The effectiveness and value of emicizumab and valoctocogene roxaparvovec for the management of hemophilia A without inhibitors

A summary from the Institute for Clinical and Economic Review's New England Comparative Effectiveness Public Advisory Council

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Hemophilia A is an X-linked, recessive disorder characterized by increased bleeding tendency due to deficiency of factor VIII. It is the most common of the hemophilias, with an incidence of 1 in 5,000 male births, and about two-thirds have severe disease.[1] Patients with hemophilia A, particularly those with severe disease, are at risk for life-threatening bleeding, including intracranial bleeding, but bleeding into a joint or muscle is more common and can lead to substantial disability.[2]

The use of factor VIII concentrates as on-demand treatment and prophylaxis has dramatically improved the management and clinical course of patients with hemophilia A. To reduce bleeding risk, patients with severe hemophilia A typically receive factor VIII concentrate intravenously multiple times per week.[3,4] However, the costs and burdens of prophylaxis with factor replacement are high, and it does not maintain patients at normal factor VIII levels. Furthermore, some patients with severe hemophilia A who receive factor VIII concentrates develop neutralizing antibodies known as "inhibitors,"[5] rendering factor VIII ineffective for prophylaxis and on-demand treatment in these patients.

Emicizumab (Hemlibra, Genentech), a bispecific monoclonal antibody that targets activated factor IX and factor X, the role normally played by activated factor VIII in the clotting cascade, was approved by the US Food and Drug Administration (FDA) as a prophylactic treatment for hemophilia A patients who have inhibitors to factor VIII in 2017 and later in 2018 for patients without inhibitors.[6] Emicizumab is administered subcutaneously and may be dosed weekly every 2 weeks or every 4 weeks.

Valoctocogene roxaparvovec (Roctavian, BioMarin) is an investigational gene therapy for hemophilia A that uses adeno-associated virus serotype 5 (AAV5) vector, which carries a liver-directed gene that results in factor VIII production. BioMarin submitted a biologics license application for valoctocogene roxaparvovec to the FDA in December 2019 and received a Complete Response Letter (CRL) rejecting approval in August 2020, specifying the need for longer-term results to substantiate the duration of benefit.[7]

The Institute for Clinical and Economic Review (ICER) conducted a systematic literature review and cost-effectiveness analysis to evaluate the health and economic outcomes of emicizumab and valoctocogene roxaparvovec. All results related to valoctocogene roxaparvovec in the ICER review were considered highly preliminary given the FDA CRL determination. Here, we present the summary of our findings and highlight the policy discussion with key stakeholders held at a public meeting

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of the New England Comparative Effectiveness Public Advisory Council (CEPAC) on October 30, 2020. The detailed report is available on the ICER website: https://icer.org/wp-content/uploads/2020/10/ICER_Hemophilia-A_Final-Report_112020.pdf.

Summary of Findings

CLINICAL EFFECTIVENESS

We did not identify any trial directly comparing emicizumab and valoctocogene roxaparvovec to each other. Because of major differences in study design and study characteristics, we evaluated the 2 interventions separately and did not perform a quantitative indirect comparison through network meta-analysis (NMA).

Emicizumab. The key trial for emicizumab was HAVEN 3, a randomized trial that had a primary outcome of annualized bleeding rate (ABR) for treated bleeds.[8] HAVEN 3 enrolled patients aged 12 years and older with severe hemophilia without factor VIII inhibitors; 89 who had not been on prophylaxis were randomized to receive open label emicizumab or no prophylaxis, and 63 who had been on factor VIII prophylaxis were treated with emicizumab and compared in a before/after methodology. We identified 1 randomized trial of factor VIII vs no prophylaxis (SPINART)[9] that was sufficiently similar to HAVEN 3 to allow us to conduct an NMA of emicizumab vs factor VIII prophylaxis.

NMA results showed a nonsignificant lower rate of treated bleeds (rate ratio [RR] = 0.57, 95% CI = 0.22-1.47) and treated joint bleeds (RR = 0.53, 95% CI = 0.20-1.39) with emicizumab prophylaxis compared with factor VIII prophylaxis. The before/after comparison conducted in HAVEN 3 showed a 68% reduction in treated bleeds with emicizumab prophylaxis compared with the pre-emicizumab period when patients were on factor VIII prophylaxis (ABR: 1.5 vs 4.8, RR = 0.32, 95% CI = 0.20-0.51). A benefit of reduced bleeding was also supported by 1 observational study conducted in patients with a median age of 8.6 years.[10] In this study, among 39 children without inhibitors, all of whom had been receiving factor VIII prophylaxis, fewer treated bleeds were observed in the 6 months after initiating emicizumab (ABR: 0.2, 95% CI = 0.0-0.5) compared with the pre-emicizumab period (ABR: 1.1, 95% CI = 0.5-2.2).

The most common treatment-related adverse event (AE) with emicizumab was injection site reaction, which occurred in 25% of patients on emicizumab prophylaxis in HAVEN 3. Similar patterns of AEs were observed in other emicizumab trials in this population, with very few serious AEs and those that occurred deemed not to be related to emicizumab.

Valoctocogene roxaparvovec. Evidence to inform our assessment of valoctocogene roxaparvovec gene therapy was derived from a single phase 1/2 trial and 1 ongoing phase 3 trial,[11-16] neither of which had a control arm. The key phase 1/2 multiyear study enrolled 15 adults with severe hemophilia A without inhibitors, of which 7 received the $6x10^{13}$ vg/kg dose anticipated to be used clinically. All 7 participants achieved the prespecified primary endpoint of factor VIII activity levels of 5 IU/dL or more at week 16. A nonhemophilic range is considered to be factor VIII levels >40 IU/dl. At the end of 1 year, the mean factor VIII activity level in the 7 participants was 64 IU/dl (median: 60 IU/dl; range: 11-88 IU/dl).

However, over the course of the second to the fourth year of follow-up, factor VIII levels decreased in all participants. Mean factor VIII expression dropped to 36 IU/dl in year 2, 33 IU/dl in year 3, and 24 IU/dl in year 4. At the end of the first year, 6 of the 7 participants were in the nonhemophilic range, and 1 was in the mild hemophilic range (>5 IU/dl). By the fourth year, only 1 participant was still in the nonhemophilic range; 4 participants were in the mild hemophilic range, 1 participant was in the moderate hemophilic range (1-5 IU/dl), and 1 participant was back in the severe hemophilic range (<1 IU/dl). The mean ABR for treated bleeds in the 7 participants dropped from a baseline of 16.3 events per year to a cumulative mean of 0.8 per year after 4 years of follow-up, representing a 95% reduction.

Although only limited data are available, valoctocogene roxaparvovec did not appear to be as successful in the ongoing phase 3 trial. Of the 16 participants who had reached 26 weeks at the time of an interim analysis, only 7 had achieved the prespecified factor VIII levels of 40 IU/dl or greater.

The most common treatment-related AE in the phase 1/2 study was elevation of the alanine aminotransferase level, a marker of liver inflammation, occurring in 86% of patients. All participants in the study developed anti-AAV5 antibodies.

LIMITATIONS OF THE CLINICAL EVIDENCE

For emicizumab, 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 used today in the United States. Additionally, the effect of emicizumab on inhibitor development are currently unknown. Finally, RCT evidence may overestimate adherence to a burdensome therapy such as factor VIII, and this could incorrectly characterize the relative benefits of emicizumab vs factor VIII prophylaxis in the real world.

TABLE 1 Health Care Perspective: Emicizumab vs Factor VIII Prophylaxis (Model 1)

Treatment	Drug cost	Total cost	Life-years	QALYs	Emicizumab vs factor VIII		
					Incremental cost	Incremental QALYs	Cost per QALYs
Factor VIII prophylaxis	$14,821,000	$15,104,000	29.14	24.141	Reference	Reference	Reference
Emicizumab	$13,316,000	$13,598,000	29.14	24.141	–$1,505,000	0.000	Cost Saving

QALY = quality-adjusted life-year.

The evidence base for valoctocogene roxaparvovec has many limitations that have created uncertainties. First, there are currently very few patients studied in the likely dose of $6x10^{13}$ vg/kg. Second, the duration of follow-up is currently limited, and factor VIII levels are declining over time, leading to uncertainties in the duration of benefit. Third, interim data from the phase 3 trial suggest lower rates of success in achieving factor VIII. Fourth, there is uncertainty about the long-term safety of this intervention, and the development of anti-AAV5 antibodies may preclude the ability for patients to take a subsequent gene therapy should a more effective option emerge.

LONG-TERM COST-EFFECTIVENESS

We developed 2 de novo decision analytic models for patients with hemophilia A without inhibitors to factor VIII. In the first model, we evaluated the cost-effectiveness of emicizumab vs factor VIII in patients of all ages eligible for prophylactic therapy. The second model evaluated the cost-effectiveness of valoctocogene roxaparvovec relative to factor VIII only in adult patients with severe hemophilia. The second model used the adapted methods under the ICER ultra-rare disease framework, but we selected only the health care sector perspective as the base case, given that the societal perspective was not substantially different.[17] Both models used a lifetime time horizon, and costs and outcomes were discounted at 3% per year.

Both models focused on acute bleeds as the best available outcome measure from trials that could be translated into changes in quality of life through their relationship to long-term joint damage caused by joint bleeds and the potential need for joint replacement surgery. Joint damage was measured using Pettersson scores (PS) that ranged from 0 to 28 and increased with joint bleeds.[18] Upon reaching a PS of 28, the base-case model assumed that patients had joint replacement surgery and return to a PS of 1. Transitions through the PS states in the models were based on the expected frequency of joint bleeds associated with the treatments and subsequent expected increases in the PS. In each cycle, the expected number of treated nontarget joint bleeds and treated target joint bleeds across treatments were modeled along with related costs and impacts on patient utilities.

The models were informed by key clinical trials, real-world evidence, previous relevant economic models, other published studies on hemophilia A, and stakeholder input. Dosing levels and efficacy for emicizumab and valoctocogene roxaparvovec were determined from the key clinical trials previously described. Treated bleed rates for valoctocogene roxaparvovec were modeled based on projected factor levels across time.[19] For factor VIII, we used doses consistent with current clinical practice. As such, we opted to use bleed rates for factor VIII from a recently published study that included self-reported bleed rates from patients with severe hemophilia A or B being treated in US hemophilia treatment centers.[20] We viewed this rate as an evidence-based lower bound of bleed rates associated with factor VIII at currently representative doses.

The outcomes of interest included the cost per quality-adjusted life-year (QALY) gained, cost per life-year (LY) gained, and cost per treated bleed avoided. Cost per equal value of a life-year gained (evLYG) was not calculated separately given that without a mortality benefit the QALY and evLYG would be identical. Full details on ICER's cost-effectiveness analysis and model are available on ICER's website at https://icer.org/wp-content/uploads/2020/10/ICER_Hemophilia-A_Final-Report_112020.pdf.

As shown in Tables 1 and 2, emicizumab was found to have lower costs with the same projected number of bleeds and QALYs compared with factor VIII prophylaxis and thus is a cost-saving strategy. Valoctocogene roxaparvovec, at its placeholder price of $2.5 million, was projected to have lower total costs, lower bleeds, and slightly more QALYs; therefore, it is a dominant strategy compared with factor VIII. The cost-effectiveness results for both treatments are heavily dependent on the dosing and costs of factor VIII. As

TABLE 2 Health Care Perspective: Valoctocogene Roxaparvovec vs Factor VIII Prophylaxis (Model 2)

Treatment	Drug cost	Total cost	Life-years	QALYs	Valoctocogene roxaparvovec vs factor VIII		
					Incremental cost	Incremental QALYs	Cost per QALYs
Factor VIII prophylaxis	$18,269,000	$18,722,000	26.53	19.087	Reference	Reference	Reference
Valoctocogene roxaparvovec	$13,293,000	$13,693,000	26.53	19.091	–$4,988,000	0.004	Dominant

QALY = quality-adjusted life-year.

can be seen in the tables, current pricing for factor VIII is extremely high, leading to lifetime costs above $14 million in the first model and over $18 million in the second model.

LIMITATIONS OF THE COST-EFFECTIVENESS MODEL

As previously noted, the FDA issued a CRL for valoctocogene roxaparvovec, so our analysis of this intervention is deemed preliminary. The bleed rates for valoctocogene roxaparvovec were based on a very small number of patients and had to be projected over time. As already noted, dosing levels and efficacy for factor VIII were taken from patients in US treatment centers, while those for emicizumab and valoctocogene roxaparvovec were from clinical trials. If those doses or efficacies are substantially different in practice, it could change the results. Finally, we also did not incorporate inhibitor development into the model, since we received conflicting clinical opinions about which regimen would lead to more inhibitor development, and it has already been shown that emicizumab is a dominant treatment for patients with inhibitors.[21]

Policy Discussion

The New England CEPAC is one of the independent appraisal committees convened by ICER to engage in the public deliberation of the evidence on clinical and cost-effectiveness of health care interventions. The New England CEPAC comprises medical evidence experts, including practicing clinicians, methodologists, and leaders in patient engagement and advocacy. Their deliberation includes input from clinical experts and patient representatives specific to the condition under review, as well as formal comments from manufacturers and the public. A policy roundtable concludes each meeting during which representatives from insurers and manufacturers join clinical experts and patient representatives to discuss how best to apply the findings of the evidence to clinical practice, insurance coverage, and pricing negotiations.

The ICER report on emicizumab and valoctocogene roxaparvovec for hemophilia A was the subject of a New England CEPAC meeting on October 30, 2020. Following the discussion, the CEPAC members deliberated on key questions raised by ICER's report. The panel voted 15 to 0 that the evidence was adequate to demonstrate a greater net health benefit of emicizumab over prophylaxis with factor VIII. The panel did not vote on the net health benefit of valoctocogene roxaparvovec due to the CRL issued by the FDA.

The CEPAC panel also voted on "other potential benefits" and "contextual considerations" as part of a process intended to signal to policymakers whether there are important considerations when making judgments about long-term value for money not adequately captured in analyses of clinical and/or cost-effectiveness. The results of these votes are shown in Table 3. They highlight several factors beyond the results of cost-effectiveness modeling that the CEPAC panel felt were particularly important for judgments of overall long-term value for money.

As described in ICER's Value Assessment Framework, questions on long-term value for money are subject to a value vote when incremental cost-effectiveness ratios for the interventions of interest are between $50,000 and $175,000 per QALY in the primary base-case analysis. Because the FDA issued a CRL for valoctocogene roxaparvovec and the results of cost-effectiveness modeling showed emicizumab to be cost saving and health enhancing at its current price, no votes were held on the long-term value of money for either treatment.

The policy roundtable discussion explored how best to translate the evidence and additional considerations into clinical practice and pricing and insurance coverage policies. The full set of policy recommendations can be found in the Final Evidence Report on the ICER website: https://icer.org/wp-content/uploads/2020/10/ICER_Hemophilia-A_Final-Report_112020.pdf. Several key policy recommendations for valoctocogene roxaparvovec and emicizumab are as follows:

TABLE 3 Votes on Other Benefits and Contextual Considerations for Emicizumab

Suggests lower value	Intermediate	Suggests higher value
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
0 votes	**10 votes**	5 votes
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared with that of other active treatments.
0 votes	0 votes	**15 votes**
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.
0 votes	0 votes	**15 votes**
This intervention could reduce or preclude the potential effectiveness of future treatments.		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.
0 votes	**15 votes**	0 votes
The intervention offers no special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.
3 votes	9 votes	3 votes
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.
0 votes	3 votes	**12 votes**
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
1 vote	**8 votes**	6 votes
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
3 votes	**10 votes**	2 votes
Will not significantly reduce the negative impact of the condition on family and caregivers vs the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs the comparator.
0 votes	0 votes	**15 votes**
Will not have a significant impact on improving return to work and/or overall productivity vs the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs the comparator.
0 votes	1 vote	**14 votes**

Note: bold type indicates majority.
QALY = quality-adjusted life-year.

- Pricing of factor VIII in the United States is far higher than in other developed countries and represents a failure of competition. The price is far too high, even in light of factor VIII's substantial benefits for patients; this pricing structure creates financial toxicity for patients, their families, and the health systems and builds a platform for pricing of treatments such as emicizumab and for potential cures such as gene therapy that will only exacerbate these problems.
- 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.
- Payers should explore innovative approaches to covering high-impact single-time therapies such as gene therapies for hemophilia.
- 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.

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