Drug Class Review: Hereditary Angioedema

Date of Review: March 2019

Purpose for Class Review:
The purpose of this review is to evaluate evidence for efficacy and safety of pharmacological treatments for hereditary angioedema (HAE). The review was prompted by FDA approval of 2 new therapies (subcutaneous C1 inhibitor and lanadelumab) for prophylaxis in HAE.

Research Questions:
1. What is the evidence for efficacy and harms of prophylactic or acute treatment for HAE?
2. Is there any comparative evidence on efficacy of treatments for HAE pertaining to clinical outcomes (morbidity, mortality, reduction in HAE attacks, and quality of life)?
3. Is there any comparative evidence on the harms of therapy for HAE with prophylactic or acute use?
4. Are there subpopulations of patients with HAE for which treatment may be more effective or associated with more harms?

Conclusions:
- There is no direct comparative evidence evaluating prophylactic use or acute treatment of HAE.
- There is insufficient evidence to assess long-term efficacy or safety of C1 inhibitors, lanadelumab, ecallantide, or icatibant. While there is no long-term, randomized controlled data regarding efficacy and safety of these therapies, the first C1 inhibitors were initially FDA approved in 2008. A summary of warnings and precautions associated with each treatment is available in Appendix 1.

Acute Treatment
- Compared to placebo during treatment of an acute HAE attack, time to symptom relief or resolution was improved by approximately 1-2 hours with human or recombinant C1 inhibitor (low quality evidence).\(^1-3\) For specific C1 inhibitor products, the median time to symptom relief compared to placebo was 1.5 versus 2.5 hours for Ruconest\(^\text{®}\), 0.5 versus 1.5 hours for Berinert\(^\text{®}\), and 2 versus 4 hours for Cinryze\(^\text{®}\).\(^1-3\)
- In clinical trials for treatment of acute attacks, symptom severity was statistically improved at 4 hours after treatment with ecallantide compared to placebo (difference in mean symptom complex score of 0.4 points and difference in treatment outcomes scale of 25.5 points; low quality evidence).\(^4,5\) The clinical significance of this change is unclear. Mean symptom complex score provides an average score of various symptoms and improvement over time on a severity scale of 0-3 with lower scores indicating improved symptoms. The treatment outcomes scale evaluates severity of symptoms on a -100 to 100 range associated with significantly worse to significantly improved symptoms. Scores of 0 are associated with no change from baseline and 50 points are associated with improvement.
- In patients with type 1 or 2 HAE, there is inconsistent evidence from 2 trials that icatibant may be associated with improved time to symptom improvement during an acute attack (low quality evidence).\(^6-8\) Compared to placebo, time to clinical symptom improvement was not statistically significant for a patient's

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primary symptom (median difference 2.1 hours; p=0.14, n=56), but a second study demonstrated a median time to 50% improvement in overall symptoms of 17.8 hours compared to placebo (19.8 vs. 2.0 hours; p<0.001; n=93). 6–8

Prophylactic Treatment

- In patients with a frequent history of angioedema attacks (baseline attack rate of 3–4 per month), prophylactic use of C1 esterase inhibitors (Haegarda® and Cinryze®) was associated with a mean reduction of 2.1 to 3.5 attacks per month over 12 to 16 weeks compared to placebo (low to moderate quality evidence). 9
- With prophylactic use of lanadelumab compared to placebo in patients with a baseline rate of 3–4 attacks per month, the average angioedema attack rate was reduced by 1.5 to 1.7 attacks per month compared to baseline (moderate quality evidence). 9
- There is insufficient evidence that prophylactic use of HAE treatments affects quality of life, or long-term impacts on work, school, depression or anxiety.

Recommendations:

- Recommend implementation of prior authorization criteria for non-preferred products and preferred products exceeding 6 months in duration to ensure use for appropriate indications with periodic reassessment for necessity of ongoing therapy.
- Evaluate comparative costs in executive session.

Background:

Hereditary angioedema (HAE) is caused by a deficiency or lack of function of C1 inhibitor protein. 10,11 C1 inhibitor is an important regulator of the complement system and the kallikrein-kinin pathway which is involved in formation of bradykinin. 10 A lack of functional C1 inhibitor protein can result in an overproduction of bradykinin which is the primary cause of swelling in patients with hereditary angioedema. The deficiency is most commonly hereditary, though it may also be acquired via increased catabolism of C1 inhibitor protein, often as a result of malignancy or autoantibodies, thereby decreasing inhibitor function. 10 Diagnosis is based on laboratory analysis of complement C4 and C2 levels and C1 inhibitor antigenic levels. 10,11 There are 3 types of HAE. Type 1 and type 2 are clinically indistinguishable from each other and account for the majority of cases of C1 inhibitor deficiency. Approximately 75% of patients diagnosed with HAE have a family history of angioedema. 10

Symptoms of the disease include angioedema without urticaria which typically occur in early childhood or adolescence. Attacks of angioedema worsen gradually and resolve slowly over 24-72 hours. 10 Attacks may also be preceded by a prodromal phase with symptoms such as fatigue, non-urticarial rash, or other flu-like symptoms. Attacks most commonly involve the extremities and abdomen, but can be life-threatening if they involve the oropharynx or larynx. 10 Severity and frequency of attacks is highly variable between patients. 10 Frequency of attacks may be affected by hormone levels and often occur with onset of puberty, menopause, use of contraceptives, pregnancy, or other changes in estrogen levels. Precipitating factors for attacks are often unclear though both stress and trauma have been correlated with onset of acute attacks. 10,11

Current standard of care for treatment of acute attacks of angioedema include C1 inhibitors, ecallantide or icatibant (Table 1). Guidelines from the World Allergy Organization recommend on-demand therapy be considered for treatment of acute attacks of angioedema, and that any attack affecting the upper airway be treated (based on expert consensus opinion). 11 In general, early administration of medications is associated with better treatment response. 11 Recommended first-line prophylactic therapy includes a C1 inhibitor, though guidelines did not include evidence on lanadelumab-flyo which was recently FDA-approved. 11 No recommendations are made for a specific type of C1 inhibitor therapy. Administration of other anaphylactic therapy, such as epinephrine, antihistamines, and
Corticosteroids are only recommended if the cause of swelling and diagnosis of hereditary angioedema is unclear as these therapies do not improve symptoms of HAE attacks.\textsuperscript{11}

Efficacy in acute attacks has been documented in short-term clinical trials, though the long-term effects of treatment are less clear, particularly for newer therapies. A summary of pivotal clinical trials completed for each agent is available in Table 2 and warnings and precautions associated with each therapy are documented in Appendix 1. While plasma-derived products are screened extensively, there is still a risk for transmission of infectious disease (i.e., viruses) with plasma-derived C1 inhibitors.\textsuperscript{12-14} Other major safety concerns include hypersensitivity reactions and thrombotic events which have been reported with both plasma-derived and recombinant C1 inhibitors.\textsuperscript{12-15} Anaphylaxis is also a concern with ecallantide (reported in 3-4% of patients in clinical trials) and lanadelumab-flyo, and laryngeal HAE attacks have been documented after administration of icatibant and Berinert\textsuperscript{®} (C1 inhibitor).\textsuperscript{11,16-18}

Common outcomes evaluated in clinical trials include time to symptom resolution during an acute attack and reduction in number of attacks over time with prophylactic treatment. There is no established or validated measure to evaluate symptom improvement in patients with HAE attacks, and clinical trials have used a variety of scales to evaluate symptom severity. Examples of these scales include individual or composite visual analog scales evaluating overall symptom improvement or severity at multiple sites, the mean symptom complex score, and the treatment outcome score. The mean symptom complex score evaluates symptom severity at each location on a 0 to 3 point scale. Scores at each site are averaged to achieve a total score. The treatment outcomes scale evaluates change in symptom severity over time. Lower scores are associated with worse symptoms from baseline and higher scores are associated with improved symptoms (range -100 to 100). Scores of 100 are associated significant improvement, 50 with improvement, 0 with no change, -50 with worsening, and -100 with significant worsening.\textsuperscript{19} While the minimum clinically important difference for these scales has not been established, several thresholds have been proposed. Proposed minimum thresholds associated with clinically important differences are 20-30 points on the 0-100 visual analog scales, 30 points for treatment outcomes scale, and 0.3 point on the mean symptom complex score.\textsuperscript{7,19}

Currently, in the fee-for-service (FFS) population, approximately 77 patients have a diagnosis indicating defects in the complement system (D84.1). This number is likely an overestimate of patients as this diagnosis includes conditions with other types of complement deficiencies. Administration of acute treatment may occur in the acute treatment setting (during hospitalization or an emergency department visit), and pharmacy utilization of acute or prophylactic treatments is limited with paid claims for 2 FFS members in the past year.

A summary of relevant drug information is available in Appendix 1, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

\begin{table}
\centering
\caption{FDA-approved Indications and Dosing\textsuperscript{20}}
\begin{tabular}{|l|l|l|l|}
\hline
Drug Name (Brand Name) & Indication(s) & Strength/Route & Dose and Frequency \\
\hline
\textbf{Acute Treatment} & & & \\
C1 esterase inhibitor (Berinert\textsuperscript{®}) & Treatment of acute abdominal, facial, or laryngeal HAE attacks in adults and pediatric patients & 500 units IV kit & 20 units/kg as a single dose \\
Icatibant (Firazyr\textsuperscript{®}) & Treatment of acute HAE attacks & 10 mg/mL SC solution & 30 mg once; may repeat every 6 hours if response is inadequate; maximum dose per day: 90 mg \\
\hline
\end{tabular}
\end{table}
<table>
<thead>
<tr>
<th>Treatment of acute HAE attacks in patients 12 years and older</th>
<th>10 mg/mL SC solution</th>
<th>30 mg as a single dose; may repeat once within 24 hours if attack continues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of acute HAE attacks in adult and adolescent patients. Effectiveness has not been established in laryngeal attacks</td>
<td>2100 units IV reconstituted solution</td>
<td>50 units/kg as a single dose; maximum dose: 4,200 units</td>
</tr>
</tbody>
</table>

**Prophylactic Treatment**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Lanadelumab-flyo (Takhzyro™)</td>
<td>HAE prophylaxis in patients ≥12 years of age</td>
<td>300 mg/2mL SC solution</td>
</tr>
<tr>
<td>C1 esterase inhibitor (Cinryze®)</td>
<td>HAE prophylaxis in adults, adolescents, and pediatric patients ≥6 years of age</td>
<td>500 units IV reconstituted solution</td>
</tr>
<tr>
<td>C1 esterase inhibitor (Haegarda®)</td>
<td>HAE prophylaxis in adults and adolescents</td>
<td>2000 and 3000 units SC reconstituted solution</td>
</tr>
</tbody>
</table>

**Abbreviations:** HAE = hereditary angioedema, IV = intravenous; SC = subcutaneous

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Population</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Cicardi, et al.</td>
<td>FAST 1 and FAST 2</td>
<td>HAE type I or II presenting with an acute attack and ≥ 1 moderate to severe cutaneous symptom (defined as severity of &gt;30 points on a 0-100 scale)</td>
<td>Time to clinically significant symptomatic relief in the prespecified primary symptom (decrease of 20-30 points). In patients with multiple symptoms (cutaneous swelling, cutaneous pain, or abdominal pain), a single symptom was chosen for assessment.</td>
<td>FAST 1: 1. Median 2.5 hours (IQR 1.1 to 6.0) 2. Median 4.6 hours (IQR 1.8 to 10.2) Difference = 2.1 hours; p=0.14 FAST 2: 1. Median 2.0 hours (IQR 1.0 to 3.5) 2. Median 12.0 hours (IQR 3.5 to 25.4) Difference = 10 hours; p&lt;0.001</td>
</tr>
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<td>Lumry, et al.</td>
<td>FAST 3</td>
<td>HAE type I or II with acute angioedema (presenting within 6 hours of an acute attack) and with at least moderate abdominal or cutaneous symptoms or mild laryngeal symptoms</td>
<td>Subject-assessed median time to 50% reduction in mean symptom severity (3 symptoms for cutaneous attacks: swelling, skin pain, abdominal pain OR 5 symptoms for laryngeal attacks including difficulty swallowing and voice change)</td>
<td>Non-laryngeal attacks; n=88 1. 2.0 hours (95% CI 1.5 to 3.0) 2. 19.8 hours (6.1 to 26.3) Difference = 17.8 hours; p&lt;0.001 Laryngeal attacks; n=5 1. 2.5 hours (95% CI 1.3 to 3.0) 2. 3.2 hours (95% CI 1.0 to 5.4) Difference =0.7 hours; p value NR</td>
</tr>
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</table>

Table 2. Summary of Pivotal Studies Completed

<table>
<thead>
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<th>Primary Outcome</th>
<th>Results</th>
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| Author: Levy, et al. | Study Design: DB, PC, RCT, phase 3 | 1. Ecallantide 30 mg SC  
2. Placebo | Type I or II HAE ≥10 years of age  
N=96 | Change from baseline in MSCS score 4 hours after dosing (range 0-3)*  
1. -0.8 (SD 0.6)  
2. -0.4 (SD 0.8)  
Difference = 0.4 points; p=0.01 |
|---|---|---|---|---|
| Cicardi, et al. | Study Design: DB, PC, MC, RCT, phase 3 | 1. Ecallantide 30 mg SC  
2. Placebo | HAE ≥10 years of age with moderate to severe symptoms of angioedema  
N=72 | Change from baseline in TOS at 4 hours (range -100 to 100)¥  
1. 46.8 (SD 59.3)  
2. 21.3 (SD 69.0)  
Difference = 25.5 points; p = 0.004 |
| Riedl, et al. | Study Design: DB, PC, MC, RCT, phase 3 | 1. C1 inhibitor (Ruconest®) 50 IU/kg; maximum 4200 IU/treatment  
2. Placebo | HAE ≥ 13 years of age with acute angioedema (presenting within 5 hours of an acute attack) and with symptom severity of ≥ 50 points  
N=75 | Time to onset of sustained symptom relief evaluated as improved intensity and severity of symptoms (severity score of 5-7 corresponding with “a little” to “much” better on a 1-7 point scale from much worse to much better)  
1. Median 90 minutes (95% CI 61-150)  
2. Median 152 (95% CI 93 to --)  
Difference 62 minutes; p = 0.031 |
| Craig, et al. | Study Design: IMPACT1 MC, PG, PC, DB, RCT, phase 2/3 | 1. C1 inhibitor (Berinert®) 10 units/kg  
2. C1 inhibitor (Berinert®) 20 units/kg  
3. Placebo | HAE type I and II ≥6 years of age with moderate to severe abdominal or facial angioedema (presenting within 5 hours of an acute attack)  
N=125 | Time to onset of symptom relief  
Reported as mean (SD) and median (range). Time was calculated at 24 hours if any rescue, analgesic, or antiemetic therapy was given.  
1. Mean 7.47 (10.51); median 1.17 (0.17 to 24)  
2. Mean 3.89 (8.20); median 0.50 (0.17 to 24)  
3. Mean 10.27 (11.48); median 1.50 (0.2 to 24)  
1 vs. 3: median difference 0.33 hours; p=0.2731  
2 vs. 3: median difference 1 hour; p=0.0048  
1 vs. 2: median difference 0.67 hours; p=0.0025 |
| Zuraw, et al. | Study Design: DB, PC, RCT | 1. C1 inhibitor (Cinryze®) 1000 units  
2. Placebo  
A second dose was given if symptoms had not improved at 60 minutes | HAE ≥ 6 years with moderate-severe abdominal, face or genital symptoms presenting within 4 hours of attack onset  
N=207 eligible; 71 had an attack and were enrolled | Time to unequivocal symptom relief at the defining site (site with the most severe symptoms at baseline)  
1. 2 hours  
2. >4 hours  
RR 2.41, 95% CI 1.17 to 4.95; p=0.02 |
### Prophylactic Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Treatments</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longhurst, et al.</td>
<td>COMPACT DB, MC, PC, RCT, cross-over, phase 3</td>
<td>N=90</td>
<td>1. C1 inhibitor (Haegarda®) SC 40 IU/kg twice weekly 2. C1 inhibitor (Haegarda®) SC 60 IU/kg twice weekly 3. Placebo Randomized 1:1:1:1 based on dose and treatment sequence</td>
<td>Type I or II HAE age ≥ 12 years with ≥ 4 attacks over 2 months prior to screening and ≥ 2 attacks during the 8 week run-in period</td>
<td>Number of angioedema attacks over 16 weeks during treatment or placebo phases</td>
</tr>
<tr>
<td>Zuraw, et al.</td>
<td>DB, PC, cross-over, RCT</td>
<td>N=24</td>
<td>1. C1 inhibitor (Cinryze®) 1000 units every 3-4 days 2. Placebo</td>
<td>HAE ≥ 6 years enrolled in acute treatment trial with history of ≥ 2 attacks per month</td>
<td>Average number of angioedema attacks over 12 weeks</td>
</tr>
<tr>
<td>Banerji, et al.</td>
<td>HELP3 DB, PC, PG, MC, RCT, phase 3</td>
<td>N=125</td>
<td>1. Lanadelumab 150 mg SC every 4 weeks 2. Lanadelumab 300 mg SC every 4 weeks 3. Lanadelumab 300 mg SC every 2 weeks 4. Placebo</td>
<td>HAE type I or II age ≥ 12 years with ≥ 1 attack during the 4-week run-in period</td>
<td>Average monthly number of investigator-confirmed Angioedema attacks over 26 weeks</td>
</tr>
</tbody>
</table>

* MSCS is a composite score evaluating symptom severity at various sites from mild to severe on a 1-3 scale. Decreases in score represent improvement in symptoms.  
¥ TOS evaluates symptom severity on a 0-100 scale with larger scores representing more significant improvement

**Abbreviations:** CI = confidence interval; DB = double-blind; HAE = hereditary angioedema; IQR = interquartile range; MC = multicenter; MD = mean difference; MSCS = mean symptom complex score; NS = non-significant; PC = placebo-controlled; PG = parallel group; PO = oral; RCT = randomized controlled trial; SC = subcutaneous; SD = standard deviation; TOS = treatment outcome score

**Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in Appendix 2, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

Author: Servid

January 2019
The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
In 2018, the Institute for Clinical and Economic Review evaluated prophylactic therapies for type 1 or 2 HAE.⁹ The review included products approved by the Food and Drug Administration (FDA) for prophylaxis including C1 inhibitors (Cinryze® and Haegarda®) and lanadelumab. Evidence included 3 fair-quality phase 3 trials as well as data from open-label, single-arm, or extension studies. Baseline attack rate was typically 3-4 attacks per month for included trials. Evidence supported a mean reduction in HAE attacks per month compared to placebo.⁹ The average reduction in attacks per month compared to placebo was 2.1 for Cinryze®, 2.4 to 3.5 for Haegarda® (40 and 60 IU/kg, respectively), and 1.5 to 1.7 attacks for lanadelumab.⁹ Attack severity (assessed on a 1-3 point scale) was also statistically reduced with use of Cinryze® compared to placebo (1.9 vs. 1.2, mean difference 0.7) and with Haegarda® (1.6-1.8 vs. 1.9-2.0 points, mean difference 0.2-0.3).⁹ More patients treated with lanadelumab (39-44%) were attack free over 6.5 months compared to placebo (2%).⁹ There was no direct comparative data between treatments, no data on mortality, and only limited, inconsistent data on patient reported outcomes such as quality of life, or long-term impacts on work, school, depression or anxiety.⁹ Use in pediatric patients was limited, but overall outcomes were similar in patients less than 18 years of age.⁹ Serious adverse events were rare, and the most common adverse events reported in clinical trials included mild infections, headache, hypersensitivity, dizziness, and injection site reactions with subcutaneous administration.⁹ Only one long-term safety study was identified evaluating use of Cinryze® for up to 2.6 years.⁹ Over this period 5 thrombotic events were observed in patients with underlying risk factors.⁹ Two patients died of causes considered to be unrelated to Cinryze®.⁹ Overall the population evaluating long-term safety was small (n=146 participants), and information on long-term safety of all prophylactic therapies remains limited.⁹

A series of 3 CADTH rapid response reports evaluated evidence of treatment and prophylactic therapies for HAE. For prophylactic treatment, an assessment of 8 studies evaluating efficacy and safety of C1 esterase inhibitors was included.²³ Study types included 1 randomized controlled trial and data from 7 long-term prospective and retrospective observational studies.²³ Authors concluded C1 esterase inhibitors were likely effective for the prevention of HAE attacks, but there was no high-quality data available.²³ Data was limited by small population sizes, unclear methods for randomization and blinding, presence of potential confounding factors (such as androgen therapy), lack of comparator data for non-randomized studies, and use of self-reported outcomes which have a higher risk of recall bias in retrospective studies.²³ Due to these significant limitations, discussion of evidence will primarily focus on significant safety-related signals observed in the observational studies, and these outcomes should be interpreted with caution. Adverse events reported in observational studies included gastrointestinal events, major depression, musculoskeletal chest pain, lightheadedness, fever, rash, infusion-site reactions, headache.²³ Serious adverse events included thrombotic events which were reported in 3 studies.²³ The exact incidence of these events is unknown.

Two CADTH drug reviews evaluated evidence of icatibant for treatment of acute HAE attacks. No high-quality evidence was found in Type 3 HAE; evidence included only one poor quality, single-arm cohort study, 3 case series and 3 case reports.²⁴ Evidence for icatibant in patients with Type 1 or 2 HAE included 2 placebo-controlled RCTs (FAST 1 and 3) and associated open-label extension studies. On average, patients experienced more cutaneous attacks (6.7 to 9.9) compared to abdominal (3.8 to 6.8) or laryngeal attacks (0.7 to 2.8) in the 6 months before enrollment.⁶ Both trials were limited by small population sizes, potential unblinding due to injection-site reactions, and use of patient reported outcomes which may be subject to higher reporting bias.⁶ Data on patients with laryngeal attacks is limited and patients with coronary artery disease were excluded from clinical trials as animal models showed bradykinin 2 inhibition may decrease coronary blood flow.⁶ Symptom improvement was evaluated using visual analogue scales in each trial, reported as a composite of 3 symptoms (skin swelling, skin pain, and abdominal pain) in FAST 3 and reported as individual symptoms in FAST 1.⁶ Use of the composite score to evaluate symptoms has not been validated and the minimum clinically important difference has not been established. In one trial (FAST 3), median time to 50% reduction in symptoms

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January 2019
improved with icatibant compared to placebo (2.0 vs. 19.8 hours; p<0.001), but time to symptom relief (reduction of 20-30 points on a 100 point scale) was not statistically significant in the second trial (FAST 1; 2.5 vs. 4.6 hours; p=0.142). Of the patients enrolled in these clinical trials 4-11% required a second injection of icatibant to control symptoms. Neither trial included data on quality of life, daily activities, physical or mental functioning.

After review, 4 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

**Guidelines:**

**High Quality Guidelines:**
No high-quality guidelines met inclusion criteria.

**Additional Guidelines for Clinical Context:**
In 2017, the World Allergy Organization in conjunction with the European Academy of Allergy and Clinical Immunology published an updated guideline for the management of HAE. The guideline had the following limitation: more than half of members, including first authors, reported competing interests with industry, and details on the guideline development process including literature searches and process to address conflicts of interest were not available. Due to the limited evidence available for the treatment of HAE the majority of guideline recommendations are based on trials with severe methodological limitations or adapted from consensus expert opinion. Guideline recommendations based on GRADE A evidence (randomized, double-blind clinical trial of high quality) or GRADE B evidence (randomized, clinical trials of lesser quality or limited sample size) are discussed here. For each recommendation, the amount of agreement among guideline panel members was also documented.

- Acute HAE attacks should be treated with C1 inhibitors, ecallantide or icatibant (GRADE A, strong recommendation, 90% agreement)
- Attacks should be treated as early as possible (GRADE B, strong recommendation, 100% agreement)
- C1-inhibitors are recommended as first-line long-term prophylactic treatment in patients with HAE (GRADE A, strong recommendation, 50-75% agreement)

After review, 4 guidelines were excluded due to poor quality.

**References:**


Author: Servid January 2019


## Appendix 1: Specific Drug Information

### Table A1. Clinical Pharmacology and Pharmacokinetics

<table>
<thead>
<tr>
<th>Drug Name/Route</th>
<th>Mechanism of Action</th>
<th>Absorption</th>
<th>Metabolism/Excretion</th>
<th>Pharmacokinetics (mean)</th>
</tr>
</thead>
</table>
| C1 esterase inhibitor (Berinert®) intravenous | Serine protease inhibitor which inhibits several factors in the complement and coagulation cascades including complement component 1, coagulation factor XIIa, kallikrein, and coagulation factor Xla. Inhibition of these systems is thought to inhibit production of bradykinin. | NA | NA; inhibition of serine proteases results in inactivation and consumption of the C1 esterase inhibitor. | Adults  
  - Half-life: 18.4 ± 3.5 hours  
  - AUC: 12.8 ± 6.7 hr*IU/mL  
  - Vd: 35.4 ± 10.5 mL/kg |
| C1 esterase inhibitor (Cinryze®) intravenous | Serine protease inhibitor | NA | NA (see above) | Single dose of 1,000 units in adults  
  - Half-life: 56 ± 36 hours  
  - Cmax: 0.68 ± 0.08 U/mL  
  - AUC: 74.5 ± 30.3 U*hr/mL |
| C1 esterase inhibitor (Haegarda®) subcutaneous | Serine protease inhibitor | Percent bioavailability: 42.7% | NA (see above) | Twice weekly dosing  
  - Half-life: median 69 hours  
  - Cmax: 60.7%  
  - Vd: 0.05 L/kg |
| C1 esterase inhibitor, recombinant (Ruconest®) intravenous | Serine protease inhibitor | NA | NA (see above) | Single dose of 100 U/kg  
  - Half-life: 2.7 ± 0.3 hours  
  - Cmax: 2.3 ± 0.2 U/mL  
  - AUC: 10.6 ± 2.5 U*hr/mL  
  - Vd: 2.4 ± 0.5 L |
| Icatibant (Firazyr®) intravenous and subcutaneous | Bradykinin B2 receptor antagonist | Bioavailability: 97% | Metabolized by proteolytic enzymes with <10% excreted unchanged in the urine | Single 30 mg subcutaneous dose  
  - Half-life: 1.4 ± 0.4 hours  
  - Cmax: 974 ± 280 ng/mL  
  - AUC: 2165 ± 568 ng*hr/mL  
  - Vd: 29.0 ± 8.7 L |
| Ecallantide (Kalbitor®) subcutaneous | Selective, reversible inhibitor of plasma kallikrein | NA | Excreted in the urine | Single 30 mg subcutaneous dose  
  - Half-life: 2.0 ± 0.5 hours  
  - Cmax: 586 ± 106 ng/mL  
  - AUC: 3017 ± 402 ng*hr/mL  
  - Vd: 26.4 ± 7.8 L |
| Lanadelumab (Takhzyro™) subcutaneous | Plasma kallikrein inhibitor | NA | NA | 300 mg every 2 weeks  
  - Half-life: 15.0 ± 2.48 days  
  - Cmax: 34.4 ± 11.2 µg/mL  
  - AUC: 400 ± 138 µg*day/mL  
  - Vd: 16.6 ± 4.79 L |

Abbreviations: AUC = area under the curve; CI = confidence interval; Cmax = maximum plasma concentration; hrs = hours; NA = not applicable; Vd = volume of distribution

Author: Servid  
January 2019
**Use in Specific Populations:**

**Pregnancy:**
- C1 esterase inhibitor, human: There are no data available in humans or and animal studies have not been conducted.
- C1 esterase inhibitor, recombinant: There are no adequate or well-controlled trials in pregnancy. Studies in rats and rabbits could not exclude an effect on embryofetal development.
- Icatibant: There are no adequate or well-controlled trials in pregnancy. Animal studies document delayed parturition, fetal death, pre-implantation loss, premature birth, and abortion in rats or rabbits. Only use icatibant if potential benefits outweigh risks.
- Ecallantide: There are no adequate or well-controlled trials in pregnancy. Developmental toxicity has been documented in rats but not rabbits. Ecallantide should only be used during pregnancy if clearly needed.
- Lanadelumab: There are no data available on use in pregnant women. Animal data indicate no evidence of harm to the developing fetus.

**Lactation:**
- C1 esterase inhibitor, human: No information available.
- C1 esterase inhibitor, recombinant: No information available.
- Icatibant: No information available in humans. Icatibant is excreted in the milk of rats and caution is advised for this population.
- Ecallantide: No information available.
- Lanadelumab: There are no data available in presence of lanadelumab-flyo in human milk. Animal data indicate lanadelumab-flyo was detected in the milk at approximately 0.2% of the maternal plasma concentration.

**Pediatric:**
- C1 esterase inhibitor, human: Cinryze® has been studies in 12 pediatric patients, Haegarda® has been evaluated in 6 patients, and Berinert® has been evaluated in 20 pediatric patients. Results were overall consistent with an adult population.
- C1 esterase inhibitor, recombinant: Recombinant C1 esterase inhibitor has been evaluated in 17 adolescents 13 to 17 years of age. Eight (42%) of patients experienced adverse events (primarily abdominal pain, headache, and oropharyngeal pain), and none experienced severe adverse events.
- Icatibant: Safety and effectiveness in patients less than 18 years of age has not been established. Animal data indicate administration in juvenile rats delayed sexual maturation of male reproductive tissues, impaired fertility, and decreased reproductive performance. No effects were observed in females.
- Ecallantide: Ecallantide has been evaluated in patients 12-17 years of age. Data on efficacy in patients 12 to 15 years of age is extrapolated from an older population and pharmacokinetic analyses. Safety profile for adolescents is similar to the adult population. Safety and effectiveness in patients less than 12 years of age has not been established.
- Lanadelumab: Lanadelumab-flyo has been evaluated in 23 patients, 12-17 years of age. Results of the subgroup analysis by age (in 10 participants enrolled in a randomized trial) were consistent with the overall population. Safety and effectiveness in patients less than 12 years of age has not been established.

**Geriatric:**
- C1 esterase inhibitor, human: Patients over 65 years of age were not included in clinical trials. In general, conservative dosing is recommended to account for greater frequency of decreased hepatic, renal, or cardiac function.
- C1 esterase inhibitor, recombinant: No information available
- Icatibant: No information available in patients ≥ 65 years of age. Elderly patients are likely to have increased systemic exposure, but dose adjustment is not recommended.
- Ecallantide: No information available
- Lanadelumab: Lanadelumab-flyo has been evaluated in 5 patients ≥ 65 years of age. Overall results were consistent with other populations.

**Drug Safety:**

**Boxed Warnings:**
- Due to risk of anaphylaxis with ecallantide, it should be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema.\(^17\)

**Risk Evaluation Mitigation Strategy Programs:** None

**Contraindications:**
- Risk of hypersensitivity reactions with C1 esterase inhibitors and ecallantide. Do not use in patients with a history of hypersensitivity, including anaphylaxis, to these medications or their excipients.\(^17\)
- Do not use recombinant C1 esterase inhibitor (Ruconest®) in patients with known or suspected allergy to rabbits or rabbit-derived products.\(^15\)

**Table A2. Summary of Warnings and Precautions.**

<table>
<thead>
<tr>
<th>Warning/Precaution</th>
<th>C1 esterase inhibitor, human</th>
<th>C1 esterase inhibitor, recombinant</th>
<th>Icatibant</th>
<th>Ecallantide</th>
<th>Lanadelumab-flyo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypersensitivity reactions</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of infection transmission</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laryngeal HAE attacks</td>
<td>X (Berinert® only)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
**Appendix 2: Medline Search Strategy**

Ovid MEDLINE(R) 1946 to October Week 3 2018

<table>
<thead>
<tr>
<th>Step</th>
<th>Search String</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>exp Angioedemas, Hereditary/</td>
<td>936</td>
</tr>
<tr>
<td>2</td>
<td>exp complement c1 inactivator proteins/ or exp complement c1 inhibitor protein/</td>
<td>2579</td>
</tr>
<tr>
<td>3</td>
<td>exp Bradykinin Receptor Antagonists/</td>
<td>1289</td>
</tr>
<tr>
<td>4</td>
<td>ecallantide.mp.</td>
<td>138</td>
</tr>
<tr>
<td>5</td>
<td>icatibant.mp.</td>
<td>1262</td>
</tr>
<tr>
<td>6</td>
<td>lanadelumab.mp.</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>2 or 3 or 4 or 5 or 6</td>
<td>4420</td>
</tr>
<tr>
<td>8</td>
<td>1 and 7</td>
<td>653</td>
</tr>
<tr>
<td>9</td>
<td>limit 8 to (english language and humans)</td>
<td>607</td>
</tr>
<tr>
<td>10</td>
<td>limit 9 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)</td>
<td>135</td>
</tr>
</tbody>
</table>

**Appendix 3: Key Inclusion Criteria**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Patients with hereditary angioedema</td>
</tr>
<tr>
<td>Intervention</td>
<td>Pharmacotherapy listed in Appendix 1</td>
</tr>
<tr>
<td>Comparator</td>
<td>Pharmacotherapy listed in Appendix 1 or placebo</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Symptom improvement including acute or recurrent attacks of angioedema</td>
</tr>
<tr>
<td></td>
<td>Functional improvement</td>
</tr>
<tr>
<td></td>
<td>Quality of life</td>
</tr>
<tr>
<td></td>
<td>Morbidity</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
</tr>
<tr>
<td>Setting</td>
<td>Outpatient</td>
</tr>
</tbody>
</table>
### Appendix 4: Proposed Prior Authorization Criteria

#### Hereditary Angioedema

**Goal(s):**
- To promote safe and effective use of hereditary angioedema treatments.
- To promote use of preferred hereditary angioedema treatments.

**Length of Authorization:**
Up to 12 months

**Requires PA:**
- Preferred products exceeding 6 months of prophylactic treatment
- Non-preferred drugs

**Covered Alternatives:**
- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

<table>
<thead>
<tr>
<th>Approval Criteria</th>
<th>Record ICD10 code.</th>
<th>Yes: Go to Renewal Criteria</th>
<th>No: Go to #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What diagnosis is being treated?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Is this a request for continuation of prophylactic therapy previously approved through fee-for-service?</td>
<td>Yes: Go to Renewal Criteria</td>
<td>No: Go to #3</td>
<td></td>
</tr>
<tr>
<td>3. Is this an FDA approved indication?</td>
<td>Yes: Go to #4</td>
<td>No: Pass to RPh. Deny; medical appropriateness</td>
<td></td>
</tr>
<tr>
<td>Note: medications may be indicated for prophylaxis in patients with hereditary angioedema or treatment of acute hereditary angioedema attacks.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Is the diagnosis funded by OHP?</td>
<td>Yes: Go to #5</td>
<td>No: Pass to RPh. Deny; not funded by the OHP.</td>
<td></td>
</tr>
</tbody>
</table>
## Approval Criteria

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5.</td>
<td>Will the prescriber consider a change to a preferred product?</td>
<td>Yes: Inform prescriber of covered alternatives in class.</td>
</tr>
</tbody>
</table>
|   | Message:  
- Preferred products do not require a PA.  
- Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee. | No: Go to #6 |
| 6. | Is the request for treatment of a current, acute hereditary angioedema attack? | Yes: Approve for length of treatment or 7 days, whichever is less |
|   | No: Go to #7 |
| 7. | Is the request for prophylactic use in a patient with hereditary angioedema in a patient with a history of attacks? | Yes: Go to #8 |
|   | Document baseline number of recent attacks |
|   | No: Pass to RPh. Deny; medical appropriateness. |
| 8. | Have potential triggering factors for angioedema including medications such as estrogens, progestins, or angiotensin converting enzyme inhibitors been assessed and discontinued when appropriate? | Yes: Approve for up to 6 months or length of therapy, whichever is less. |
|   | No: Pass to RPh. Deny; medical appropriateness. |

## Renewal Criteria

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Since initiation of therapy, has the number of hereditary angioedema attacks decreased?</td>
<td>Yes: Go to #2</td>
</tr>
<tr>
<td></td>
<td>No: Pass to RPh. Deny; medical appropriateness.</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Has the patient been attack free for at least 6 months?</td>
<td>Yes: Go to #3</td>
</tr>
<tr>
<td></td>
<td>No: Approve for up to 12 months.</td>
<td></td>
</tr>
</tbody>
</table>
## Renewal Criteria

| 3. Is there documentation from the prescriber that they have evaluated continued necessity of long-term prophylactic treatment at the current dose? | **Yes:** Approve for up to 6 months. | **No:** Pass to RPh. Deny; medical appropriateness. |

*P&T/DUR Review: 3/19 (SS)*  
*Implementation: TBD*