Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Final Policy Recommendations

December 22, 2022

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the CTAF public meeting on the use of etranacogene dezaparvovec and valoctocogene roxaparvovec for the treatment of hemophilia B and A. At the meeting, ICER presented the findings of its revised report on these treatments and the CTAF voting council deliberated on key questions related to their comparative clinical effectiveness, potential other benefits and contextual considerations, and long-term value for money at current prices. Following the votes, ICER convened a Policy Roundtable of two patients, two clinical experts, two payers, and two representatives from pharmaceutical manufacturers to discuss how best to apply the evidence and votes to real-world practice and policy. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed here, and a recording of the voting portion of the meeting can be accessed here. More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's report on these treatments, which includes the same policy recommendations, can be found here.

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

All Stakeholders

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.

New single and short-term therapies offer the potential for significant health gains for patients, including in some cases the possibility of a lifelong cure from a chronic illness. The value of such treatments is substantial, in part because they may obviate the need for years of expensive chronic care. But that value must be tempered by several considerations. First, at launch only relatively short-term data are available, and therefore there is relatively high uncertainty regarding the durability of the beneficial treatment effect, while unknown long-term risks are also possible. And second, when the costs of the current standard of care exceed levels that reflect the opportunity cost for new treatments in the health system, simply aggregating those costs over the lifetime of patients and assigning all potential cost offsets to the "value" of the new one-time therapy,

magnifies the existing distortion of value and pricing in the US health care system, denying the chance for the health system to recoup some of the cost savings so that innovation can be kept more affordable for all patients. Assigning the full cost offset to the single price of a gene therapy also creates a distortion in the incentives for innovation, skewing them strongly away from addressing conditions that are either fatal in the short term, such as genetic diseases of newborns, or that have few added health care costs, such as blindness. As one of the CTAF voting members said at the public meeting "*Today we had to consider a standard of care that is priced at levels that are not consistent with our society's views. Although the easiest thing to do is to endorse anything cheaper than that, I think in doing so we will encourage unsustainable pricing that will limit the care we can provide to all patients."*

Given these contextual factors, all stakeholders and policymakers should avoid using traditional cost-effectiveness analysis alone as a guide to considerations of fair pricing. Capping credit for cost offsets in some way should be explored further as an alternative approach to calculating ranges of fair pricing. This report provided several different scenarios of ways to "share savings" from a potential cure. These options and other ways to address these broader questions should be considered today to prepare for "fair pricing" of the cures of tomorrow.

Payers

Recommendation 1

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.

Payers should ensure that they have addressed key details when operationalizing any outcomes-based agreement for gene therapies for hemophilia. The outcomes used to define treatment failure need to be clear and should include both low factor levels and clinical bleeding. Failing by either criterion should trigger the rebate or warranty provision. Payers may also want to negotiate to have the manufacturer at risk for full coverage of any factor therapy used during the warranty period. In addition, just as patients with their providers decide whether and when to choose gene therapy, they should be empowered to decide when gene therapy has failed, and the patient should have no barriers in receiving coverage for resuming factor prophylaxis. It should be noted

that patients treated with gene therapy will still require on-demand factor therapy, which should be available when needed for situations such as trauma and surgery in addition to spontaneous bleeding episodes.

Because small employers are at risk for severe financial toxicity if one or two of their covered employees/families require a gene therapy, payers should consider offering programs that protect plan sponsors (and their employees) by mechanisms such as carved out PMPM coverage plans for cell and gene therapies.

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy: https://icer.org/wpcontent/uploads/2020/11/Cornerstones-of-Fair-Drug-Coverage-_-September-28-2020.pdf

Drug-specific Coverage Criteria

Coverage Criteria Considerations for Etranacogene dezaparvovec for Hemophilia B.

Patient Eligibility Criteria

a. **Diagnosis**: Hemophilia B is often diagnosed in infancy based on testing performed at birth if there is a maternal family history or if there is clinical concern raised by bleeding. Repeated testing to confirm eligibility is not necessary.
b. **Clinical eligibility**: Patients eligible for gene therapy will likely be all patients with "severe phenotype" hemophilia B (nearly all patients with "severe" hemophilia B as defined by a factor activity level <1%) and some patients with "moderate" hemophilia B as defined by a factor activity level between 1% and 5%. Clinical experts argue that phenotype is the most important way to determine when patients with factor activity level between 1% and 5% require factor IX prophylaxis, but some payers may wish to establish a specific factor level (e.g. 2%) below which all patients qualify for coverage, whereas patients with higher factor level will require some history of use of prophylaxis based on bleeding history. Because of the limited evidence base, it is highly likely that payers will limit coverage to patients matching the inclusion criteria of the phase 3 clinical trial: males ≥ 18 years of age currently on a stable dose of factor IX prophylaxis with at least 150 exposure days of prophylaxis with factor IX.
c. **Exclusions**: Clinical experts and patient representatives have argued for many years that payers should not exclude patients who have never bled from receiving prophylaxis and should not require a specific number or location of bleeds for coverage of prophylaxis or gene therapy. Exclusion criteria from the pivotal clinical trial include the presence of factor IX inhibitors, uncontrolled HIV, and active hepatitis B or C infection.

Step Therapy

There are no other treatments other than factor prophylaxis and therefore the potential for step therapy is not applicable.

Provider Qualification Restrictions

a. **Payers should require that the delivery of gene therapy with *etranacogene dezaparvovec* be done by or in consultation with a Hemophilia Treatment Center (HTC).** Gene therapy is in its infancy and patients may only get one chance to be treated, at least with an AAV-vector delivery system. In addition, the initial monitoring and management are unique and are best delivered by experienced centers. Payers should be vigilant to ensure that patients who live far from an HTC have adequate coverage of travel or other necessities required to be able to access care.

Duration of coverage and renewal criteria:
Not applicable as this is a one-time therapy.

Coverage Criteria Considerations for Valoctocogene roxaparvovec for Hemophilia A.

Patient Eligibility Criteria

a. **Diagnosis**: Hemophilia A is often diagnosed in infancy based on testing performed at birth if there is a maternal family history or if there is clinical concern raised by bleeding. Repeated testing to confirm eligibility is not necessary.
d. **Clinical eligibility:** If approved by the FDA, patients eligible for gene therapy will likely include all patients with "severe" hemophilia A. One way to define severe hemophilia A is reflected in the phase 3 clinical trial eligibility criteria: patients with factor activity level <1%. Because of the limited evidence base and high cost, payers are likely to limit coverage to patients matching this and other inclusion criteria of the phase 3 clinical trial, but payers should expand coverage criteria to include patients currently on emicizumab prophylaxis: males ≥ 18 years of age currently on a stable dose of factor VIII or emicizumab prophylaxis for ≥12 months and with at least 150 exposure days of prophylaxis with factor VIII if that is the chosen prophylactic therapy.
e. Payers should also consider whether to include coverage provisions for some patients with factor activity level between 1% and 5%. Clinical experts argue that phenotype is the most important way to determine when patients with factor activity level between 1% and 5% require factor VIII prophylaxis, and therefore payers should consider providing coverage for patients with factor levels between 1% and 5% if they are on routine prophylaxis due to a history of significant bleeds.
f. **Exclusions**: Clinical experts and patient representatives have argued for many years that payers should not exclude patients who have never bled from receiving prophylaxis and should not require a specific number or location of bleeds for coverage of prophylaxis or

gene therapy. Exclusion criteria from the pivotal clinical trial include the presence of factor VIII inhibitors, uncontrolled HIV, and active hepatitis B or C infection.

Step Therapy

At least one national payer has suggested to patient representatives that step therapy with emicizumab is being considered prior to provision of coverage for Valrox. 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 one-time fee for gene therapy while assuming that patients may switch insurers before the cost-saving potential of gene therapy is fully realized. In short, step therapy does not appear to be a reasonable consideration for this treatment.

Provider Qualification Restrictions

a. **Payers should require that the delivery of gene therapy with *valoctocogene roxaparvovec* be done by or in consultation with a Hemophilia Treatment Center (HTC).** Gene therapy is in its infancy and patients may only get one chance to be treated, at least with an AAV-vector delivery system. In addition, the initial monitoring and management are unique and are best delivered by experienced centers. Payers should be vigilant to ensure that patients who live far from an HTC have adequate coverage of travel or other necessities required to be able to access care.

Duration of coverage and renewal criteria:
Not applicable as this is a one-time therapy.

Manufacturers

Recommendation 1

The pricing in the US of all factor replacement therapies and of emicizumab represents a failure of competition and is far too high, even considering the substantial benefits of prophylaxis 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. Concrete steps by the federal government are likely needed to achieve prices more reasonably aligned with patient benefit.

Factor prices have not come down despite competition among multiple products and the loss of 60% of overall market share of factor VIII therapy to emicizumab. There are several different options for addressing the lack of market forces to restrain pricing. The US could follow the European model of having the government ask companies to compete for a sole tender and pick a single or a more limited set of factor products, using a competitive bidding process to keep prices closer to a reasonable alignment with overall patient benefit. Alternatively, in the multi-payer commercial insurance market, PBMs and health plans could seek to use the same approach to seek

deeper rebates using narrower formularies, but even large PBMs are likely to lack the market power to restrict access in this way. Perhaps the best way to maintain broad access to multiple agents within a more affordable framework would be for the US to negotiate or set price ceilings for all factor agents based on value assessment. This approach would retain substantial incentives for future innovation, particularly for one-time curative therapies, but would ensure that the prices paid for hemophilia treatment accomplishes more good than the harm that arises from increasing health insurance costs for vulnerable individuals.

Patient Organizations

Recommendation 1

Patient organizations are to be praised for their proactive development of objective descriptions of the risks and benefits of gene therapies to support shared decision-making for every patient.

The hemophilia patient community is particularly sophisticated in their understanding of the uncertainties and potential harms of novel therapies given the devastating experience of the community with hepatis C and HIV infections. Patient groups should continue to collaborate to develop education materials that educate patients about the potential risks and benefits of gene therapies and continue their work with other stakeholders to develop and disseminate evidence-based, balanced materials that are accessible to all patients, including those with low health literacy. It is essential that patients receive a consistent set of information about the potential benefits and harms from advocacy organizations, their health care providers and from the manufacturers to ensure true shared decision-making when considering an irreversible treatment like gene therapy.

Recommendation 2

Patient organizations have a powerful voice and should apply it to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system.

We applaud the National Hemophilia Foundation, Hemophilia Foundation of America, and the Coalition for Hemophilia B for their joint public comments on our draft report highlighting that 'the current cost of hemophilia treatment is "financially toxic" for PwH, their families, and the health care systems on which they depend. The finding that gene therapy is cost effective does not mean it is affordable, that it will be accessible within the marketplace post- approval, or that it is an optimal treatment for every eligible patient. We remain concerned that high target prices will impede access to these potentially transformative therapies.'

Patient groups should also take responsibility to publicly promote both improved access and fair pricing of new therapies for Hemophilia A and B. Patient groups should additionally follow-up such

statements with organized campaigns to advocate for fair pricing, for example, by encouraging patients and families to write to Congress or launch public relation campaigns with such messaging.

Patient groups should also continue their efforts to ensure that patients are aware of programs to assist them and their families with insurance coverage and care. For example, patients over the age of 21 in California may be eligible for coverage and other assistance under the Genetically Handicapped Persons Program (GHPP). Living with Hemophilia is challenging for all, but especially those with socioeconomic barriers, and to improve health equity within the hemophilia community special efforts should be made to reach out to individuals and families who may not be as "plugged in" to current options for best care.

Researchers/Regulators

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.

Currently we have only two to three years of follow-up for patients enrolled in the phase 3 clinical trials of these two gene therapies for hemophilia. We need much longer follow-up to better understand the benefits and potential harms of these therapies. Both cancer incidence and liver disease as well as factor levels and bleeding rates merit particular focus in these studies. Given the rarity of hemophilia and expected incidence of potential harms, all gene therapy recipients should be enrolled in a longitudinal global research / surveillance registry. Regulators should require manufacturers to underwrite the cost of these registries.

Because of the novelty of gene therapy, the complexity of its delivery, and ongoing safety concerns, the FDA should put in place a Risk Evaluation and Mitigation Strategy (REMS) as requested by the National Hemophilia Foundation on July 1, 2022 for both etranadez and valrox.

Specifically, the NHF requested that the FDA should include the inclusion and exclusion criteria from the phase 3 trials in the labeling of the therapies. In addition, there should be a certification process for each center that administers these gene therapies and specific training for physicians and other healthcare providers delivering gene therapy and following patients after they have received gene therapy. The intent of the proposed REMS is to ensure safe and appropriate use of the gene therapy.

Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the November 18 Public meeting of CTAF.

Appendix Table 1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Belen Herce-Hagiwara, BA,* Research Assistant, ICER	**David Rind, MD, MSc**,* Chief Medical Officer, ICER
Yasmine Kayali, BA,* Program Coordinator, ICER	**Liis Shea, MA,*** Program Director, ICER
Shahariar Mohammed Fahim, PhD,* Research Lead, Evidence Synthesis, ICER	**Jeff Tice, MD,*** Professor of Medicine, ICER
Ashton Moradi, PharmD, MS,* Health Economist, ICER	**Surrey Walton, PhD**,* Professor, College of Pharmacy-Pharmacy Systems Outcomes and Policy, UIC

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Appendix Table 2. CTAF Panel Member Participants and COI Disclosures

Participating Members of CTAF	
Ralph G. Brindis, MD, MPH* Clinical Professor of Medicine, UCSF	**Jeffrey Klingman, MD*** Chair of Neurology, Kaiser Permanente Northern California
Felicia Cohn, PhD* Bioethics Director, Kaiser Permanente Orange County	**Joy Melnikow, MD, MPH*** Professor emeritus, UC Davis
Robert Collyar* Patient Advocates in Research (PAIR)	**Ann Raldow, MD, MPH*** Assistant Professor, Department of Radiation Oncology at UCLA
Sanket Dhruva, MD, MHS* Assistant Professor of Medicine, UCSF	**Rita F. Redberg, MD, MSc*** Professor of Medicine, UCSF
Rena K. Fox, MD* Professor of Medicine, UCSF	**Richard Seiden, JD*** Patient Advocate, Retired Partner, Foley & Lardner LLP
Kimberly Gregory, MD, MPH* Vice Chair OB GYN Cedars-Sinai	**Anthony Sowry, BA*** Patient Advocate and Lead Volunteer, National Patient Advocate Foundation
Paul Heidenreich, MD* Professor Medicine, Stanford University	

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Appendix Table 3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Debbie Bensen-Kennedy, MD, CSL Behring	Dr. Bensen-Kennedy is a full-time employee of CSL Behring.

Chuck Bucklar, BS, BioMarin	Mr. Bucklar is a full-time employee of BioMarin.
Miguel A. Escobar, MD, McGovern School of Medicine	Dr. Escobar has received honoraria from NovoNordisk, CSL Behring, Genentech, Biomarin, Sanofi, Takeda, Pfizer, NHF, Bayer, Hemabiologics/LFB, UniQure, Magellan.
Leslie Fish, PharmD, IPD Analytics	Dr. Fish is a full-time employee of IPD Analytics.
Brian O'Mahony, FACSLM, Irish Hemophilia Society	Mr. O'Mahony has received consulting fees or honoraria from Bayer Healthcare and BioMarin.
Margaret Ragni, MD, MPH, University of Pittsburgh Medical Center, Hemophilia Center of Western PA	Dr. Ragni is a member of BioMarin Advisory Board; Consultant, Advisory Board member and Symposium Speaker for Takeda. Her university also receives funding from Biomarin and SPARK.
Michael Sherman, MD, MBA, MS, Point32Health	Dr. Sherman is a full-time employee of Point32Health.
Mark Skinner, JD, Institute for Policy Advancement Ltd.	Mr. Skinner has received honoraria from F. Hoffman-La Roche / Genentech, Bayer Healthcare, BioMarin, Novo Nordisk and the Blue Cross Blue Shield Association.