

Introduction

HEMOPHILIA A

Hemophilia A is an inherited condition that results in a deficiency in the factor VIII blood clotting protein. Individuals with hemophilia A are at risk for life-threatening bleeding; bleeding into a joint or muscle is common and can lead to substantial disability.

To reduce the risk of bleeding, patients with severe hemophilia A administer **factor VIII concentrate** intravenously several times per week. About 25% of these patients develop “inhibitors” that make the factor ineffective.

TREATMENT OPTIONS FOR PEOPLE WITH INHIBITORS

In about three-quarters of patients, inhibitors can be eliminated through a process called **immune tolerance induction (ITI)**. In the remaining one-quarter of patients, ITI is unsuccessful. These patients are treated with **bypassing agents (BPAs)** such as activated prothrombin complex concentrate (aPCC; FEIBA™, Shire) or recombinant activated factor VII (NovoSeven®, Novo Nordisk).

BPAs typically need to be administered multiple times per week. They can be used on demand to treat bleeding events or for prevention of bleeds (prophylaxis). The therapies come with high annual costs: **treatment of a single bleed can cost over \$50,000, and costs including prophylaxis can range from \$300,000 to \$2.5 million per year.**

Due to the complexity and frequency of treatment, only about 50% - 70% of patients adhere to prophylaxis with BPAs.

Emicizumab-kxwh (Hemlibra®, Genentech) was approved by the FDA in 2017 as prophylaxis for people with hemophilia A and inhibitors. Administered by injection and dosed weekly, emicizumab offers added convenience over other treatments. For bleeding events, patients taking emicizumab will generally still need to be treated with a BPA.

SUMMARY

For patients with hemophilia A and inhibitors, ICER's review found that emicizumab:



The report was reviewed during a public meeting of the New England CEPAC. A majority of the Council voted that evidence demonstrates a net health benefit of emicizumab compared either to no prophylaxis or to prophylaxis with bypassing agents.

KEY POLICY IMPLICATIONS

- Payers, manufacturers, and policy makers need to seek new approaches to address financial toxicity in the hemophilia treatment landscape.
- When new therapies appear cost-saving at a high price given high existing costs, reasonable value-based pricing requires consideration of a new paradigm for “shared savings” between innovators and society.
- In assessing the value of treatments for hemophilia, payers should consider benefits and contextual considerations not captured in typical cost-effectiveness analyses.

Clinical Analyses: ICER Evidence Rating

How strong is the evidence that emicizumab improves outcomes in patients with hemophilia A and inhibitors for whom ITI has been unsuccessful or is not an option?

Adults and children

Evidence provides **high certainty of a small or substantial net health benefit** in comparison to prophylaxis with BPAs

ICER’s analyses also found high certainty of a substantial net health benefit of emicizumab in patients 12 years and older and of a small to substantial net health benefit in children under 12 when compared to no prophylaxis.

KEY BENEFITS STUDIED IN CLINICAL TRIALS

 BLEEDING EVENTS	 HEALTH-RELATED QUALITY OF LIFE*	 OTHER OUTCOMES
<p>Compared to no prophylaxis:</p> <ul style="list-style-type: none"> Substantially reduced in adolescents and adults ages 12 years and older, and appeared to be substantially reduced in children younger than 12. <p>Compared to prior prophylaxis:</p> <ul style="list-style-type: none"> Appeared to be substantially reduced in children, adolescents, and adults. 	<p>Compared to no prophylaxis:</p> <ul style="list-style-type: none"> Improvement in quality of life <p>Compared to prior prophylaxis:</p> <ul style="list-style-type: none"> Prophylaxis with BPAs has not been shown to significantly improve health-related quality of life.* <p><i>*As measured by the Haem-A-QoL and EQ-5D-5L quality of life scales.</i></p>	<ul style="list-style-type: none"> Improvement in caregiver burden Improvement in school and work attendance (<i>statistical significance not reported</i>) Improvement in hospitalized days (<i>statistical significance not reported</i>)

Clinical Analyses: ICER Evidence Rating (continued)

HARMS

The most common adverse events observed in trials were injection site reactions, occurring in 15% - 17% of patients. Serious adverse events occurred in 9% - 11% of patients, including five patients who experienced thrombotic microangiopathy (damage and clotting in small blood vessels) or thrombotic events (blood clots) after receiving multiple large doses of aPCC, a type of BPA, for treatment of bleeding events while taking emicizumab.

SOURCES OF UNCERTAINTY

Lack of long-term safety data: It is possible that so-far undetected toxicities and adverse events will be encountered over time or that the rates of observed events will be higher than seen in trials.

Observational Data: We have only observational data comparing emicizumab prophylaxis with BPA prophylaxis.

Trial Design: The open-label, unblinded design of the HAVEN 1 trial raises concerns of bias in assessing subjective outcome measures, such as quality of life, and even in a seemingly objective outcomes, like treated bleeds, as knowledge of a patient's emicizumab use could have affected the decision to treat bleeding.

Event Reporting: Bleeding events were not consistently defined and recorded across trials of different drug therapies, making inter-trial comparisons difficult.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS

Does emicizumab meet established thresholds for long-term cost-effectiveness?

Compared to no prophylaxis or BPA prophylaxis, emicizumab offers **improved health outcomes and overall cost savings**, both from a health system perspective considering only direct medical costs, and from a societal perspective considering broader benefits.



**Improved
Outcomes**



**Lower
Costs**

What is a fair price for emicizumab based on its value to patients and the health care system?

The wholesale acquisition cost (WAC) of emicizumab is approximately \$482,000 for the first year of treatment and \$448,000 for subsequent years.

Value-based price benchmarks were not calculated for emicizumab in this population, as treatment at the current price is cost-saving and provided additional benefit compared with no prophylaxis or BPA prophylaxis for patients with hemophilia A and inhibitors to factor VIII.

This judgment applies only to the currently indicated population and would not necessarily apply to broader populations potentially included in any future expanded indications.

Economic Analyses (continued)

POTENTIAL SHORT-TERM BUDGET IMPACT

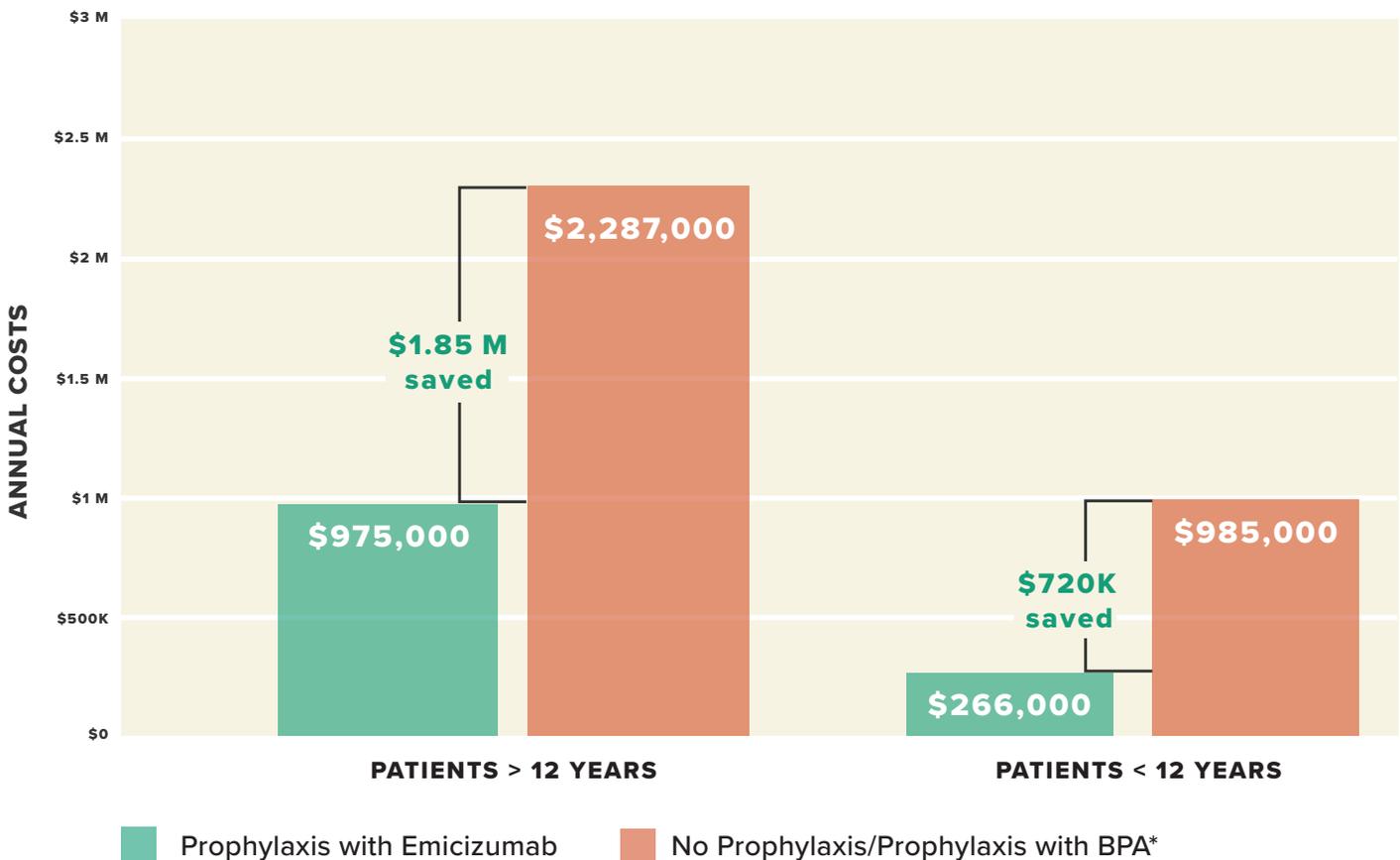
What cost savings does emicizumab offer?

ICER's analyses estimated that roughly 1,000 individuals would be eligible for treatment with emicizumab and estimated a 20% uptake over five years.

Under these assumptions, treatment with emicizumab, compared to a mix of prophylaxis with BPAs and no prophylaxis, could result in savings of about \$1.85 million per year in people age 12 and older and approximately \$720,000 per year in children under age 12.

The estimated annual savings from using emicizumab for the entire eligible cohort of patients with inhibitors to factor VIII is **\$706 million per year in people age 12 and older**, and **\$146 million per year in children under 12**.

Potential Cost Savings of Emicizumab



* It was assumed that 50% of this group would receive no prophylaxis, and 50% would receive prophylaxis with BPAs.

Voting Results

The New England CEPAC deliberated on key questions raised by ICER's report at a public meeting on March 29, 2018. The results of the votes are presented below. More detail on the voting results is provided in the [full report](#).

CLINICAL EVIDENCE

For patients with hemophilia A and inhibitors, who will not be treated with ITI or for whom ITI has been unsuccessful, a majority of the Council voted that evidence demonstrates a **net health benefit of emicizumab compared to no prophylaxis or prophylaxis with bypassing agents**.

OTHER BENEFITS

In further votes, Council members noted that emicizumab offers numerous benefits beyond clinical outcomes, including reduced complexity of administration, reduced caregiver or family burden, increased productivity, a positive impact on schools and communities, and a novel mechanism of action that will provide a new option for patients for whom other treatments have failed.

Value votes were not taken due to ICER's finding that the therapies are cost-saving.

Key Policy Implications

The New England CEPAC participated in a moderated policy discussion that included patients, clinicians, payer representatives, and manufacturer 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](#).

PRICING AND PAYMENT

- Payers, manufacturers, and policy makers need to recognize the seriousness of financial toxicity in the hemophilia treatment landscape and seek new approaches to address it. Although the progress in treatment has been welcomed, high prices paired with an insurance structure that often requires significant cost sharing by patients results in financial toxicity that significantly affects families.
- Innovation that addresses unmet clinical need and produces overall cost savings in the health system should be encouraged. However, in situations where new or emerging therapies appear cost-saving at a high price given high existing costs, reasonable value-based pricing requires consideration of a new paradigm for “shared savings” between innovators and society.
- In assessing the value of treatments for hemophilia, payers should be aware of important benefits and contextual considerations that are not typically captured in cost-effectiveness analyses.
- Given that emicizumab may gain indications for broader use, indication-specific pricing will likely be essential in order to tailor the price to reflect the clinical and economic value of the drug in different patient populations.

Key Policy Implications (continued)

- The Centers for Medicare and Medicaid Services (CMS) and private payers should carefully consider the ramifications of a potential switch of coverage of emicizumab within the insurance structure from the medical benefit to the pharmacy benefit.
- State Medicaid programs should carefully evaluate the policy options and experiences of states that have opted for mandates for patients to receive their hemophilia therapies through Hemophilia Treatment Centers.
- Instead of relying on manufacturers to design trials to evaluate the short-term outcomes of specific agents, specialty societies need to urgently develop a set of prototypical pathways of care around the use of ITI, emicizumab, and other treatments so that future research can offer the opportunity for every patient to enroll in trials of pathways of care that will address the key clinical options available to patients.
- As leaders in working with manufacturers and other stakeholders to develop core sets of patient-important outcomes for clinical trials, hemophilia patient organizations should continue to advance this work and serve as mentors for other patient groups seeking to introduce more patient-centric outcomes in clinical research.

RESEARCH

- Despite challenges to conducting randomized trials in small patient populations such as hemophilia A, patients and clinicians should recognize the importance of such trials in developing the rigorous evidence needed to help guide treatment as more treatments and treatment pathway choices emerge.
- Given that emicizumab has a novel mechanism of action and that clinical studies have not yet evaluated long-term safety, all stakeholders need to be vigilant regarding new information on longer-term outcomes of patients treated with emicizumab.

- The patient community should be aware of the potential for relationships with manufacturers to introduce conflicts of interest for them and for clinicians.

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).