

THEMES AND RECOMMENDATIONS

	Evidence Rating	Health-Benefit Price Benchmark
Etranacogene Dezaparvovec	B+ (when compared to factor prophylaxis)	\$2.93 M – \$2.96 M
Valoctocogene Roxaparvovec	C++ (when compared to factor prophylaxis) I (when compared to emicizumab)	\$1.96 M

“Hemophilia is a serious, lifelong disease, that leads to pain and disability as a result of repeated bleeds into joints and muscles, and can limit options for education, employment, and recreation. Prophylaxis with factor replacement is burdensome and does not achieve normal clotting although, for patients with hemophilia A, emicizumab has reduced burdens and improved outcomes. The new gene therapies can result in successfully treated patients appearing ‘cured’ for at least a period of time. During this period, these gene therapies will eliminate the need for expensive prophylactic treatment. However, the duration of this ‘cure’ and the safety of therapies remain important uncertainties. At least with valoctocogene roxaparvovec, patients will eventually return to needing prophylaxis.”

– ICER’s Chief Medical Officer, David Rind, MD

THEMES AND RECOMMENDATIONS

- 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.
- 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.
- Because of the novelty of gene therapy and the uncertainties about the long-term benefits and harms of these interventions, all patients treated with gene therapy should be enrolled in long term follow-up registries.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Hemophilia A and B are conditions of increased tendency to bleed due to inherited deficiencies of factor VIII and factor IX, respectively, which disrupt the clotting cascade. Both have X-linked recessive inheritance, and so predominately affect males. Approximately 76% of all male hemophilia patients in the US have hemophilia A and the remainder have hemophilia B. The exact prevalence of hemophilia in the United States (US) is not known, but is estimated to be around 30,000 to 33,000.

Patients with both 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. 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 have typically administered factor concentrate intravenously several times each week. Several factor preparations are available for prophylaxis, some prepared from human plasma, some prepared using recombinant technology including some with modifications to extend the half-life of the therapy. Many patients with hemophilia A now use a non-factor replacement therapy, emicizumab, a monoclonal antibody that can be administered monthly by subcutaneous injection, for prophylaxis in preference to factor VIII; no similar prophylaxis is currently available for hemophilia B.

Valoctocogene roxaparvovec (Valrox) is an adeno-associated virus serotype 5 (AAV5) mediated gene therapy for hemophilia A. It is a one-time infusion of a B-domain-deleted factor VIII gene to cells in the liver, resulting in production of an active variant of factor

VIII.

Etranacogene dezaparvovec (Etranadez) is an AAV5-mediated gene therapy for hemophilia B. It is a one-time infusion of the highly active Padua variant of the gene for factor IX to cells in the liver, resulting in production of an active variant of factor IX.

Etranacogene Dezaparvovec Compared with Factor IX Prophylaxis in Adults with Hemophilia B

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. No patients successfully treated with etranacogene dezaparvovec had to go back on factor prophylaxis during the first 18 months of therapy. It is not yet clear that the initial increase in factor IX levels will be maintained for decades, though the results are encouraging. Finally, the reduction in burden of therapy – no longer needing weekly or more frequent IX factor therapy is a major benefit for patients. 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. We conclude that there is moderate certainty of a small or substantial health benefit with high certainty of at least a small net health benefit (B+) for etranacogene dezaparvovec compared with factor IX prophylaxis.

Valoctocogene Roxaparvovec Compared with Emicizumab in Adults with Hemophilia A

There is no direct evidence comparing valoctocogene

Clinical Analyses

roxaparvovec with emicizumab. Indirect evidence suggests that the short-term reduction in bleeding rates with valoctocogene roxaparvovec compared with factor prophylaxis are at least as great as that observed with emicizumab compared with factor prophylaxis. However, differences in the patient populations studied in the trials could be responsible for the observed benefits. Furthermore, there are clear initial adverse events with valoctocogene roxaparvovec (high risk of elevated liver enzymes requiring prolonged corticosteroid therapy). 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 valoctocogene roxaparvovec compared with emicizumab. In particular, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma. Finally, as factor levels have been observed to decline over time, the benefits of valoctocogene roxaparvovec could be relatively short-lived. The lack of direct data comparing the two therapies, the small number of treated patients, and the modest long-term follow-up leave considerable uncertainty about the net health benefits. Thus, we conclude that there is low certainty about the net health benefit (I) for valoctocogene roxaparvovec compared with

emicizumab.

Valoctocogene Roxaparvovec Compared with Factor VIII Prophylaxis in Adults with Hemophilia A

In ICER's 2020 review of valoctocogene roxaparvovec compared with factor VIII prophylaxis, we gave valoctocogene roxaparvovec a promising, but inconclusive (P/I) rating. It is clear that some patients get a significant benefit, while others get minimal to no benefit from valoctocogene roxaparvovec. 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 valoctocogene roxaparvovec compared with factor VIII prophylaxis. In particular, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma. Finally, as factor levels have been observed to decline over time, the benefits of valoctocogene roxaparvovec could be relatively short-lived. Thus, we conclude that there is moderate certainty of a comparable, small, or substantial health benefit with high certainty of at least a comparable net health benefit (C++) for valoctocogene roxaparvovec compared with factor VIII prophylaxis.

Economic Analyses

LONG-TERM COST EFFECTIVENESS

We conducted an economic evaluation of etranacogene dezaparvovec for the treatment of hemophilia B patients without inhibitors compared with prophylactic treatment. We also updated our economic evaluation of valoctocogene roxaparvovec for the treatment of hemophilia A patients without inhibitors compared with emicizumab.

Lifetime costs for the gene therapies as well as for

the comparators in each model were substantial. Using a traditional analysis that includes the full cost offset of standard of care, we found that both etranacogene dezaparvovec at a price of \$3,500,000 and valoctocogene roxaparvovec at a placeholder price of \$2,500,000 were dominant treatments with substantial cost savings along with projected gains in quality adjusted life years. These findings were robust to numerous sensitivity analyses and scenario analyses.

Economic Analyses

ICER has concluded that in a situation where a large percentage of the traditional Health Benefit Price Benchmark (HBPB) comes from cost offsets of therapies that, themselves, have prices that are not believed to be aligned with benefits to patients, ICER will present ranges from shared savings calculations as the most policy-relevant HBPBs. We calculate that more than 99% of the traditional HBPB results for both valoctocogene roxaparvec and etranacogene

dezaparvec come from offsetting the price of prophylaxis with existing agents that cost far in excess of \$300,000 per year.

In shared savings scenarios that use an annual cap of \$150,000 on cost offsets, for valoctocogene roxaparvec the HBPB is \$1.96 million and for etranacogene dezaparvec the HBPB is \$2.93 million to \$2.96 million.

POTENTIAL BUDGET IMPACT

All patients could be treated with etranacogene dezaparvec at price without crossing the annual budget impact threshold. As the HBPB range for etranacogene dezaparvec is lower than its price, this estimate held true for HBPB price estimates as well. At its price, etranacogene dezaparvec accounted

for 49% (\$377 million) of the annual budget impact threshold of \$777 million. These findings were driven by the high costs of factor therapy at baseline (i.e., “current” budget impact analysis scenario).

Public Meeting Deliberations

VOTING RESULTS

For adults ≥ 18 years of age with hemophilia B without inhibitors who would be appropriate for routine prophylaxis with factor replacement:

- A majority of panelists (10-2, 1 abstained) found that the evidence is adequate to demonstrate a net health benefit of etranacogene dezaparvec compared to prophylaxis with Factor IX.

For adults ≥ 18 years of age with hemophilia A without inhibitors who would be appropriate for routine prophylaxis with factor replacement:

- A majority of panelists (11-2) found that the evidence is adequate to demonstrate a net health benefit of valoctocogene roxaparvec compared to prophylaxis with Factor IX.

- All panelists (13-0) found that the evidence is not adequate to demonstrate a net health benefit of valoctocogene roxaparvec compared to prophylaxis with emicizumab.

During their deliberations, panel members also weighed the therapy’s other potential benefits, disadvantages, and contextual considerations. Voting highlighted the following as particularly important for payers and other policymakers to note:

- Magnitude of the lifetime impact on individual patients;
- Patients’ ability to achieve major life goals related to education, work, or family life;
- Caregivers’ quality of life and/or ability to achieve major life goals related to education,

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work, or family life;

- Patients' ability to manage and sustain treatment given the complexity of regimen.

After reviewing the clinical evidence and considering the treatments' other potential benefits, disadvantages, and contextual considerations noted above, the CTAF evaluated the long-term value of etranacogene dezaparovec at a manufacturer-suggested price of \$4 million (higher than the eventual list price of \$3.5 million):

- At a price of \$ 4 million, a majority of panelists found that etranacogene dezaparovec compared to prophylaxis with Factor IX represents "low-to-intermediate" long-term value for money.

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.org).