Summary

WHAT IS HEMOPHILIA A?

Hemophilia A is a condition of increased tendency to bleed due to an inherited deficiency of factor VIII, a protein that aids in blood-clotting. Hemophilia A has X-linked recessive inheritance, and so predominately affects males. It is the most common of the hemophilias with an incidence of one in 5,000 male births. Patients with hemophilia A, particularly those with severe disease, are at risk for life-threatening bleeding, including intracranial bleeding, but bleeding into a joint (hemarthrosis) or muscle is more common and can lead to substantial disability. Hemarthroses cause ongoing joint inflammation and damage and also increase the likelihood of further bleeding into the same joint.

To reduce the risk of bleeding, patients with severe hemophilia A have typically administered factor VIII concentrate intravenously multiple times per week. The use of factor concentrates both as treatment and prophylaxis has dramatically altered the management and clinical course of patients with hemophilia A.

TREATMENT OPTIONS

- Factor VIII: Factor VIII concentrate is given intravenously, whether administered on-demand or prophylactically. Prophylaxis is administered multiple times per week, which is burdensome.

- Emicizumab (Hemlibra®, Genentech): a monoclonal antibody with dual targets that allow it to bridge activated factor IX and factor X, the role normally played by activated factor VIII in the clotting cascade. Emicizumab was approved by the US Food and Drug Administration (FDA) as a prophylactic treatment for hemophilia A in patients who have inhibitors to factor VIII in 2017 and in those without inhibitors in 2018.

- Valoctocogene roxaparvovec (Roctavian™; BioMarin): gene therapy with valoctocogene roxaparvovec results in factor VIII production in the liver, but not in the cells in the liver that normally produce factor VIII.

KEY REPORT FINDINGS

- Emicizumab is assessed as providing comparable or better clinical benefits when compared to common current dosing levels of prophylactic factor VIII; it is also cost-saving but only because factor VIII prices are extremely high and have not moderated with competition.

- This review of valoctocogene roxaparvovec is based on data available prior to the FDA decision to request longer-term outcomes; preliminary analyses suggest that at a price of $2.5 million, valoctocogene roxaparvovec would also be cost-saving compared to the high costs of current factor VIII dosing levels.

- ICER has not calculated health-benefit price benchmarks for either treatment because this preliminary analysis of valoctocogene roxaparvovec will need to be updated when the company reports longer-term safety and efficacy data requested by the FDA, and because the results for emicizumab suggest that any price lower than that of factor VIII would make it a preferred strategy and because emicizumab is also importantly used for prophylaxis in patients with inhibitors to factor VIII.

KEY POLICY RECOMMENDATIONS

- It is counterintuitive to pay more for new treatments simply because the existing treatments are overpriced.

- Considering the evidence of equivalent to improved comparative effectiveness, patient preference, and lower overall cost, payers should work with clinicians and patients to encourage the use of emicizumab over Factor VIII for prophylaxis unless it is contraindicated.

- Manufacturers and researchers should ensure that clinical trials capture a core set of outcomes that are important to patients.

Clinical Analyses

How strong is the evidence that these therapies improve outcomes in patients with hemophilia A?

ICER EVIDENCE RATINGS

Interventions	ICER Evidence Rating
Valoctocogene Roxaparvovec Versus Factor VIII Prophylaxis	**P/I:** moderate certainty of a small or substantial net health benefit, with a small likelihood of a negative net health benefit
Emicizumab Versus Factor VIII Prophylaxis	**C++ :** moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
Valoctocogene Roxaparvovec Versus Emicizumab	**Insufficient:** any situation in which the level of certainty in the evidence is low

- The evidence provides high certainty that emicizumab provides at least a comparable net health benefit compared with factor VIII prophylaxis at the doses now typically used in the US, but limitations in long-term outcome data provide only moderate certainty regarding whether it provides a small or substantial net health benefit. As such, in patients with severe hemophilia A without inhibitors, ICER rates emicizumab as “comparable or better” (C++) to factor VIII prophylaxis.

- For valoctocogene roxaparvovec, with the data available at this time, while it provides clear clinical benefits for many patients, the durability of these benefits, the implications for disqualification from treatment with other adeno-associated virus type 5 (AAV5) therapies, and potential long-term harms such as liver disease are all uncertain. In total, therefore, we have judged that the current evidence does provide moderate certainty of a small or substantial benefit of valoctocogene roxaparvovec compared with factor VIII prophylaxis, but a small likelihood remains that further evidence will demonstrate net harm over a longer time frame. As such, in adults with severe hemophilia A without inhibitors, ICER rates valoctocogene roxaparvovec as “promising but inconclusive” (P/I) when compared to factor VIII prophylaxis.

Clinical Analyses (continued)

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

How effective are these therapies in people with hemophilia A without inhibitors to factor VIII who would be appropriate for routine prophylaxis?

	Factor VIII Activity*	Bleeding Events	Health-Related Quality of Life¥
Valoctocogene Roxaparvovec	⬆ Substantially increased in most patients (to non-hemophilic or mild hemophilic range) for a period of years	⬇ Significantly reduced compared to baseline	⬆ Significantly improved compared to baseline
Emicizumab	Not applicable	⬇ Reduced compared to a lower dose of factor VIII prophylaxis assessed in 1 trial No high-quality data versus factor VIII prophylaxis at current real-world doses	⬆ Significantly improved compared to no prophylaxis Nearly all patients prefer prophylaxis with emicizumab, but changes in quality of life were not statistically significant

*: As measured by one-stage assay or chromogenic assay

¥: As assessed by hemophilia-specific validated instrument

Clinical Analyses (continued)

HARMS

All participants in the Phase I/II trial of valoctocogene roxaparvovec experienced one or more adverse events. The most common treatment-related AE was the elevation of liver enzymes, occurring in 86% of patients.

85% of patients on emicizumab experienced one or more adverse events. The most comment treatment-related AE was injection site reaction occurring in 25% of patients.

SOURCES OF UNCERTAINTY

Valoctocogene Roxaparvovec:

Limited data: Data are limited to only one single-arm trial, with very few patients. Interim data from the larger ongoing Phase III trial appear to show lower success rates.

Duration of benefit: Duration of follow-up is currently limited, and factor VIII levels are declining over time, leading to uncertainties in the duration of benefit.

Long-term safety: Target cells for valoctocogene roxaparvovec are hepatocytes, rather than endothelial cells, the liver cells that normally produce factor VIII. It is uncertain whether this could result in chronic liver inflammation or other liver disorders over the long term.

Emicizumab:

Limited data: No head-to-head trial of emicizumab versus factor VIII prophylaxis; therefore, our comparison was indirect. However, the best-randomized control trial (RCT) evidence of factor VIII prophylaxis that was most comparable to the emicizumab trial used doses of factor VIII prophylaxis lower than typically today in the US.

Inhibitor development: Effects on inhibitor development are currently unknown.

Adherence: RCT evidence may overestimate adherence to a burdensome therapy like factor VIII, and this could incorrectly characterize the relative benefits of emicizumab versus factor VIII prophylaxis in the real world.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS

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

Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Factor VIII	Reference	Reference	Reference
Valoctocogene Roxaparvovec	-$4,988,000	0.004	Dominant

In this analysis of valoctocogene roxaparvovec, deemed preliminary due to issuance by the FDA of a complete response letter to its licensing application, and using a placeholder price of $2.5 million, the therapy was found to be a dominant treatment for adult patients with hemophilia A without inhibitors when using doses of factor VIII consistent with typical current practice in the US.

Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Factor VIII	Reference	Reference	Reference
Emicizumab	-$1,505,000	0.000	Cost Saving

Emicizumab was found to be a highly cost saving treatment, with equal efficacy to factor VIII. In fact, using the base case doses for factor VIII, we would find emicizumab to be cost effective even if factor VIII were curative.

Economic Analyses (continued)

HEALTH-BENEFIT PRICE BENCHMARKS

What is a fair price for these therapies based on their value to patients and the health care system?

The HBPB is a price range suggesting the highest US price a manufacturer should charge for a treatment, based on the amount of improvement in overall health patients receive from that treatment, when a higher price would cause disproportionately greater losses in health among other patients in the health system due to rising overall costs of health care and health insurance. In short, it is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good.

Health benefit price benchmarks were not calculated for emicizumab for this population of hemophilia patients without inhibitors, as treatment at the current price compared with factor VIII is projected to be cost saving and produce at least as many QALYs. Additionally, unless indication specific pricing occurred, the HBPB for emicizumab should include its use in patients with inhibitors.

Given the FDA decision to issue a CRL for valoctocogene roxaparvovec, ICER is also not presenting health benefit price benchmarks for valoctocogene roxaparvovec in the Evidence Report.

POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients can be treated before crossing ICER's $819 million budget impact threshold?

Given the FDA decision to issue a CRL for valoctocogene roxaparvovec, ICER is not presenting a potential budget impact analysis for valoctocogene roxaparvovec.

Emicizumab already has an established presence in the market and so no potential budget impact analysis is included for emicizumab.

Voting Results

The New England CEPAC deliberated on key questions raised by ICER's report at a public meeting on October 30, 2020. 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 without inhibitors to Factor VIII, all panelists found the evidence adequate to demonstrate that the emicizumab provides a net health benefit over prophylaxis with factor VIII.

LONG-TERM VALUE FOR MONEY

For the reasons below, **we did not conduct a vote on long-term value for money:**

- The FDA issued a CRL for valoctocogene roxaparvovec and so no price is available
- Emicizumab was found to be cost saving

OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

ICER asks panelists to vote on whether specific potential other benefits, disadvantages, and contextual considerations are important to weigh in judging the long-term value for money of the intervention. In regards to emicizumab, a majority or plurality of the panel voted that:

- Economic model assumptions created no significant risk that base-case cost-effectiveness estimates were too optimistic or pessimistic.
- Emicizumab offers a new mechanism of action compared to that of other active treatments.
- Emicizumab's delivery mechanism or relative simplicity of regimen is likely to result in much higher real world adherence and better outcomes relative to Factor VIII than estimated from clinical trials.
- Emicizumab will not have an impact on reducing or increasing access to future treatment that may be approved over the course of a patient's lifetime.
- Emicizumab offers some special advantages to patients when compared to Factor VIII prophylaxis by virtue of presenting an option with a notably different balance or timing of risks and benefits.
- Emicizumab will differentially benefit a historically disadvantaged or underserved community.
- The level of health loss of patients with Hemophilia A is "intermediate" as measured by the absolute QALY shortfall without treatment with emicizumab.
- The level of health loss of patients with Hemophilia A is "intermediate" as measured by the proportional QALY shortfall without treatment with emicizumab.
- Emicizumab will significantly reduce the negative impact of hemophilia A on family and caregivers when compared to Factor VIII prophylaxis.
- Emicizumab will have a significant impact on improving return to work and/or overall productivity when compared to Factor VIII prophylaxis.

Policy Recommendations

For Patient Advocacy Organizations

- Patient groups should fully embrace their power to speak explicitly about the impact of the high prices of treatments for hemophilia A. General statements of concern about "costs" shifts the focus subtly away from prices, which is consistent with the interests of the life science industry. Doing so deflects from the reality that drug makers have the power to set prices in the United States and the result produces affordability concerns for health systems, financial toxicity for patients and families, and barriers to the ability of patients to gain access to optimal clinical care. Hemophilia patient groups should be willing to name the problem and bear witness to the harms that excessive prices cause.

- Patient groups should be fully transparent about the sources and levels of their funding from industry sources.

For Payers

- Payers should cover factor VIII prophylaxis at levels adequate to achieve higher troughs than the 1%level used in the past.

- Considering the evidence of equivalent to improved comparative effectiveness, relative convenience, and lower overall cost, emicizumab will be the preferred agent for prophylaxis for many patients. Payers should ensure appropriate access to emicizumab and may wish to share information with clinicians and patients regarding its potential advantages over Factor VIII prophylaxis.

- Payers may wish to require that management of factor VIII be done by or in consultation with a Hemophilia Treatment Center.

- Payers should explore innovative approaches to covering high-impact single time therapies such as gene therapies for hemophilia.

For Regulators

- Regulators should require manufacturers of expensive therapies such as those for hemophilia A to provide packaging that minimizes wastage.

For Manufacturers and Clinical Researchers

- Pricing of factor VIII represents a failure of competition and is far too high, even in light of factor VIII's substantial benefits for patients; this pricing structure creates financial toxicity for patients and their families, financial toxicity for health systems, and builds a platform for pricing for potential cures that will only exacerbate these problems.

- In order to facilitate broad access to the current standard for clinically superior care, both in the US and abroad, drug makers should commit to pricing Factor VIII so that the cost to achieve trough levels of 3-5% is the same or lower than what it cost in the past to achieve a 1% trough level.

- Manufacturers and Researchers should ensure that clinical trials capture a core set of outcomes that are important to patients.

- Trials of gene therapies for hemophilia need to be long enough to assess whether the benefits are durable enough to outweigh the risks, particularly since patients may be unlikely to be able to receive a second gene therapy using the same viral vector.

- Manufacturers and researchers should study the effects of emicizumab on the development of inhibitors in infancy and early childhood.

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).