Summary

WHAT IS HEREDITARY ANGIOEDEMA?

Hereditary Angioedema (HAE) is a rare genetic disorder that causes painful attacks of swelling in the face, hands, feet, and stomach, as well as potentially life-threatening swelling of the throat. Most HAE is caused by a deficiency (Type 1 HAE) or dysfunction (Type 2 HAE) of a protein called C1 esterase inhibitor. Attacks can last for up to four days, and can be spontaneous or triggered by stress, medical procedures, and certain medications like oral contraceptives or ACE inhibitors. Attacks can occur rarely or as often as once every few days. Because of their severity and unpredictability, attacks can significantly reduce a patient's quality of life.

TREATMENT OPTIONS (LONG-TERM PROPHYLAXIS)

The goal of HAE treatment is to reduce the duration, frequency, and severity of attacks. *On-demand treatments* are used to reduce the duration and severity of a single attack. *Long-term prophylactic treatments*, the focus of this report, are taken regularly to prevent attacks from occurring and to reduce attack severity.

Current treatment options for long-term prophylaxis include **C1-inhibitors (Cinryze**®, Shire Plc; and **Haegarda**®, CSL Behring GmbH) and androgens such as danazol. C1-inhibitors, used to increase the level of C1-esterase in the blood, are considered first-line therapies. Androgens are generally used as second-line therapies due to their side effects. Cinryze is approved for patients ages 6 and older and is taken intravenously every three to four days. Haegarda is approved for patients ages 12 and older and is injected under the skin twice a week.

Lanadelumab (Takhzyro™, Shire Plc) is a newly developed drug that targets a different pathway than the C1 inhibitors. Approved by the FDA in August 2018 for long-term prophylaxis for adults and adolescents, lanadelumab is injected under the skin once every two or four weeks.

KEY REPORT FINDINGS

ICER's report found that long-term prophylaxis with either of the C1 inhibitors or lanadelumab resulted in fewer acute attacks and improved quality of life for people living with HAE, but current pricing of all three treatments exceeds traditional cost-effectiveness thresholds. Decision makers will need to be aware that even minor adjustments in the key assumptions (e.g., frequency of attacks) could result in substantially different cost-effectiveness results. The report was the subject of a public meeting of the California Technology Assessment Forum (CTAF).

KEY POLICY RECOMMENDATIONS

- Payers seeking to negotiate better prices may consider giving all market share to the two injectable treatments, Haegarda and lanadelumab, due to these therapies' simpler administration compared to intravenous drugs.
- Prior authorization criteria should be based on clinical evidence with input from clinical experts and patient groups. Insurers crafting coverage policy may seek to confirm HAE through lab tests or physician attestation, determine the appropriateness of long-term prophylaxis based on the frequency and severity of attacks, and use a patient's weight to more precisely manage dosing of weight-based treatments.
- Specialists involved in the care of patients with HAE should convene and work with patients to develop a consensus statement to guide policymakers and payers on the appropriate use of long-term prophylaxis for patients with Type 1 or Type 2 HAE.

Clinical Analyses: ICER Evidence Ratings

How strong is the evidence that lanadelumab and C1 inhibitors improves outcomes in patients with HAE?

Evidence rating for long-term prophylaxis, as compared to on-demand treatment only

✓ **Cinryze:** High certainty of a substantial net health benefit.

✓ **Haegarda:** High certainty of a substantial net health benefit.

? **Lanadelumab:** Promising but inconclusive. Although results from a pivotal clinical trial demonstrated important clinical benefits in terms of reducing HAE attacks, the possibility of net harm cannot be ruled out for a new biologic therapy with no long-term safety data.

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

	Compared to On-Demand Treatment Only		
	CINRYZE	**HAEGARDA**	**LANADELUMAB**
Frequency, severity and duration of HAE Attack	↓ Reduced frequency, severity and duration of HAE attacks in patients 6 years and older	↓ Reduced frequency, severity, and duration of HAE attacks in patients 12 years and older	↓ Reduced frequency and severity of HAE attacks in patients 12 years and older
Use of Rescue Therapy	↓ Reduced need for rescue medication	↓ Reduced need for rescue medication	↓ Reduced need for rescue medication
Quality of life	↑ Improved quality of life*	↑ Improved quality of life*	↑ Improved quality of life

** Statistical significance not reported in the clinical trials*

Clinical Analyses: ICER Evidence Ratings (continued)

HARMS

Mild infections, headaches, hypersensitivity, dizziness, and injection site reactions were the most common side effects during the trial periods. Serious adverse events and adverse events leading to trial discontinuation were rare.

SOURCES OF UNCERTAINTY

Data Limitations: Although trials of long-term prophylactic treatment with C1-INHs and lanadelumab showed benefits in reducing the frequency of HAE attacks with few harms, the evidence base is limited—

- **Comparability of evidence:** There are currently no clinical trials comparing either of the C1 inhibitors to lanadelumab or each other. Further, due to differences in the trial design and study populations, we were unable to use statistical techniques to indirectly compare the comparative effectiveness and harms of each drug.
- **Durability of effect and safety profile:** The trials were short (4-26 weeks), leaving questions about the treatment's long-term effectiveness and also about the safety of lanadelumab.
- **Patient-important outcomes:** Quality of life measures were infrequently and inconsistently measured across the trials, and no trials to date have used the disease-specific HAE-QoL as an assessment of quality of life. Even less evidence exists on the treatments' effect on school or work, depression, and anxiety.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS

Compared to on-demand therapy only, and at the assumed annual net prices,* all three prophylactic treatments **exceed commonly-cited thresholds for cost-effectiveness** of $50,000 to $150,000 per quality-adjusted life year (QALY) gained. However, because this calculation is highly dependent on the baseline frequency of HAE attacks and other assumptions as well, the overall cost-effectiveness of these treatments is less certain.

The FDA label for lanadelumab suggests that patients who remain attack-free for six months may be considered for less-frequent dosing (one dose every 4 weeks instead of every 2 weeks). However, the real-world proportion of patients who will switch to – and remain on – the less-frequent dose is unknown. Lanadelumab **would** meet commonly-cited cost-effectiveness thresholds if approximately 75% of eligible patients switch to the less-frequent dosing.

Do these treatments meet established thresholds for long-term cost-effectiveness?

NO	**Cinryze:** $5.95 million per QALY gained
NO	**Haegarda:** $328,000 per QALY gained
NO	**Lanadelumab:** $1.11 million per QALY gained

**Annual net prices used were $401,512 for Cinryze, $377,786 for Haegarda, and $423,344 for lanadelumab.*

ICER's report notes that decision-makers often give special considerations to therapies for ultra-rare diseases such as HAE, which may lead to coverage and funding decisions at higher thresholds for cost-effectiveness.

Economic Analyses (continued)

VALUE-BASED PRICE BENCHMARKS

What is a fair price for C1-INHs inhibitors and lanadelumab based on their value to patients and the health care system?

	Annual List Price	Annual Net Price	Annual Price to Achieve $100,000 per QALY Threshold	Annual Price to Achieve $150,000 per QALY Threshold	Discount from List Price Required to Reach Threshold Prices	Net price within range?
Cinryze	$539,670	$401,512	$216,000	$218,000	60%	NO
Haegarda	$509,792	$377,786	$366,000	$369,000	28%	NO
Lanadelumab	$565,557	$423,344	$372,000	$375,000	34%	NO

POTENTIAL FIVE-YEAR BUDGET IMPACT

How many patients can be treated with lanadelumab before crossing ICER's $991 million potential budget impact threshold?

The annual potential budgetary impact of treating the entire eligible population with lanadelumab (compared with a mix of other currently approved prophylactic treatments and no prophylaxis) **did not exceed** the $991 million ICER potential budget impact threshold. In fact, due to the higher costs associated with the other prophylactic treatments, lanadelumab may be cost-saving at its assumed net price.

Voting Results

CTAF deliberated on key questions raised by ICER's report at a public meeting on October 25, 2018. The results of the votes are presented below. More detail on the voting results is provided in the full report.

CLINICAL EVIDENCE

The panel found that the evidence demonstrated a net health benefit for using the C1 inhibitors as long-term prophylaxis, but that the evidence was insufficient to distinguish between Cinryze and Haegarda. The panel also found that current evidence was not adequate to determine whether or not long-term prophylaxis with lanadelumab is superior to on-demand therapy alone.

LONG-TERM VALUE FOR MONEY

The panel voted that both Cinryze and lanadelumab represent a low long-term value for money when compared to on-demand therapy. When evaluating the long-term value for money of Haegarda, the panel's majority vote was split evenly between low and intermediate value.

OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

Before voting on value, panel members weighed the therapies' other benefits and contextual considerations. The panel underscored how HAE represents a particularly high lifetime burden of illness, and that all three prophylactic treatments may significantly improve both patients' and caregivers' ability to return to work or school. The panel recognized that Haegarda and lanadelumab offer simpler administration – injections under the skin – which may achieve better patient outcomes over a treatment like Cinryze, which is administered intravenously. The panel also noted significant uncertainty about lanadelumab's long-term durability of benefit and risk of serious side effects.

Policy Recommendations

The CTAF Panel participated in a moderated policy discussion that included physicians, patient advocates, manufacturer representatives, and payer representatives. None of the resulting policy statements should be taken as a consensus view held by all participants. For a more detailed discussion, please see the full report.

FOR PAYERS

- Payers seeking to negotiate better prices may consider giving all market share to the two injectable treatments, Haegarda and lanadelumab, due to these therapies' simpler administration compared to intravenous drugs.
- Prior authorization criteria should be based on clinical evidence with input from clinical experts and patient groups. Insurers crafting coverage policy may seek to confirm HAE through lab tests or physician attestation, determine the appropriateness of long-term prophylaxis based on the frequency and severity of attacks, and use a patient's weight to more precisely manage dosing of weight-based treatments. *Specific options are described in greater detail within the full report.*
- Given that the cost effectiveness of lanadelumab can be vastly improved by switching attack-free patients from every 2 week to every 4 week dosing, payers should work with clinicians to encourage trial periods of the less-frequent dosing if patients are attack-free after 6 months of therapy.

FOR MANUFACTURERS

- Innovation that addresses unmet clinical need and produces overall cost savings in the health system is ideal and should be encouraged. However, treatments like Haegarda and lanadelumab can appear cost-saving at a very high price only because of the extremely high annual costs for on-demand treatment of many patients with HAE. In these situations, reasonable value-based pricing for new treatments requires consideration of a new paradigm for "shared savings" between innovators and society.
- Manufacturers should ensure that developmental trials consider, whenever possible, adaptive designs that incorporate head-to-head comparison of drugs and standardized, universally recognized quality of life measures to capture a more comprehensive response to treatment. Such information can be then used in to improve patient/provider decision-making and payer evaluation of value.

FOR PROVIDERS AND SPECIALTY SOCIETIES

- There are currently no consensus criteria on when to consider starting long-term prophylaxis for patients with Type 1 or Type 2 HAE. Specialists involved in the care of patients with HAE should convene and work with patients to develop a consensus statement to guide policymakers and payers on the appropriate use of long-term prophylaxis for patients.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit ICER's website (www.icer-review.org).