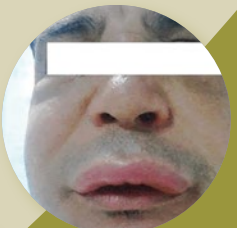
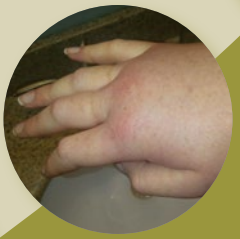
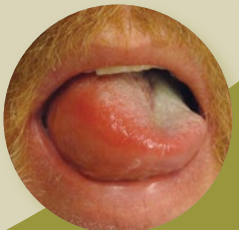
Meeting Managed Care's Challenges
in Managing Hereditary Angioedema (HAE)

# HEREDITARY ANGIOEDEMA MANAGED CARE TOOLKIT







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*This toolkit is supported by an educational grant from CSL Behring*

# HAE MANAGED CARE TOOLKIT

## ACKNOWLEDGMENTS

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# HEREDITARY ANGIOEDEMA
## Disease Burden Overview[1-8]

There are an estimated
**4,000 TO 10,000 HAE PATIENTS**
in the United States.

Hereditary angioedema (HAE) is a **rare and potentially life-threatening** genetic condition that occurs in about **ONE in 50,000 PEOPLE**.

**5 OUT OF 6 INDIVIDUALS** who asphyxiated during an acute HAE attack had never experienced upper airway impairment during previous attacks.

On average, untreated individuals have an attack **EVERY ONE TO TWO WEEKS**, with most episodes **LASTING AROUND THREE TO FOUR DAYS**.

Before therapy became available, the **MORTALITY RATE CAUSED BY AIRWAY SWELLING** was reported to be **AS HIGH AS 40%**.

**50% OF HAE PATIENTS** experience at least **ONE LARYNGEAL ATTACK** in their lifetime.

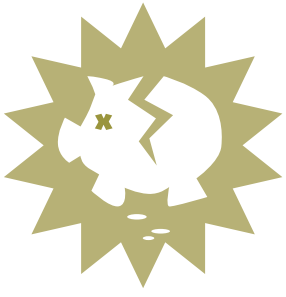
- HAE is characterized by recurrent attacks of severe swelling in the limbs, face, intestinal tract, and airway.
- HAE attacks are painful, unpredictable, and debilitating and often require emergency medical attention.
- Episodes involving the intestinal tract cause severe abdominal pain, nausea, vomiting and can be mistaken for appendicitis or intestinal obstruction resulting in unnecessary surgery.
- Swelling of the airway is particularly dangerous, as it can cause death by asphyxiation.

**87%** OF PATIENTS report experiencing a prodromal symptom (rash, fatigue, muscle or joint ache, stomach ache or nausea, abdominal pain, numbness or tingling, and headache).

**QUALITY OF LIFE**

Patients experience substantial impairment physically and emotionally between and during attacks.

- Diagnosis is often delayed for years, with patients receiving ineffective treatment and unnecessary medical procedures prior to correct diagnosis.
- **38%** have clinically meaningful **ANXIETY** and **14%** suffer **DEPRESSION.**



- Patients report **HIGH RATES OF MISSED WORK, LOST PRODUCTIVITY, and LOST INCOME**, culminating in indirect costs totaling **$16,000 ANNUALLY** for the average patient.
- One claims analysis found 12-month HAE total direct cost-of-care of **$409,925** with HAE medication-costs totaling **$395,507 (97%)**.

# Diagnosis and Coding

## Types of Angioedema

Hereditary angioedema (HAE) has to be distinguished from other types of angioedema. All patients with recurrent angioedema without urticaria should be evaluated to exclude a diagnosis of HAE.

| Types of Angioendema[9-13] | | | | |
|---|---|---|---|---|
| **Syndrome** | **Pathophysiology** | **Affected Groups** | **Estimated Prevalence** | **Comments** |
| **Idiopathic** | Unknown – often associated with urticaria | Unknown | Unknown | Typically treated with steroids and antihistamines. |
| **IgE-mediated** | Allergic reaction to foods, drugs, insect stings , latex | All | Unknown | Urticaria, Responds to steroids, antihistamines, and epinephrine. |
| **Non-IgE; non-bradykinin mediated** | Direct MAST cell activation by NSAIDs, opiates radiocontrast media | All | Unknown | Responds to antihistamines. |
| **Hereditary Type I (HAE Type I)** | C1 esterase inhibitor (C1-INH) deficiency | All | 1:50,000 | No urticaria, No response to steroids, antihistamines, or epinephrine, 85% of HAE C1-INH deficiency cases. |
| **Hereditary Type II (HAE Type II)** | Functional abnormality of C1-INH | All | 1:250,000 | No urticaria, No response to steroids, antihistamines, or epinephrine, 15% of HAE C1-INH deficiency cases. |
| **Hereditary Type III (HAE Type III, Normal C1-INH)** | Unknown (FXII, PLG, ANGPT1 mutations known) | All, but more women | 1:250,000 to 1:500,000 | No urticaria, No response to steroids, antihistamines, or epinephrine, Increased estrogen state (pregnancy, hormone replacement therapy, oral contraceptive use) is often required for attacks to occur |
| **Acquired Angioedema** | Excessive consumption of C1 –INH leading to deficiency; Secondary to underlying lymphoproliferative disorder or autoantibody to C1-INH | Older patients | 1:250,000 | Treatment of underlying disease may be helpful |
| **ACE-Inhibitor Induced** | Inhibition of bradykinin catabolism | All, increased in African Americans | 1:250 | Discontinue ACE-inhibitor |

## HAE Diagnosis

The three types of HAE can be differentiated from each other, and other forms of angioedema, by complement and antibody testing. The laboratory tests should be repeated one to three months after initial testing to confirm results. Blood samples should be handled with care to avoid decay of functional C1-INH, which may produce equivocal result.

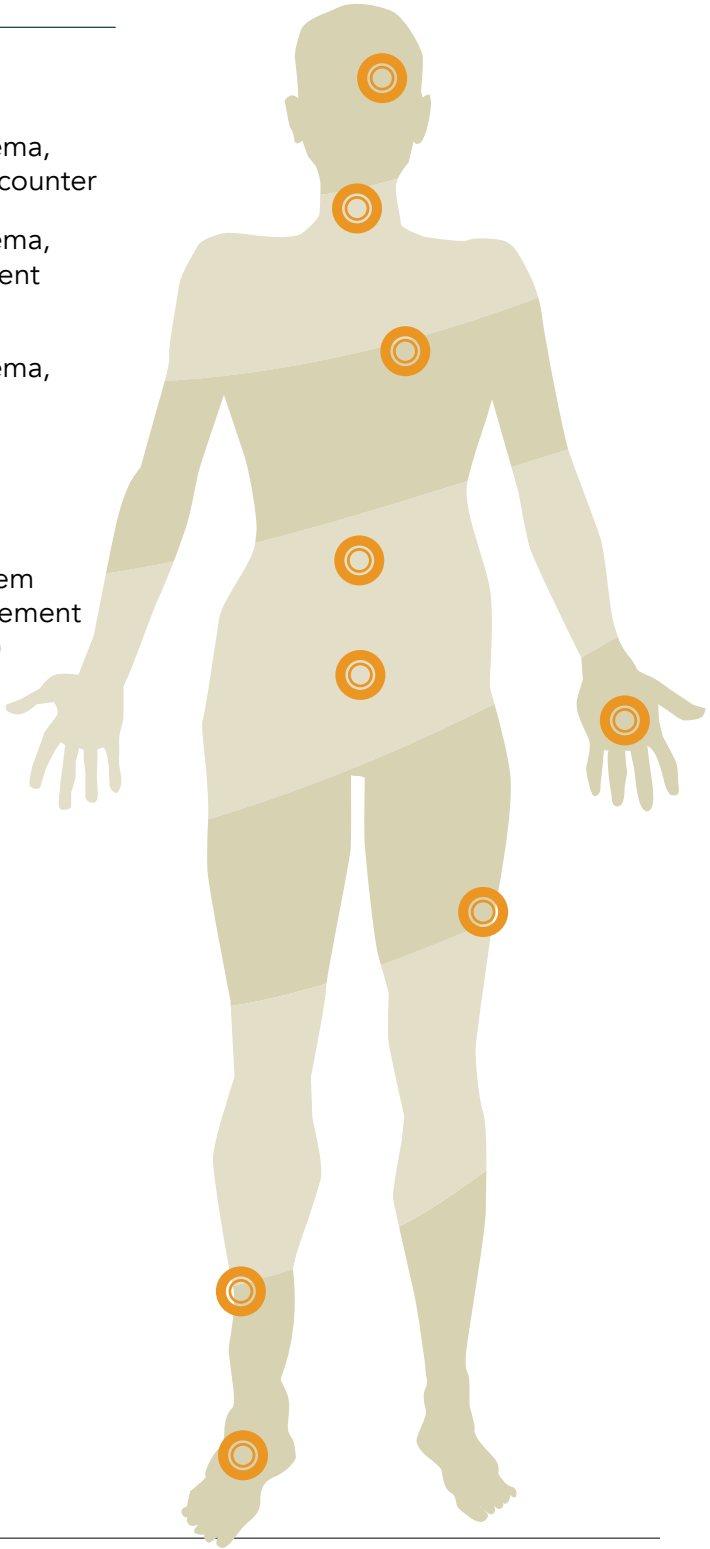
**Distinguishing HAE from Other Types of Angioedema[9-15]**

| | C1-INH Quantitative | C1-INH Function | C4 | C2 | C1q | Auto-antibody |
|---|---|---|---|---|---|---|
| **HAE Type I** | ↓ | ↓ (< 50%) | ↓ | ↓ | NL | Absent |
| **HAE Type II** | NL or ↑ | ↓ (< 50%) | ↓ | ↓ | NL | Absent |
| **HAE Type III** | NL | NL | NL | NL | NL | Absent |
| **Acquired Angioedema** | NL or ↓ | ↓ | ↓ | ↓ | ↓ | Present |
| **ACE Induced Angioedema** | NL | NL | NL | NL | NL | Absent |
| **Idiopathic** | NL | NL | NL | NL | NL | Absent |

C = complement
NL = normal

# ICD-10 Diagnostic Codes for Angioedema[16]

| ICD-10-CM | Description |
|---|---|
| **ALLERGIC ANGIOEDEMA** | |
| **T78.3XXA** | Angioneurotic edema (angioedema, allergic with urticaria) – initial encounter |
| **T78.3XXD** | Angioneurotic edema (angioedema, allergic with urticaria) – subsequent encounter |
| **T78.3XXS** | Angioneurotic edema (angioedema, allergic with urticaria) – sequela |
| **HEREDITARY ANGIOEDEMA** | |
| **D84.1** | Defects in the complement system (used for other defects in complement besides hereditary angioedema) |
| **ACQUIRED ANGIOEDEMA** | |
| **D47.9** | Acquired angioedema due to lymphoproliferative disorder |



# Clinical Management[14,17,18]

The following is a high-level overview of the treatment of HAE.

## ACUTE MANAGEMENT

- Most HAE attacks can be treated at home.
- Patients should have a management plan in place with ready access to their health care provider during an acute attack and know when to seek care at a medical facility.
- All patients with HAE due to C1-INH deficiency should have access to at least two standard doses of an FDA approved medication for on-demand treatment of acute HAE attacks.
- FDA approved options include plasma-derived C1-INH, recombinant C1-INH, icatibant and ecallantide.
- In cases in which more than one on-demand medication is prescribed, the justification for use of more than a single medication should be both explicit and understood by the patient.
- There should be ongoing monitoring of frequency and efficacy of on-demand treatments by the provider with regular follow-up visits.
- Patients who experience symptoms of laryngeal, tongue, or throat swelling should seek emergency medical care as soon as possible, even after initial self-treatment.

## PROPHYLACTIC TREATMENT

- In addition to treating acute attacks of angioedema, patients with HAE may require prophylactic treatment.
- The goal of prophylactic treatment is either to reduce the likelihood of swelling in a patient undergoing a stressor or procedure likely to precipitate an attack (short-term prophylaxis) or to decrease the number and severity of angioedema attacks (long-term prophylaxis).

### Short-Term Prophylaxis

- Trauma and stress are well-known triggers of HAE attacks.
- Dental surgery in particular is associated with swelling of the oral cavity that can progress and cause airway obstruction.
- Short-term prophylaxis may be indicated before medical, surgical, or dental procedures, however, relatively little is known about the risk of swelling after such procedures. The extent of the local trauma may influence the decision.

# Clinical Management (CONTINUED)

- C1-INH given for short-term prophylaxis should be administered 1 to 12 hours before the stressor.
- Anabolic androgens used for short-term prophylaxis should be started 7 to 10 days before the stressor.
- Effective on-demand treatment must be available during and after the procedure whether the patient is given short-term prophylaxis or not.

## Long-Term Prophylaxis

- Decisions regarding which patients should be considered for long-term prophylaxis should take into account attack frequency, attack severity, comorbid conditions, access to emergent treatment, and patient experience and preference.
- Because disease severity may change over time, the need to start or continue long-term prophylaxis should be periodically reviewed and discussed with the patient.
- The optimal dose of prophylactic medication is not predicted by the C4 or C1-INH levels but must be determined clinically.
- Prophylactic medications should be titrated to the lowest effective dose that controls disease activity and maintains normal quality-of-life.
- FDA approved options include anabolic androgens, plasma-derived C1-INH, and lanadelumab.
- The use of anabolic androgens for long-term prophylaxis in patients under the age of 16 years, in pregnant or breastfeeding women, and in those with intolerable adverse effects should be avoided.
- The U.S. Hereditary Angioedema Association Medical Advisory Board guidelines recommend that patients should not be required to fail androgen therapy as a prerequisite to receiving prophylactic C1-INH.
- Patients on a prophylactic treatment regimen must also have access to effective on-demand treatment for acute attacks.
- Efficacy and safety of long-term prophylactic treatment should be monitored.
- Although trials of long-term prophylaxis with C1-INH and lanadelumab showed benefits in reducing the frequency of HAE attacks with few harms, the evidence base is limited to small trials of short duration, leaving questions about the durability of treatment response and long-term safety. There are fewer concerns about the safety profile of C1-INH products given the longer experience with their use in both acute treatment and prophylaxis.

# Clinical Efficacy of Prophylaxis

There are no head-to-head comparative trials for prophylaxis so superiority of any one agent cannot be determined. The table below presents data from individual trials and a retrospective study of danazol use.

**Clinical Efficacy of Medications for Long-Term Prophylaxis of HAE 1/2 Compared with Placebo[19-25]**

| | Mean HAE Attacks per Month (prophylaxis vs placebo) | Percentage Reduction in Total HAE Attacks Compared to Placebo | Percentage attack Free (prophylaxis vs placebo) | Other Outcomes Compared to Placebo |
|---|---|---|---|---|
| Intravenous C1-INH (Cinryze® 1,000 IU) | 2.1 vs 4.2*<br>0.19 ^ | 50.5%<br>97% ^ | 18.3%<br>34.9% ^ | • Significantly reduced severity and duration of HAE attacks and use of rescue medication Improved health related QOL (SF-36)<br>• Sustained efficacy out to 2.6 years |
| Subcutaneous C1-INH (Haegarda® 60 IU/kg**) | 0.5 vs 4.0*** | 95% | 40% vs 9% | • Rescue drug use per month 0.32 vs 3.89<br>• Decreased HAE attack days per month and attack severity<br>• Clinically-meaningful improvement on work presenteeism and productivity |
| Lanadelumab (Takhyzro®) 300 mg q 2 weeks | 0.3 vs 2.0*** | 87% | 44% vs 2%<br>77%# | • Improved scores on the angioedema quality of life questionnaire |
| Lanadelumab 300 mg q 4 weeks | 0.5 vs 2.0*** | 73% | 31% vs 2%<br>45%# | |
| Danazol | N/A | 16.2%## | 45.8% (attack free or one attack or less per year) | N/A |

Based on data from individual trials and a retrospective review for danazol

* Estimated from result presented over 12 weeks
^ Open label study out to 2.6 years
** 60 IU/kg is FDA approved dose, 40 IU/kg also studied but lower rates of success
*** p value < 0.001
# Post-hoc analysis, at 3 months
## Compared to patient's own baseline without medication

# Sample Health Plan Care Coordination and Medical Management Hierarchy[17]

## EMERGENCY ROOM PHYSICIAN/ PRIMARY CARE PROVIDER

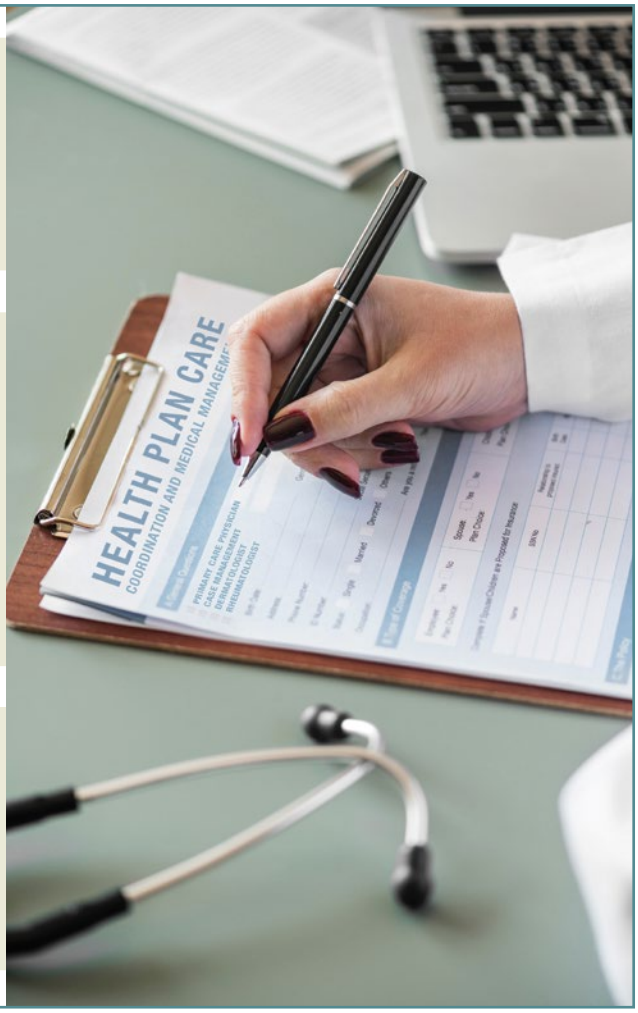
- Initial assessment
- Referral to specialist

## SPECIALIST (IMMUNOLOGIST, ALLERGIST)

- Diagnosis
- Management of therapy
- Referral to other specialists
- Communication with primary care provider

## CASE MANAGEMENT

- Coordination of referrals
- Mitigation of insurance issues
- Cost effective medication use



# Pharmacy Coverage and Benefit Design

| Treatment Comparison[17,24,26-32] | | | | | |
|---|---|---|---|---|---|
| **Drug** | **FDA Indications** | **Mode of Administration Usual Adult Dose*** | **Mechanism** | **Potential Adverse Effects** | **Comments** |
| **ACUTE/ON-DEMAND TREATMENT** | | | | | |
| C1 esterase inhibitor, human (Beninert®, plasma derived) | Treatment of acute abdominal, facial, or laryngeal HAE attacks in adult and pediatric patients. | IV<br>20 U/kg | C1 esterase inhibitor which inhibits plasma kallikrein, coagulation factors Xlla and Xla, C1s, C1r, MASP-1, MASP-2, and plasmin | *Most Common:* dysgeusia.<br>*Rare*: anaphylaxis, serious arterial and venous thromboembolic events.<br>*Theoretical:* transmission of infectious agent. | Efficacy +++<br>Approved for self-administration |
| C1 esterase inhibitor, recombinant (conestat alpha, Ruconest®) | Acute attacks in adult and adolescent patients with HAE | IV<br>50 U/kg | C1 esterase inhibitor (same as above) | *Most Common*: headache, nausea, diarrhea.<br>*Rare:* anaphylaxis (rabbit derived product), serious arterial and venous thromboembolic events. | Efficacy +++<br>Approved for self-administration |
| Icatibant (Firazyr®) | Acute attacks of HAE in adults 18 years of age and older | Sub-Q<br>30 mg | B2 bradykinin receptor antagonist | *Most Common*: injection site reactions.<br>*Theoretical:* worsening of an ongoing ischemic event. | Efficacy +++<br>Approved for self-administration (Maximum 3 injections in 24 hours) |
| Ecallantide (Kalbitor®) | Acute attacks of HAE in patients 12 years of age and older | Sub-Q<br>30 mg | Kallikrein Inhibitor | *Most Common:* headache, nausea, diarrhea, pyrexia, injection site reactions.<br>*Uncommon*: anaphylaxis (4%) | Efficacy +++<br>Labeled for administration by health care professional only (Maximum 2 injections in 24 hours) |
| Fresh frozen plasma | | IV<br>2 units | C1 esterase inhibitor (same as above) | *Rare*: anaphylaxis.<br>*Possible*: transmission of infectious agent; sudden worsening of an attack. | Efficacy ++<br>In healthcare setting only |
| **PROPHYLACTIC TREATMENT** | | | | | |
| C1 esterase inhibitor, human (Cinryze®, plasma) | Routine prophylaxis against angioedema attacks in adults, adolescents, and pediatric patients (6 years of age and older) with HAE | IV<br>1000 U every 3 to 4 days (≥ 12 years old)<br>500 U every 3 to 4 days (6 to 11 years of age) | C1 esterase inhibitor (same as above) | *Most Common:* headache, nausea, rash, vomiting, and fever.<br>*Rare*: risk of anaphylaxis, serious arterial and venous thromboembolic events. *Theoretical*: transmission of infectious agent. | Approved for home infusion.<br>Maximum dose:<br>2500 U (≥ 12 years old)<br>1000 U (6 to 11 years of age) |

## Pharmacy Coverage and Benefit Design (CONTINUED)

| Treatment Comparison[17,24,26-32] | | | | | |
|---|---|---|---|---|---|
| **Drug** | **FDA Indications** | **Mode of Administration Usual Adult Dose*** | **Mechanism** | **Potential Adverse Effects** | **Comments** |
| **PROPHYLACTIC TREATMENT** | | | | | |
| C1 esterase inhibitor, human (Haegarda®) | Routine prophylaxis to prevent HAE attacks in adolescent and adult patients | Sub-Q<br>60 U every 3 to 4 days | C1 esterase inhibitor (same as above) | *Most Common:* injection site reaction, hypersensitivity, and dizziness.<br>*Rare*: risk of anaphylaxis, serious arterial and venous thromboembolic events.<br>*Theoretical*: transmission of infectious agent. | Approved for self-administration |
| Lanadelumab-flyo (Takhyzro®) | Prophylaxis to prevent attacks of HAE in patients 12 years of age and older | Sub-Q<br>300 mg every 2 weeks (q 4 weeks may be option) | Kallikrein inhibitor | *Most Common*: injection site reactions, headache, rash, myalgia, dizziness, and diarrhea.<br>*Rare*: anaphylaxis | Approved for self-administration |
| Anabolic steroids<br>Danazol (Danacrine®)<br>Stanozolol (Winstrol®)<br><br>Oxandralone and methyl-testosterone used but not FDA approved | Prophylaxis in adults | Oral<br>200 mg/d or less and<br>2 mg/d or less, respectively | 17-a-alkylated androgen, mechanism of action unknown | *Common*: weight gain, virilization, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities, increase in liver enzymes, hypertension, and alterations in lipid profile<br>*Uncommon:* decreased growth rate in children, masculinization of the female fetus, cholestatic jaundice, peliosis hepatis, and hepatocellular adenoma | Oral and inexpensive compared to others. Recommended second line by WAO/EAACI guidelines because of adverse effects 49% discontinued for adverse effects |
| Antifibrinolytics<br>Epsilon aminocaproic acid (Amicar®)<br>Tranexamic acid (Lysteda®) | Not FDA approved for HAE | Oral<br>1 - 2 g TID and<br>1 g BID, respectively | Mechanism of action in HAE is unknown | *Common*: nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps, muscle injury.<br>*Uncommon*: thrombosis, seizures | |

*Prophylactic doses must be individualized

BID = Twice a day
TID = 3 times a day
MASP = mannose-associated serine protease
Sub-Q = subcutaneous

## Cost-Effectiveness of Prophylaxis

Therapy for HAE with the newer agents is over $400,000 annually and can be over $1 million annually per patient.

| Cost of Prophylaxis Medications[19] | | | | |
|---|---|---|---|---|
| | **Administration Route** | **Unit** | **Big 4 or FSS Price per Package/Dose*** | **ASP per Unit/Dose†** |
| **Cinryze®** | IV | 500 IU | $2,012 | $3,049 |
| **Haegarda®** | SC | 2,000 IU | $1,393 | – |
| **Haegarda®** | SC | 3,000 IU | $2,090 | – |
| **Lanadelumab** | SC | 300 mg | $16,250 | – |

* Big 4 or Federal Supply Schedule price as of October 1, 2018.
† Average Sales Price as of June 13, 2018, plus 9% markup for units administered in physicians' office, home infusion, and hospital outpatient settings.

## Institute for Clinical and Economic Review

A cost-effectiveness analysis of prophylaxis, from the Institute for Clinical and Economic Review, has been published. All three treatments far exceed commonly cited thresholds of $50,000 to $150,000 per quality-adjusted life-year (QALY) gained, with some caveats. Based on this analysis, subcutaneous C1-INH (Haegarda®) appears to be the most cost-effective of the three options.

| Incremental Results versus No Prophylaxis for the Base-Case Analysis[19,33] | | | |
|---|---|---|---|
| | **Cinryze®** | **Haegarda®** | **Lanadelumab** |
| **Total Costs - U.S. Health System Perspective** | $4,443,000 | $390,000 | $1,321,000 |
| **Prophylaxis Drug Costs** | $9,469,000 | $8,897,000 | $9,970,000 |
| **Acute Treatment Costs** | -$5,026,000 | -$8,507,000 | -$8,648,000 |
| **Acute Treatment Costs (Drugs)** | -$4,648,000 | -$7,814,000 | -$7,999,000 |
| **Acute Treatment Costs (Other Services)** | -$378,000 | -$693,000 | -$650,000 |
| **LYs Gained** | 0.00 | 0.00 | 0.00 |
| **QALYs Gained** | 0.75 | 1.19 | 1.19 |
| **Number of Attacks Avoided** | 860 | 1,430 | 1,480 |
| **ICER – U.S. Health System Perspective** | $5,954,000 | $328,000 | $1,108,000 |
| **$/Attack Avoided - U.S. Health System Perspective** | $5,168 | $273 | $892 |

Incremental cost-effectiveness ratios are rounded to the nearest $1,000; incremental cost-effectiveness ratios are rounded to the nearest $10,000 when over $1 million.

## Caveats

The results of the cost-effectiveness models were very sensitive to baseline attack rates, prophylactic and on-demand medication costs, and treatment effect estimates. The table below provides an analysis based on baseline attack rate. For example, these medications will achieve cost-effectiveness at a threshold of $150,000 per quality-adjusted life-year for a monthly baseline attack rate of 3.47 for subcutaneous C1-INH, 3.82 for lanadelumab, and 5.92 for intravenous C1-INH. Additionally, if the approximately 75 percent of eligible patients on lanadelumab, who are attack-free for six months, increase their dosing interval to every four weeks, this agent would be cost-effective at the $150,000 willingness-to-pay threshold.

**Threshold Analysis on Baseline Attack Rate[19,33]**

| | Attack Rate to Achieve $50,000 per QALY | Attack Rate to Achieve $100,000 per QALY | Attack Rate to Achieve $150,000 per QALY | Attack Rate to Achieve $250,000 per QALY | Attack Rate to Achieve $500,000 per QALY |
|---|---|---|---|---|---|
| **Cinryze®** | 5.99 | 5.95 | 5.92 | 5.84 | 5.66 |
| **Haegarda®** | 3.52 | 3.49 | 3.47 | 3.43 | 3.32 |
| **Lanadelumab** | 3.87 | 3.85 | 3.82 | 3.77 | 3.65 |

## Comments

### On-Demand Treatment

- Intravenous and subcutaneous C1-INH products for self-administration have to be reconstituted at time of administration and require significant patient/caregiver training for appropriate use.
- Because C1-INH only comes in select one-time use vial sizes, it is important for the correct vial size to be prescribed to minimize waste.
- Ecallantide also requires reconstitution and drawing up into a syringe and is labeled for healthcare personnel administration only.
- Icatibant comes in prefilled syringes that only require attaching a needle to administer.
- There are no head-to-head trials of on-demand treatment so one cannot say any FDA approved agent is better than another in terms of efficacy.

### Prophylactic

- Intravenous and subcutaneous C1-INH has all the issues with patient administration as noted above.
- Lanadelumab does not have to be reconstituted but does have to be drawn into a syringe.
- All agents, except androgens, are expensive in terms of acquisition costs. Plans will need to monitor impact on total health care costs for a given patient to determine benefit of long-term prophylaxis.
- There are no head-to-head trials of prophylactic treatment so one cannot say any FDA approved agent is better than another in terms of efficacy.
- Payers seeking to negotiate better prices may consider giving all market shares to the two treatments administered subcutaneously, due to the simpler administration of these therapies compared with intravenous drugs.
- Prior authorization criteria should be based on clinical evidence with input from clinical experts and patient groups. Suggestions for elements of coverage criteria include, confirmation of HAE through lab tests or physician attestation, determination of the appropriateness of long-term prophylaxis based on the frequency and severity of attacks, and use of a patient's actual weight to more precisely manage dosing of weight-based treatments. Specific coverage criteria options are described in greater detail in the final evidence report.
- Given that the cost-effectiveness of lanadelumab can be vastly improved by switching the dosing for attack-free patients from every two weeks to every four weeks, payers should work with clinicians to encourage trial periods of the less frequent dosing if patients are attack-free after six months of therapy.

# SAMPLE MONOGRAPH TEMPLATE FOR P&T REVIEW AND BENEFIT DESIGN CONSIDERATION[34]

## HAE: Formulary Monograph Template

### INDIVIDUAL DRUG REVIEW

| | |
|---|---|
| Generic Name: | [Name] |
| Brand Name: | [Name] |
| Manufacturer: | [Text] |
| Date of Review: | [Month/Year] |
| Reason for Review: | [Text] |

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