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The effectiveness and value of gene therapy for hemophilia: A Summary from the Institute for Clinical and Economic Review's California Technology Assessment Forum

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Patients with hemophilia A and B have an increased tendency to bleed because of inherited deficiencies of factor VIII and factor IX, respectively, which disrupt the clotting cascade. Both have X-linked recessive inheritance, and therefore, predominately affect males. Approximately 76% of all male patients with hemophilia in the United States have hemophilia A and the remainder have hemophilia B.[1] The exact prevalence of hemophilia in the United States is estimated to be approximately 30,000 to 33,000.[1]

Patients with hemophilia A and B, 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 leads to substantial disability from pain and loss of mobility.[2] 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 typically administer factor concentrate intravenously several times each week.[3,4] In addition, a nonfactor replacement therapy, emicizumab, a monoclonal antibody administered monthly by subcutaneous injection, has also become a mainstay of prophylactic treatment for patients with hemophilia A. No similar nonfactor prophylaxis is currently available for hemophilia B.

Etranacogene dezaparvovec (Hemgenix) is a gene therapy approved by the US Food and Drug Administration (FDA) in November 2022 for adults with hemophilia B who currently use factor IX prophylaxis therapy, or have a current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes. It is a 1-time infusion of an adeno-associated virus vector containing the gene for factor IX to cells in the liver, resulting in production of an active variant of factor IX.

Valoctocogene roxaparvovec is a gene therapy for hemophilia A that received conditional market authorization with requirements for additional monitoring by the European Medicines Agency on August 24, 2022. In the United States, after prior rejection by the FDA, the biologics license application for valoctocogene roxaparvovec was resubmitted on October 13, 2022, and has an expected decision date of March 31, 2023.

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 etranacogene dezaparvovec and valoctocogene roxaparvovec gene therapies for hemophilia B and hemophilia A, respectively. Complete details of ICER's systematic literature search and protocol, as well as the methodology and model structure for the economic evaluation, are available on ICER's website. In this paper, we present the summary of our findings and highlights of the policy discussion with key stakeholders held at a public meeting of the California Technology Assessment Forum (CTAF) on November 18, 2022. The full report is available on the ICER website at https://icer.org/wp-content/uploads/2022/05/ICER_Hemophilia_Final_Report_12222022.pdf.

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Summary of Findings

CLINICAL EFFECTIVENESS

Etranacogene Dezaparvovec for Hemophilia B. There are 2 single-arm trials of etranacogene dezaparvovec. The Hope-B trial included 54 adult males with severe or moderately severe hemophilia B who were currently on factor IX prophylaxis and had at least 150 exposure days of treatment with factor IX.[5] A phase 2B trial of 3 patients with moderately severe to severe hemophilia B was included as those patients had longer follow-up.[6] The patients in these 2 trials received a single dose of etranacogene dezaparvovec 2×10^13 gc/kg. The annualized bleeding rate at 52 weeks was assessed as a primary outcome in the HOPE-B trial, whereas factor IX activity was considered as a primary outcome for the phase 2B trial.

Patients treated with etranacogene dezaparvovec had an 80% reduction in treated joint bleeds and similar reductions in other bleeds when compared with their bleeding rates on factor prophylaxis prior to gene therapy, though the absolute bleeding rate was quite low on factor prophylaxis. No patients successfully treated with etranacogene dezaparvovec restarted factor prophylaxis during the first 18 months of therapy. The initial increase in factor IX levels appeared to remain stable over 18 months in contrast with the clear decline in factor VIII levels following therapy with valoctocogene roxaparvovec (Table 1). Finally, the reduction in the burden of therapy—no longer needing weekly or more frequent factor IX therapy—is a major benefit for patients. The most significant harm following treatment with etranacogene dezaparvovec was liver enzyme elevation, which required treatment with corticosteroids in 17% of patients for a mean duration of 11 weeks.[5] Because of the uncontrolled study design, small numbers of patients studied, and relatively short follow-up, there is still considerable uncertainty about the long-term net benefits of etranacogene dezaparvovec compared with factor IX prophylaxis. In particular, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma.

Valoctocogene Roxaparvovec for Hemophilia A. The phase 3 GENEr8-1 study was a single-arm study that included 134 patients with a 2-year follow-up of factor VIII activity as the primary outcome.[7] A second phase 1/2 study with 7 patients followed for 6 years.[8] Both factor VIII usage and annualized bleeding rate were assessed as secondary outcomes in these 2 trials. For comparisons with eculizumab, we used group D of the phase 3 HAVEN-3 trial, which included 48 patients aged 12 years or older with severe hemophilia A.[9] Since the earlier 2021 ICER review, the liver histology slides were reassessed by a single panel of pathologists as mandated by the FDA. In addition, longer follow-up data were available.

TABLE 1 Factor Levels Over Time in the Phase 3 Studies

	Month 6	Month 12	Month 18	Month 24
Hemophilia B: Etranacogene dezaparvovec				
Factor IX activity (IU/dL)	39.0	41.5	36.9	NR
Hemophilia A: Valoctocogene roxaparvovec				
Factor VIII activity (IU/dL)	NR	42.9	NR	24.2[a]

[a]*N = 17 patients with data at 24 months.*
IU/dL = international units per deciliter; NR = not reported.

At 24 months, patients treated with valoctocogene roxaparvovec had an 84% reduction in treated joint bleeds and similar reductions in other treated bleeds when compared with their bleeding rates on factor prophylaxis prior to gene therapy, though the absolute bleeding rate was quite low on factor prophylaxis. The most significant harm was liver enzyme elevation requiring treatment with corticosteroids in 79% of patients for a mean duration of 35 weeks.[10] For this gene therapy as well, there remains considerable uncertainty about the long-term net benefits of valoctocogene roxaparvovec because of the uncontrolled study design, small numbers of patients studied, and relatively short follow-up. There are also the same uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma. Unlike the gene therapy for hemophilia B, however, there is greater uncertainty about the durability of effect, with factor levels dropping almost 50% between months 12 and 24 (Table 1). The longer-term trajectory of factor levels, and subsequent impact on bleeding, are important unknowns for valoctocogene roxaparvovec.

There is no direct evidence comparing valoctocogene roxaparvovec with emicizumab. However, unadjusted indirect comparison of results from phase III trials suggests that the short-term reduction in bleeding rates with valoctocogene roxaparvovec is at least as great as that observed with emicizumab.[9] Differences in the patient populations studied in these trials could be responsible for the observed benefits; therefore, we could not conduct a more formal indirect comparison and draw any definitive conclusions about the comparative effectiveness of the 2 therapies.

LONG-TERM COST-EFFECTIVENESS

We developed separate decision analytic models for each gene therapy among patients without inhibitors by looking at costs and effects from the health care sector perspective and a full

lifetime horizon. In addition, as both treatments being evaluated are one-time gene therapies, we incorporated ICER's High-Impact Single and Short-Term Therapies framework,[11] including specific scenario analyses looking at optimistic and conservative assumptions about the duration of effect and different ways to "share" the value of cost offsets between the manufacturer and the health system. Furthermore, a specific outcomes-based warranty design suggested by the manufacturer of valoctocogene roxaparvovec was incorporated as the base case pricing assumption for that therapy.

The models were informed by key clinical trials, real-world evidence, previous relevant economic models, other published studies on hemophilia A and B, and stakeholder input. A detailed description of each model and key assumptions can be found in the full report: https://icer.org/wp-content/uploads/2022/05/ICER_Hemophilia_Final_Report_12222022.pdf.

Using a traditional analysis that assigns the full amount of any cost offset of therapy to the value of the therapy, we found that both etranacogene dezaparvovec at $3,500,000 and valoctocogene roxaparvovec at a placeholder price of $2,500,000 were dominant treatments with substantial cost savings compared with prophylactic factor therapy or eculizumab (hemophilia A only). These findings were robust to numerous sensitivity analyses and scenario analyses.

However, our primary approach to determining a Health Benefit Price Benchmark (HBPB) adopted a different scenario in which cost offsets are not fully assigned to the manufacturer. We argue that alternative scenarios are more policy relevant in situations in which a large percentage of the traditional HBPB comes from cost offsets of therapies such as factor replacement that have prices that are not believed to be aligned with benefits to patients. In this case, our analyses showed that more than 99% of the HBPB for both valoctocogene roxaparvovec and etranacogene dezaparvovec calculated from traditional cost-effectiveness analysis comes from cost offsets of eliminating the need for future factor prophylaxis. Therefore, we calculated HBPB ranges for these therapies using a $150,000 annual cap on offsets, a method proposed in our previously published framework for evaluations of single-time therapies.[11] Using this alternative method, for valoctocogene roxaparvovec, the HBPB is approximately $2,000,000, and for etranacogene dezaparvovec, the HBPB is approximately $3,000,000 (Table 2).

TABLE 2 Threshold Price With Savings Capped at $150,000 per Year

	Unit price to achieve $50,000 per QALY gained	Unit price to achieve $100,000 per QALY gained	Unit price to achieve $150,000 per QALY gained	Unit price to achieve $200,000 per QALY gained
Hemophilia B				
Etranacogene dezaparvovec	$2,894,000	$2,926,000	$2,958,000	$2,990,000
Hemophilia A				
Valoctocogene roxaparvovec	$1,951,000	$1,956,000	$1,961,000	$1,966,000

QALY = quality-adjusted life year.

LIMITATIONS OF THE COST-EFFECTIVENESS MODEL

Both gene therapies were evaluated in small, single-arm trials of limited duration. Factor VIII levels fell steadily with time following treatment with valoctocogene roxaparvovec, so the long-term benefits are uncertain. The decline in factor IX levels appeared slower following treatment with etranacogene dezaparvovec, but follow-up was limited, so our projections may not be accurate. Finally, we used a placeholder price for valoctocogene roxaparvovec as it has not been approved by the FDA.

Policy Discussion

The CTAF is one of the independent appraisal committees convened by ICER to engage in the public deliberation of the evidence on the clinical and cost-effectiveness of health care interventions. The CTAF is composed of 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. In addition, 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 gene therapies for hemophilia was the subject of a CTAF meeting on November 18, 2022. Following the discussion, the CTAF panel members deliberated on key questions raised by ICER's report (Table 3). For the population of patients with hemophilia B, the panel voted 10 to 2 that the evidence was adequate to demonstrate that the net health benefit of etranacogene dezaparvovec is superior to that provided by prophylaxis with factor IX. For the population of patients with hemophilia A, the panel voted 11 to 2 that the evidence was adequate to demonstrate that the net health benefit of valoctocogene roxaparvovec is superior

TABLE 3 California Technology Assessment Forum Votes on Comparative Clinical Effectiveness Questions for Hemophilia B and Hemophilia A

Question	Patient population	Yes	No
1			
Is the evidence adequate to demonstrate that the net health benefit of etranacogene dezaparvovec is superior to that provided by prophylaxis with factor IX?	Adults aged ≥18 years with hemophilia B without inhibitors who would be appropriate for routine prophylaxis with factor replacement.	10	2
2			
Is the evidence adequate to demonstrate that the net health benefit of valoctocogene roxaparvovec is superior to that provided by prophylaxis with factor VIII?	Adults aged ≥18 years with hemophilia A without inhibitors who would be appropriate for routine prophylaxis with factor replacement.	11	2
3			
Is the evidence adequate to distinguish the net health benefit between valoctocogene roxaparvovec and prophylaxis emicizumab?	Adults aged ≥18 years with hemophilia A without inhibitors who would be appropriate for routine prophylaxis with factor replacement.	0	13

TABLE 4 Votes on Contextual Considerations for Hemophilia B and Hemophilia A: When Making Judgments of Overall Long-Term Value for Money, What is the Relative Priority That Should be Given to Any Effective Treatment for Hemophilia A and B?

Contextual consideration	Very low priority	Low priority	Average priority	High priority	Very high priority
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability					
Hemophilia A	3	3	6	0	0
Hemophilia B	2	2	6	1	1
Magnitude of the lifetime impact on individual patients of the condition being treated					
Hemophilia A	0	0	1	8	4
Hemophilia B	0	0	0	6	7

to that provided by prophylaxis with factor VIII. All panel members voted that there was inadequate evidence to distinguish the net health benefit between valoctocogene roxaparvovec and emicizumab.

The CTAF 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 fully represented in analyses of clinical and/or cost-effectiveness. The results of these votes are shown in Tables 4-6. They highlight several factors beyond the results of cost-effectiveness modeling that the CTAF panel felt were particularly important for judgments of the overall long-term value for money of treatments for hemophilia. A majority of the panel voted that etranacogene dezaparvovec would have a major positive effect on patient's ability to achieve major life goals related to education, work, or family life and a minor positive effect on a caregiver's ability to achieve such goals. Despite the intense monitoring required in the first year of treatment, a majority of the panel voted that etranacogene dezaparvovec would have a major positive effect on patients' ability to manage and sustain treatment. For valoctocogene roxaparvovec, most panel members voted that this treatment would have a minor positive effect on patients' ability to achieve major life goals and their ability to manage and sustain treatment given the complexity of regimen.

The final votes on the long-term value for money reflect the integration of the contextual considerations, other potential benefits, and the cost-effectiveness results. For patients with hemophilia A, the 13 CTAF members were asked to consider a price of $4,000,000 for etranacogene dezaparvovec based on the input from the manufacturer. A majority of the panel (12 of 13) voted that etranacogene dezaparvovec provides low to intermediate long-term value at that price (Table 6). Because no price was available for valoctocogene roxaparvovec, no vote was taken on its long-term value for money.

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/2022/05/ICER_Hemophilia_Final_Report_12222022.pdf.

Several key policy recommendations follow:

1. The value of high-impact single and short-term therapies should not be determined exclusively by estimates of long-term cost offsets, particularly when the existing standard of care is acknowledged to be priced significantly higher than reasonable, cost-effective levels.

TABLE 5 Votes on Other Benefits for Hemophilia B and Hemophilia A

Potential other benefit or disadvantage	Major negative effect	Minor negative effect	No difference	Minor positive effect	Major positive effect
What are the relative effects of etranacogene dezaparvovec vs prophylaxis with factor IX on the following outcomes that inform judgment of the overall long-term value for money of etranacogene dezaparvovec?					
Patients' ability to achieve major life goals related to education, work, or family life	0	0	1	2	10
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	0	11	2
Patients' ability to manage and sustain treatment given the complexity of regimen	0	0	0	4	9
What are the relative effects of valoctocogene roxaparvovec vs prophylaxis with emicizumab on the following outcomes that inform judgment of the overall long-term value for money of valoctocogene roxaparvovec?					
Patients' ability to achieve major life goals related to education, work, or family life	0	0	3	9	1
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	9	3	1
Patients' ability to manage and sustain treatment given the complexity of regimen	0	0	1	9	2

TABLE 6 California Technology Assessment Forum Votes on Long-Term Value for Money at Current Prices for Hemophilia A

Question	Low long-term value for money at current pricing	Intermediate long-term value for money at current pricing	High long-term value for money at current pricing
Given the available evidence on comparative effectiveness, incremental cost-effectiveness, and potential other benefits or disadvantages, what is the long-term value for money of treatment at current pricing with etranacogene dezaparvovec vs prophylaxis with factor IX?	5	7	1

2. Payers should work with manufacturers to develop and implement outcomes-based agreements to address the uncertainty and the high cost of gene therapies for hemophilia. Although there are important practical challenges, the best approach available for US payers to address the uncertainty and high cost of gene therapies is to work with manufacturers to develop and implement outcomes-based agreements. An important principle in this effort should be to start with a fair price. Although manufacturers hold substantial leverage in price negotiation over promising gene therapies, they should not set prices beyond reasonable levels linked to cost-effectiveness analyses simply to cover the costs of paying back higher rebates should treatments not meet expected targets for safety or durability of benefits.
3. Step therapy is not a reasonable consideration for gene therapy for hemophilia. At least 1 national payer has suggested to patient representatives that step therapy with emicizumab is being considered prior to provision of coverage for valoctocogene roxaparvovec. Clinical experts and patient experts view this approach as lacking any clinical justification and appears to be only a method for trying to avoid the high 1-time fee for gene therapy while assuming that patients may switch insurers before the cost-saving potential of gene therapy is fully realized.

DISCLOSURES

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