Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value

Revised Background and Scope

May 10, 2018

Background

Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent episodes of tissue swelling in various parts of the body, including the face, hands, feet, airways, and intestinal tract.[1] The disease affects approximately 1 in 50,000 individuals, with males and females equally affected.[2] Attacks can happen at any age after birth, and the mean age for a first attack is 10 years old.[3] HAE affects patients' physical and mental health, with patients reporting significantly poorer health-related quality of life and high rates of depression and anxiety.[4,5] Additionally, attacks are associated with up to 20 days per year of missed school or work and impairment in career advancement.[4]

HAE can be caused by several different genetic mutations, leading to different subtypes of disease. The majority of patients are affected by HAE Type 1 or Type 2 disease (HAE-1/2), which are caused by one of more than 450 possible mutations in the SERPING1 gene that codes for C1-inhibitor (C1-INH), also called C1-esterase inhibitor.[6] C1-INH limits the production of bradykinin, so deficient (Type 1) or dysfunctional (Type 2) C1-INH leads to an increase in bradykinin production, which can lead to intermittent episodes of extreme dilation of blood vessels with leakage of plasma and tissue swelling. Tissue swelling can be at any site in the body but is most commonly found under the skin (subcutaneous swelling, occurs in 91% of patients), under a mucous membrane such as in the bowel wall (submucosal swelling causing abdominal pain in 74% of patients), and in the upper airway (laryngeal swelling occurring in 47% of patients).[7] Type 1 HAE is five to six times more common than Type 2 HAE.[1] Additionally, there is a third type of HAE where patients have normal C1-INH levels and function (HAE nC1-INH).[8] Clinically, patients with HAE nC1-INH may present with similar features to patients with HAE-1/2; however, treatment of HAE nC1-INH has yet to be fully defined, as there are no placebo-controlled trials in this population.[9]

Potential triggers for HAE include mechanical trauma, mental stress, respiratory infections, and certain medications such as oral contraceptives and angiotensin-converting enzyme (ACE) inhibitors. Attacks can be spontaneous or the result of trauma, and are usually self-limited, lasting two to four days. However, swelling of the airways during an attack is potentially life-threatening,

with a 30% risk of death due to asphyxiation if untreated.[10] Attack frequency can range from rare to once every three days.[1,10] Patients with HAE have significantly reduced quality of life, in part due to the unpredictability of attacks.[5,11-13]

Management of HAE consists of drug therapy and avoidance of such triggers. Medications for HAE can be categorized into on-demand therapies, which are taken during an attack; preprocedural prophylaxis (i.e., premedication before a known precipitant for an attack); and long-term prophylaxis of attacks. Since treatment during an attack with C1-INH concentrate, ecallantide (a kallikrein inhibitor), or icatibant (a bradykinin-receptor antagonist) is effective in shortening attack duration,[14-16] guidelines recommend that all attacks be considered for treatment.[17,18] To prevent potentially fatal laryngeal edema, preprocedural prophylaxis is recommended for any medical, surgical, or dental procedure that may involve manipulation of the airways.[17,18] Regular use of medications for long-term prophylaxis is more controversial. Guidelines from the World Allergy Organization (WAO) and the European Academy of Allergy and Clinical Immunology recommend individualized decisions between patients and physicians for prophylaxis, and that prophylaxis be particularly considered for patients who face events in life that are associated with increased disease activity, and for all severely symptomatic HAE patients.[18] Indications for long-term prophylaxis in children also remain ill-defined, as evidence is scarce. An international consensus document recommends individualized decisions on long-term prophylaxis in pediatric patients, with the focus on minimizing the impact of HAE on patients' quality of life.[17] Since long-term prophylaxis could involve self-administration of intravenous or subcutaneous medications on a regular basis, there may be barriers to successful long-term treatment, including difficulty with self-administration and cost.[19-21]

In this review, we will focus on long-term prophylaxis for HAE-1/2. Until recently, the only human plasma-derived C1-INH approved for long-term prophylaxis for adults and adolescents 12 years or older was Cinryze® (Shire), which requires intravenous administration every three to four days.[22] More recently, a subcutaneous form of human-derived C1-INH, Haegarda® (CSL Behring), was approved for long-term prophylaxis for adults and adolescents.[23] Ruconest® (Pharming), a recombinant form of C1-INH already approved for treatment of acute attacks, is under review by the United States (US) Food and Drug Administration (FDA) for long-term prophylaxis for adults and adolescents, with an expected decision date of September 21, 2018.[24] Lanadelumab (Shire), a newly developed monoclonal antibody targeting plasma kallikrein, is also under review by the FDA for long-term prophylaxis for HAE in adults and adolescents, with an expected decision date of August 26, 2018.[25] No drug is currently approved for long-term prophylaxis for children under 12 years old, although use of Cinryze in children older than six is being evaluated by the FDA for expanded approval, with an expected decision date of June 20, 2018.[26]

Although HAE is rare, the symptoms have substantial impact on quality of life. Effective treatments exist; however, questions remain regarding the indications, timing, safety, acceptability, and the cost-effectiveness of long-term prophylaxis.

Stakeholder Input

This document incorporates feedback gathered during calls with stakeholders and open input submissions from the public. We sought input from patient advocacy groups, practicing allergists, payers, and pharmaceutical manufacturers to inform the research direction outlined in this scope. Patient groups emphasized the importance of prophylaxis on improving the quality of life of HAE patients. They also highlighted the importance of the patient-physician relationship in the decision-making process and expressed hope that patients would continue to have full access to treatment. Clinicians described the challenges of treating HAE patients due to the variability in disease activity, lack of biomarkers for treatment guidance, as well as high treatment costs. Payers and pharmaceutical manufacturers discussed the difficulties posed by the fact that HAE is a rare disease with a small, heterogeneous population and cautioned that outcome and quality of life data may be limited. ICER looks forward to continued engagement with stakeholders – including patients and their families, clinicians, and researchers - throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments for HAE-1/2.

The final scope has been updated to reflect the feedback provided by stakeholders on the draft scope. We have clarified that our comparison group for our assessments and models will be patients who are being treated with on-demand therapy for acute attacks and short-term prophylaxis for procedures only and no long-term prophylaxis. We acknowledge the challenges posed by the fact that HAE is a rare disease with a heterogeneous clinical presentation and will consider, as data permit, assessing subgroups of patients based on factors such as age and disease severity. We have also added to the Key Outcomes and Harms a plan to include associated cost and quality of life data pertaining to infusion therapy, including the use of ports.

Report Aim

This project will evaluate the health and economic outcomes of long-term prophylaxis for HAE-1/2. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions. Because of the low prevalence of this condition, we intend to use ICER's value framework for ultra-rare diseases, (i.e., conditions where less than 10,000 individuals are affected).

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-

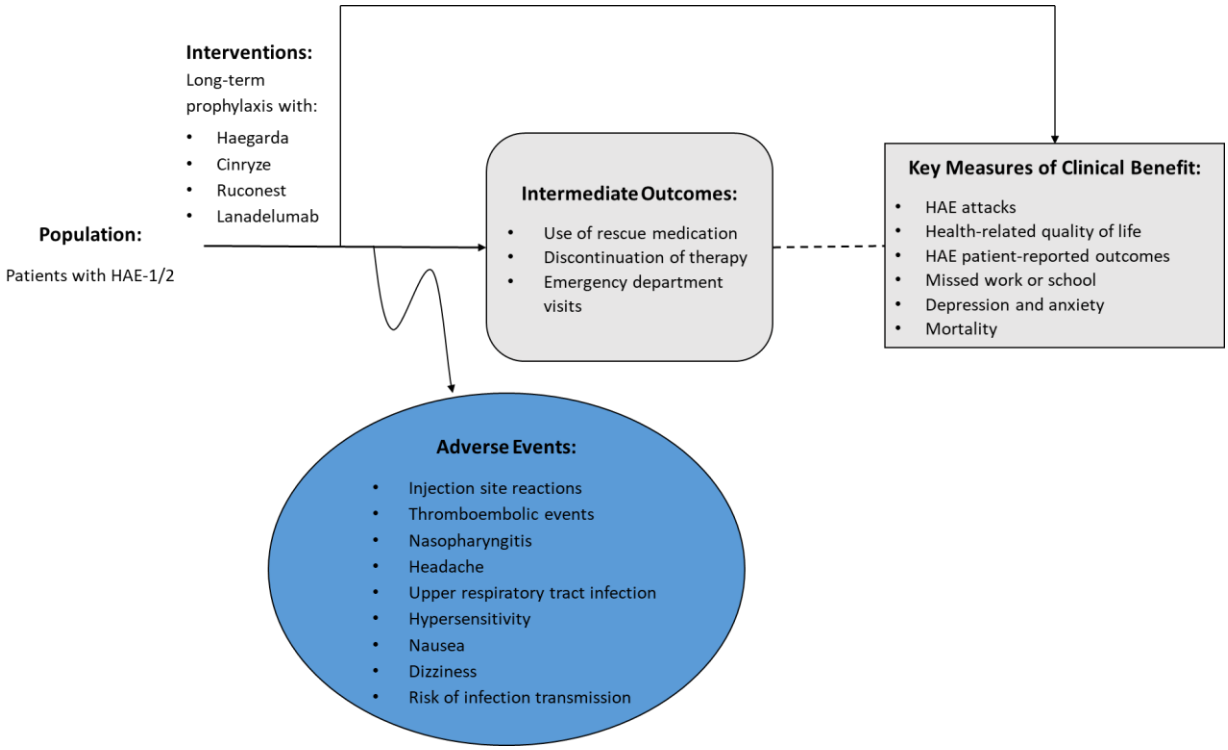
quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework for assessment of therapies for HAE-1/2 is depicted in Figure 1.1.

Figure 1.1. Analytic Framework: Long-term Prophylaxis for HAE-1/2



HAE: hereditary angioedema

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes

(e.g., use of rescue medication), and those within the squared-off boxes are key measures of benefit (e.g., HAE attacks). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipsis.[27]

Populations

The review will focus on patients with HAE-1/2. As data permits, we will also examine the effect of long-term prophylaxis in children under 12 years old and in subgroups of patients with varying degrees of attack frequency and severity.

Interventions

The following therapies will be evaluated when used as long-term prophylaxis:

- Lanadelumab
- Haegarda®
- Cinryze®
- Ruconest®

Comparators

Data permitting, we intend to compare all the agents to one another and to no long-term prophylaxis. We will assume that all patients, whether or not they are receiving long-term prophylaxis, will be treated for acute attacks and receive short-term prophylaxis for procedures.

Outcomes

The outcomes of interest are described in the Table 1.1 below.

Table 1.1. Key Outcomes and Harms

Outcomes	Key Harms
HAE attacks	Thrombotic events
Quality of life	Injection site or infusion reactions
Impact of attacks on school or work	Complications related to having an infusion port
Depression and anxiety	Headache
Use of rescue medication	Hypersensitivity
Emergency department visits	Nasopharyngitis or upper respiratory tract injection
Mortality	Nausea or vomiting
	Dizziness
	Transmission of infectious disease for plasma-derived products (e.g., Hepatitis, Creutzfeldt-Jakob Disease)
	Adverse events leading to discontinuation of therapy

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in Table 1.2.

Table 1.2. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
This intervention will have a significant positive impact outside the family, including on schools and/or communities.
This intervention will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a *de novo* simulation model to assess the lifetime cost-effectiveness of lanadelumab, Haegarda, Cinryze, and Ruconest for long-term prophylaxis against acute attacks of HAE-1/2, compared to no long-term prophylaxis. All patients will receive on-demand therapy for acute attacks and periprocedural short-term prophylaxis. The model structure will be informed by the disease process and previously developed economic models of HAE.[28-30] The model will include HAE-1/2 patients with C1-INH deficiency who are at risk of acute attacks. The preliminary model will be either a two-state Markov model with HAE and death health states or a three-state Markov model with HAE without laryngeal attack, HAE with a laryngeal attack, and death health states. A cohort of patients will transition between the health states during predetermined cycles over a lifetime time horizon. The model will track costs and the outcomes of number of acute attacks and quality-adjusted life years. A 3% discount rate will be applied to both costs and outcomes.

Under ICER's modifications to the value assessment framework for treatments for ultra-rare diseases, we will consider dual "base cases," reflecting the health system perspective (i.e. focusing on direct medical costs only) and modified societal perspectives. A societal perspective base case will be included if appropriate data are available, and if it is found that the impact of the treatment on patient and caregiver productivity, education, disability, and nursing home costs are substantial, and large relative to health care costs. If not assessed as a dual base case, a societal perspective will be considered in a scenario analysis.

Key model inputs will include disease-specific outcomes such as probabilities/rates of acute attacks, probabilities of treatment-related adverse events, and HAE-specific and health-related quality of life (during and between acute attacks). Model cost inputs will include those of the treatments (including but not limited to drug administration and drug monitoring), costs of acute attacks, costs of treatment-related adverse events, and supportive care. As noted previously, if appropriate data are available, we will include productivity and other indirect costs and associated offsets either as a dual base case or as a scenario analysis. Pairwise comparisons will be made between prophylactic therapies and no long-term prophylaxis. Results will be expressed in terms of the incremental cost per acute attack avoided and incremental cost per QALY gained.

In a separate analysis, we will explore the potential budgetary impact of long-term prophylaxis with the treatments under FDA review for new or expanded prophylaxis indications. This analysis will examine the potential budget impact over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for prophylaxis and results from

the simulation model for treatment costs and any cost offsets from reductions in use of other health care resources. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of these interventions.

More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2018/05/ICER-value-assessment-framework-Updated-050818.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by long-term prophylaxis with C1-INH products or lanadelumab (e.g., use of rescue medications, emergency department visits), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of HAE beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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