:ti,ab,kw OR hae:ti,ab,kw	7,934
#3	#1 OR #2	28884
#4	'c1 esterase inhibitor':ti,ab,kw OR 'c1 inh':ti,ab,kw OR pdc1inh:ti,ab,kw OR rhc1inh:ti,ab,kw OR c1inh:ti,ab,kw OR cinryze:ti,ab,kw OR haegarda:ti,ab,kw OR berinert:ti,ab,kw OR ruconest:ti,ab,kw OR lanadelumab:ti,ab,kw OR berotralstat:ti,ab,kw OR danazol:ti,ab,kw OR ecallantide:ti,ab,kw OR icatibant:ti,ab,kw	8,919
#5	('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti) AND [english]/lim	3,162,533
#6	#3 AND #4 AND #5	668
#7	#3 AND #4 AND #5 AND [2021-2024]/py	88
#8	'conference abstract'/it OR 'conference review'/it	5,208,989
#9	7 NOT #8	**40**

E. Ovid-Medline Clinical Guidelines Search for the Treatment of HAE

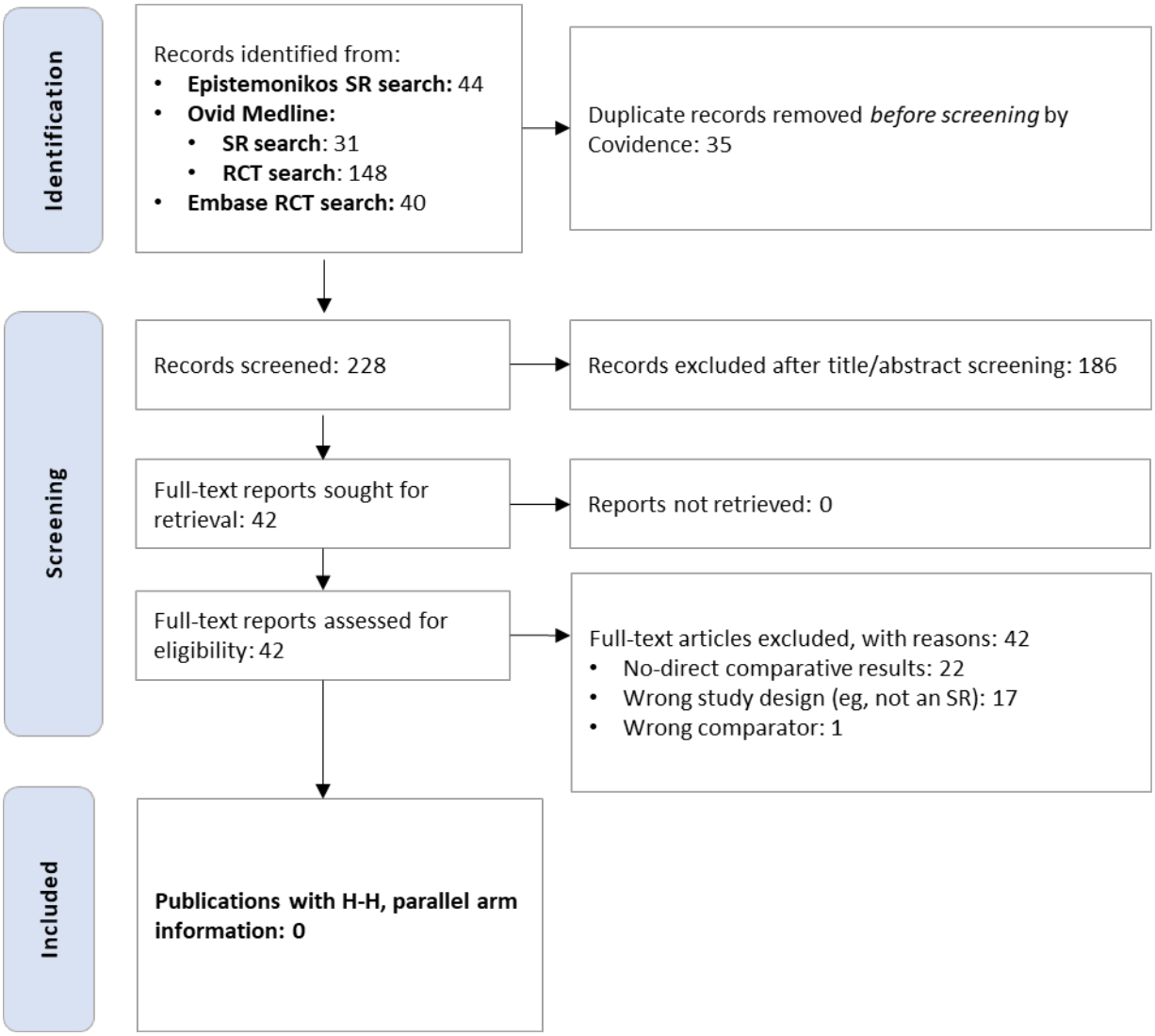
Database(s): Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily June 11, 2024

#	Searches	Results
1	((angioedema* adj3 hereditary) or HAE).ti,ab,kw,kf. or exp Angioedemas, Hereditary/	4491
2	exp clinical pathway/ or exp clinical protocol/ or clinical protocols/ or exp consensus/ or exp consensus development conference/ or exp consensus development conferences as topic/ or critical pathways/ or exp guideline/ or guidelines as topic/ or exp practice guideline/ or practice guidelines as topic/ or health planning guidelines/ or treatment guidelines/ or Clinical Decision Rules/	437454
3	(guideline or practice guideline or consensus development conference).pt.	48345

4	(position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw.	50679
5	(standards or guideline or guidelines).ti,kf,kw. or ((practice or treatment* or clinical) adj guideline*).ab. or (CPG or CPGs).ti. or consensus*.ti,ab,kf,kw.	402101
6	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.	28878
7	recommendat*.ti,kf,kw. or guideline recommendation*.ab.	62951
8	(care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.	92309
9	(algorithm* adj2 (pharmacotherap* or therap* or treatment* or intervention*)).ti,ab,kf,kw.	13846
10	exp practice guideline/ or (recommend* or guid* or consensus or position).ti. or *Advisory Committees/st or guideline.pt.	390566
11	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	919157
12	1 and 10	83
13	1 and 11	194
14	limit 12 to yr="2019 -Current"	**39**
15	limit 13 to yr="2019 -Current"	82
16	15 not 14	**50**

APPENDIX B - SCREENING OF STUDIES

Appendix B, Figure 1. PRISMA Flow Chart[a] for Publication Screening



Abbreviations: H-H, head-to-head; RCTs, randomized controlled studies; SR, systematic review
[a] Modified from Page et al. 2021[25]

APPENDIX C - EXCLUDED REFERENCES FROM LITERATURE SEARCH

Wrong Study Design (eg, not a Systematic Review)

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Wrong Comparator

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APPENDIX D – ADDITIONAL BACKGROUND INFORMATION

Diagnosis of HAE

For patients greater than 1 year of age, diagnosis of HAE is based on a history of angioedema (unattributable to another cause) without urticaria, coupled with positive laboratory markers. Diagnosis of HAE-nl-C1INH additionally requires either evidence of causative genetic mutations, or a history suggesting inherited angioedema that is not allergy-mediated.[5] Most patients with HAE (ie, type 1 and type 2 HAE) have low activity of C1INH and therefore C1 esterase depletes C4, resulting in low C4 levels, particularly at times of an HAE attack.[3] Nonetheless, factors such as infection can temporarily increase C4, causing a missed or delayed diagnosis of HAE.[62]

Screening for HAE among children is recommended when a parent has the disorder.[35] Diagnosis in children is similar to that of adults, although children may not have adult levels of complement proteins used in the diagnosis (ie, C4) until after at least 12 months of age; thus, waiting to perform this test once at the age of 1 is suggested.[32] C1INH antigenic and functional levels can be reliably tested in children of all ages including before 1 year of age.[17] Notably, "Until a full investigation for HAE-1/2 is complete, all offspring of parents with HAE-1/2 should be considered to also have the disease" (page 1974, Mauer et al).[1]

Acquired angioedema with low C1 inhibitor levels (AAE-C1INH) presents with similar symptomatology and some similar laboratory findings as with HAE-C1INH type 1 (low C1INH function and antigen levels, and C4). Nonetheless, the disorders can usually be diagnostically distinguished based on C1q level which is expected to be within normal limits in HAE but is usually low in AAE-C1INH cases.[26] AAE-C1INH is usually associated with lymphoproliferative or autoimmune disorders, or malignancy, and the age of onset is usually later than HAE-C1INH.

Table D1 shows HAE diagnostic criteria per the 2020 US Hereditary Angioedema Association (HAEA) medical advisory board guideline. Other recent guidelines are in agreement with recommended tests for diagnosis.[13,35] The 2020 US Hereditary Angioedema Association (HAEA) guideline advocates for repeat testing only if the diagnosis is unclear.[5] If testing is repeated, the 2019 Canadian/International guideline does not recommend delaying access to HAE treatments before availability of the confirmatory test.[13] Consultation with a specialist for diagnosis of HAE-nl-C1INH of unknown cause (ie, patients without a known causative gene variant) is recommended.[13]

Table D1. HAE Diagnostic Criteria per the US Hereditary Angioedema Association[5]

Criteria	HAE Subtype	
	HAE-C1-INH (type 1 and type 2)[a]	**HAE-nl-C1-INH**[b]
Recurrent angioedema[c] without urticaria	✓	✓
Low C1-INH activity (low antigenic level and/or functional capacity)	✓ (low antigenic level for type1; low protein activity for both type 1 and type 2)	✗
Low C4 level[d]	✓	✗
Normal (or not substantially reduced) levels of: C4, C1-INH antigen, C1-INH function	✗	✓
Confirmed HAE-associated mutation[e] **OR** Positive family history for recurrent angioedema *plus* lack of response to high-dose antihistamines[f]	✗	✓

Abbreviations: C1-INH, C1 Esterase Inhibitor; HAE, hereditary angioedema; HAE-C1-INH, hereditary angioedema without functional C1 inhibitor; HAE-nl-C1INH, hereditary angioedema with normal levels of C1 inhibitor;

[a] *Other supportive findings (but not required for diagnosis): confirmed SERPING1 mutation; positive family history of repeated angioedema; symptom presentation before age 40*

[b] *Other supportive findings (but not required for diagnosis): response to medication targeting bradykinin; angioedema can be observed visibly (eg, including by imaging for abdominal angioedema)*

[c] *Should not be due to another cause such as medications (although medications such as ACE inhibitors can also precipitate an attack among people with HAE)*

[d] *Levels are usually reduced for HAE type 1 or 2, but sensitivity/specificity is limited,*[35] *and levels may not be low when tested outside of the window of an HAE attack*[13] *or may be temporarily normalized during an infection.*[62] *Sensitivity of C4 for HAE diagnosis when an attack is not occurring is about 81 to 96%.*[5]

[e] *Examples of genes where mutational variants are associated with HAE-nl-C1INH: F12 (factor XII), ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen 1).*[26]

[f] *Duration of high-dose antihistamines should be long enough to expect at least 3 angioedema attacks, or at least 1 month (choose the longest option). Example of high-dose antihistamine: cetirizine 40 mg daily.*

Table D2. Guideline Recommendations for On-Demand Treatment of HAE Attacks

International World Allergy Organization and European Academy of Allergy and Clinical Immunology (WAO/EAACI) Joint Guideline, 2021[1]	Recommendation Strength (LOE)
Recommendations are intended for HAE-C1INH (ie, HAE type 1 or HAE type 2) only	
All HAE attacks should be considered for on-demand treatment	Strong (D)
• An HAE attack affecting or potentially affecting the upper airway should be treated	Strong (C)
• HAE attacks <u>should be treated as early as possible</u>	Strong (B)
• Patients should have enough on-demand medication supply to treat at least 2 attacks, and patients should carry their on-demand medication at all times	Strong (D)
• Consider intubation or surgical airway intervention early in the progression of upper airway edema due to an HAE attack	Strong (A)
Intravenous C1INH, ecallantide, or icatibant are recommended options for on-demand treatment of acute HAE attacks	Strong (A)
• All patients should be considered for home therapy and self-administration of treatment • If the above options are unavailable, solvent detergent-treated plasma (SDP) or fresh frozen plasma (FFP) can be considered as available. • The use of antifibrinolytics (eg, tranexamic acid) or attenuated androgens (eg, danazol) for on-demand treatment is *advised against* because they have no or only minimal benefit.	Not graded
CHILDREN	
• C1INH or icatibant are recommended for the treatment of attacks in children under the age of 12	Strong (A)
• If first-line options are unavailable, SDP (preferred) or FFP are second-line	Not graded
DURING PREGNANCY OR BREASTFEEDING	
• pdC1INH is the preferred agent for the management of HAE during pregnancy and lactation	Strong (D)

US Hereditary Angioedema Association Medical Advisory Board (HAEA) Guideline, 2020[5]	Recommendation Strength (LOE)	
	HAE-C1INH	HAE-nl-C1INH
Patients *must have* on-demand medication <u>readily accessible</u> to respond to the onset of an HAE attack; an **FDA-approved, on-demand agent is preferred for use (eg, ecallantide, icatibant, pdC1INH, or rhC1INH) whenever possible** • <u>Self-administered, on-demand treatment</u> (or by caregiver) is recommended whenever feasible, unless receiving ecallantide which must be administered in a healthcare setting by the provider • All HAE attacks are eligible for treatment irrespective of the location of the swelling or the severity of the attack	Strong (high)	Strong (low)

Table D2. Guideline Recommendations for On-Demand Treatment of HAE Attacks

CHILDREN The same treatment approach applies as in adults; yet, regulatory differences may affect use for some agents, per approved patient age for use	Strong (moderate)
• Clinical trials primarily focused on adults; several effective medications are not yet FDA-approved for children	Not graded
• pdC1INH is preferrable in children due to long-term safety data • Data for rhC1INH is limited but positive for treatment of attacks in children • Ecallantide is an option for attacks, with US approval for patients older than 12	Not graded
• Although icatibant lacks US approval for pediatrics, it has positive evidence and approval for HAE attack treatment in other countries for as young as the age of 2	
DURING PREGNANCY OR BREASTFEEDING • C1INH is the treatment of choice for acute and prophylactic treatment (pdC1INH has the most data; data for rhC1INH is limited but "reassuring")	Strong (moderate)
Canadian Hereditary Angioedema Network and International Experts Joint Guideline, 2019[13]	**Recommendation Strength (LOE)**
An effective therapy should be used to treat an HAE attack to reduce the severity and duration of the attack	Strong (high)
Medication options: • Intravenous pdC1INH, intravenous rhC1INH, icatibant, and ecallantide are effective for on-demand treatment	Strong (high)
• FFP can be considered for acute-treatment of HAE attacks if other first-line options are not available	Strong (low)
• Attenuated androgens or tranexamic acid should not be used for on-demand treatment	Strong (low)
Attacks should be **treated early** to reduce morbidity and mortality	Strong (moderate for morbidity and consensus for mortality)
Patients should be trained to self-administer of HAE-specific medication, if a suitable candidate; otherwise, a plan should be in place to access appropriate therapies	Strong (low)
HAE attacks in the upper airway are medical emergencies and must be treated immediately	Strong (low)
PREGNANCY • For pregnant patients with HAE type 1 or 2, pdC1INH is the preferred on-demand agent	Strong (consensus)
PEDIATRIC PATIENTS • All patients with HAE should have access to on-demand treatment, including those that are symptom free	Strong (consensus)
Medication options: • Intravenous pdC1INH is effective for on-demand treatment in pediatric patients with HAE type 1 or 2	Strong (moderate)

Table D2. Guideline Recommendations for On-Demand Treatment of HAE Attacks

• rhC1INH or icatibant are effective for on-demand treatment in pediatric patients with HAE type 1 or 2	Strong (consensus)
• Ecallantide is effective for on-demand treatment in adolescents with HAE type 1 or 2	Strong (consensus)
HAE-NL-C1INH • pdC1INH is effective for on-demand treatment of HAE attacks in patients with HAE-nl-C1-INH	Strong (moderate)
• Icatibant is effective for on-demand treatment of HAE attacks in patients with HAE-nl-C1-INH	Strong (consensus)
International Consensus for Pediatric HAE Treatment (2017)[17]	**LOE**
PEDIATRIC PATIENTS WITH HAE-C1INH • Level I evidence for acute treatment of HAE-C1INH was reviewed for pdC1INH (Berinert and Cinryze), rhC1INH (as Rhucin or Ruconest), ecallantide (Kalbitor), and icatibant (Firazyr) ○ Refer to the guideline to view which countries have authorized which product for pediatric use. For example, while not approved in the US, Cinryze is approved in Europe for pediatric on-demand treatment.	Not graded
• "All swelling events are eligible for acute treatment" • Upper airway attacks should be treated with on-demand treatment as early as possible (with prompt follow-up in the emergency room) since earlier treatment is associated with shorter attack duration and improved treatment outcomes	III
• For *all patients*, a self-administered, on-demand agent should be considered (ie, for home use or administered by patient's caregiver). Facilitate administration training for patient and caregiver.	I
• If licensed on-demand medication is inaccessible, SDP (preferred) or FFP can be used	III

Abbreviations: C1INH, C1 inhibitor concentrate product; FDA, US Food and Drug Administration; FFP, fresh frozen plasma; HAE, hereditary angioedema; HAE-C1INH, hereditary angioedema due to C1 inhibitor deficiency; HAE-nl-C1INH, hereditary angioedema with normal levels of C1 inhibitor; LOE, level of evidence; RCTs, randomized controlled trials; rhC1INH, recombinant C1 inhibitor product; SDP, solvent detergent-treated plasma; pdC1INH, plasma-derived C1 inhibitor product

Evidence ratings from the WAO/EAACI 2021 guideline:
- *Strong recommendation: almost all informed people would select this choice; appropriate for policy for most clinical situations.*
- *Weak recommendation: most but not all informed people would select this choice; individualize therapy and debatable for implementation into policy*
- *Level of evidence (based on GRADE criteria):*
  - *A: based on high-quality trial(s) that minimizes bias (eg, randomized, double-blinded)*
  - *B: based on lower-quality trial(s) with smaller size or with risk of bias*

Table D2. Guideline Recommendations for On-Demand Treatment of HAE Attacks

- *C: based on trial(s) with serious risk of bias, or retrospective observational studies*
- *D: Consensus or expert opinion*

Evidence rating from US HAEA 2020:

- *Strong recommendation: authors have confidence in the recommendation based on existing evidence or compelling risk/benefit ratio.*
- *Weak recommendation: authors with less confidence in the recommendation based on evidence or less clear risk/benefit ratio*
- *Level of evidence:*
  - *High quality: evidence from well-designed RCTs or observational studies with very large and clinically important effect sizes.*
  - *Moderate quality: evidence from RCTs with important limitations or observational studies with clear and consistent effect sizes.*
  - *Low quality: evidence that failed to achieve either high or moderate quality*

Evidence rating from Canadian/International Experts 2019:

- *Recommendation strength: determined based on LOE, balance of desired and undesired effects, certainty of preferences/values, and costs*
- *LOE (high, moderate, low, or very low): based on GRADE criteria; all RCTs assigned high while all non-randomized studies assigned low. Quality of RCTs was downgraded 1 level (or 2 levels if considered a significant limitation) based on risk of bias and/or inconsistency of the treatment effect.*

Evidence rating from international consensus expert panel 2017:

- *I: evidence from at least one properly designed RCT*
- *III: descriptive studies, or based on clinical experience or the opinion of experts*

Table D3. Guideline Recommendations Regarding HAE Prophylaxis

International World Allergy Organization and European Academy of Allergy and Clinical Immunology (WAO/EAACI) Joint Guideline, 2021[1]	Recommendation Strength (LOE)
Recommendations are intended for HAE-C1INH (ie, HAE type 1 or HAE type 2) only	
Consider short-term prophylaxis (STP) before medical, surgical, or dental procedures as well as before exposure to other attack triggers	Strong (C)
• **Intravenous pdC1INH** is the preferred first-line agent **for STP**	Strong (C)
Evaluate patients for long-term prophylaxis (LTP) initiation at each clinic visit if not yet started: consider disease activity, burden, and control, as well as patient preference	Strong (D)
• **pdC1INH, lanadelumab, or berotralstat are recommended first-line for LTP**	Strong (A)
• Androgens are recommended only as second-line LTP options	Strong (C)

CHILDREN
• STP is recommended prior to medical, surgical, or dental procedures associated with any mechanical impact to the upper aerodigestive tract
  ○ **pdC1INH is the preferred first-line option**
  ○ Acute uses of attenuated androgens are second line if C1INH concentrate is unavailable
• Indications for LTP in adolescents are the same as in adults
  ○ For children younger < 12 years of age, **pdC1INH is the treatment of choice** for LTP
  ○ If C1INH therapy is unavailable for LTP, antifibrinolytics (eg, tranexamic acid) are preferred to androgens because of their better safety profile; yet, efficacy is questionable and not yet established by robust studies
  ○ Androgens are not recommended for LTP prior to Tanner Stage V
	Not graded

DURING PREGNANCY OR BREASTFEEDING • pdC1INH is the preferred therapy of choice for the management of HAE (for on-demand treatment, STP, and LTP)	Strong (D)
• SDP can be used if C1INH is unavailable; FFS is also a second-line option but secondary to SDP	Not graded

US Hereditary Angioedema Association Medical Advisory Board (HAEA) Guideline, 2020[5]	Recommendation Strength (LOE)	
	HAE-C1INH	HAE-nl-C1INH
Short-term prophylaxis (STP): recommended for known, upcoming potential triggers (eg, trauma, planned invasive medical or dental procedures, stressful events)	Strong (moderate)	Weak (low)
Medication options for STP, especially for HAE type 1 or 2: • Single dose of pdC1INH (eg, 20 IU/kg 1–12 hours before trigger) • Anabolic androgens (eg, danazol 400–600 mg 5 to 7 days before trigger; continue for 2 to 5 days post-trigger) • rhC1INH (50 IU/kg), but limited by less evidence/experience • FFP if other options are not available	Not graded	

Table D3. Guideline Recommendations Regarding HAE Prophylaxis

• May consider the same treatments for HAE-nl-C1INH; however, robust evidence is lacking in this population to guide selection of a particular therapy		
Long-term prophylaxis (LTP) initiation should be decided based on individual patient needs	Strong (high)	Strong (low)
Medication options for HAE type 1 or 2 LTP: • **First-line, recommended medications are IV or SC C1INH** (eg, Cinryze, Haegarda), **or lanadelumab** (Takhzyro)	Strong (high)	NA
• Second-line options may include attenuated androgens or antifibrinolytics	Not graded	NA
Medication options for LTP in HAE-nl-C1INH: • **First-line therapy: progestin-only medication or antifibrinolytics** (eg, norethindrone 0.35 mg daily; or tranexamic acid 650 mg twice daily)	NA	Weak (low)
• Others: attenuated androgens; trial of C1INH if frequent symptoms despite other options (some case reports showed benefit in certain subtypes); lanadelumab (theoretical benefit, and may have advantages over C1INH concentrate)	NA	Not graded
CHILDREN The same treatment approach applies as in adults; yet, regulatory differences may affect use, per patient age, for some agents	Strong (moderate)	
• Clinical trials primarily focused on adults; several effective medications are not yet FDA-approved for children • pdC1INH is preferrable due to long-term safety data • Data for rhC1INH is limited but positive for treatment in children • Lanadelumab is an option, with US approval for patients older than 12 • Anabolic androgens are generally discouraged for patients <16 years	Not graded	
DURING PREGNANCY OR BREASTFEEDING C1INH is the treatment of choice for acute and prophylactic treatment (pdC1INH has the most data; data for rhC1INH is limited but "reassuring")	Strong (moderate)	
• Androgens are contraindicated during pregnancy. • Tranexamic acid, an antifibrinolytic, crosses into placenta but limited data suggests it may not be harmful • Androgens and antifibrinolytics are not recommended during breastfeeding since they pass into breast milk • There was no data, at the time of the guideline's writing, for the use of other agents during pregnancy: lanadelumab, berotralstat	Not graded	
Canadian Hereditary Angioedema Network and International Experts Joint Guideline, 2019[13]	**Recommendation Strength (LOE)**	
SHORT-TERM PROPHYLAXIS Consider before known patient-specific trigger and prior to any medical, surgical, or dental procedure (inferred as applying to all patients with HAE, including HAE-nl-C1INH)	Strong (low)	
• IV pdC1INH should be used for STP in patients with HAE (eg, 20 U/kg up to 1 hr before procedure); inferred as applying to all patients with HAE, including HAE-nl-C1INH)	Strong (consensus)	
• Alternative options: ○ Danazol (eg, 2.5 to 10 mg/kg/day; max 600 mg/day)	Not graded	

Table D3. Guideline Recommendations Regarding HAE Prophylaxis

○ FFP ○ Antifibrinolytics are a last-line option due to unclear efficacy ○ Not recommended: lanadelumab or subcutaneous C1INH because of the considerable delay in reaching therapeutic steady state	
LONG-TERM PROPHYLAXIS (FOR HAE TYPE 1 AND TYPE 2) LTP may be appropriate for some patients to decrease frequency, duration, and severity of HAE attacks	Strong (high)
Recommended Medications for HAE type 1 and type 2 LTP: • Medications considered effective: pdC1INH, lanadelumab	Strong (high)
• Medications considered effective *for some patients*: attenuated androgens	Strong (moderate)
• **Recommended as first-line: SC C1-INH or lanadelumab**	Strong (consensus)
• Agents that should not be used first-line therapy: androgens or antifibrinolytics	Strong (consensus)
LONG-TERM PROPHYLAXIS FOR HAE-NL-C1INH: consensus not reached for making a recommendation for particular agents due to limited data	NA
LTP FOR CHILDREN WITH HAE • **Preferred option: pdC1-INH**	Strong (consensus)
• Other options: as: SC pdC1-INH, lanadelumab (indicated for LTP for people ≥ 12 years old)	Not graded
• Avoid androgens for pediatric LTP	Strong (moderate)
○ androgens have safety risks before puberty (Tanner stage 5); may consider lowest effective dose after puberty if necessary	Not graded
• Not recommended for LTP: antifibrinolytics (due to lack of evidence)	Not graded
LTP FOR PREGNANT PEOPLE WITH HAE • **Preferred option: pdC1-INH**	Strong (consensus)
• Avoid attenuated androgens during pregnancy and breastfeeding	Strong (consensus)
International Consensus for Pediatric HAE Treatment (2017)[17]	**LOE**
SHORT-TERM PROPHYLAXIS • Indications for STP (ie, triggers) are similar as to adults: eg, medical or dental procedures • Generally, "minor interventions" that don't involve manipulation of the airway can be managed with an approved on-demand acute medication if it is readily available on-hand, in the event of precipitating an attack	Not graded
• For interventions involving the airway or where tissue swelling is anticipated: use pdC1INH (eg, Berinert 15 to 30 mg/kg; no consensus on timing or max dose) • Second line: attenuated androgens (eg, danazol or oxandrolone) or antifibrinolytics (eg, tranexamic acid), 5 days before and continued to 2 days after the procedure • Other options: solvent degenerated plasma or FFP	III
LONG-TERM PROPHYLAXIS Consider LTP to minimize the impact of C1-INH-HAE on patients' quality of life • Antifibrinolytics (tranexamic acid or epsilon aminocaproic acid) were considered first-line • pdC1INH was consider second-line (preferred over attenuated androgens)	III

Table D3. Guideline Recommendations Regarding HAE Prophylaxis

○ At the time of writing this guideline, minimal evidence for long-term use of pdC1INH was available according to the authors; however they further described that "To date, safety, efficacy, and tolerability of pdC1-INH appear to be similar in pediatric and adult patients"[17] ○ Attenuated androgens are a last line option and should not be used before Tanner Stage V (danazol, stanozolol, oxandrolone)	
- Training for home-based self-administration is preferred to administration in healthcare facilities (provides greater patient freedom). Panel expert notes that even younger children can learn to self-administer IV or SQ medications.	III

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