Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A without Inhibitors: Final Policy Recommendations

November 20, 2020

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the October 30, 2020 New England CEPAC public meeting on valoctocogene roxaparvovec and emicizumab for Hemophilia A. At the meeting, ICER presented the findings of its revised report on these treatments and the New England 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 patient experts, two clinical experts, two payers, and three representatives from a pharmaceutical manufacturer 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.

Manufacturers

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.

Factor VIII prices have not come down despite multiple products and the loss of 60% of overall market share to emicizumab. There are several different options for solving this. 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 VIII 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 VIII 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 on vulnerable individuals.

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.

The revenues received by drug companies for factor VIII were already substantial when the accepted minimal standard of care was to seek a 1% trough level. As insurers have moved to cover higher doses to achieve 3-5% troughs it would not be unreasonable to ask drug makers to commit to a shared responsibility for affordability by reducing their prices so that the overall costs of care are held stable while patients and clinicians determine what the optimal trough level should be for each individual patient.

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.

The request by the FDA for longer-term data on valoctocogene roxaparvovec highlights the fact that the beneficial effects of some gene therapies may not be durable over the intermediate or long term. Given the decline in factor VIII seen over time with valoctocogene roxaparvovec, and the concerns that gene therapies may have potential harms and may induce immunity to the particular viral vector employed, it is clear that trials must be continued long enough to provide adequate information on the stability and durability of benefits for regulators, patients, clinicians, and payers to judge the relative balance of these benefits to any potential risks. The time horizon for trials will need to be tailored to the specific mechanism of action and early data. For all emerging gene therapies, results should be made public as they become available and should be published and not simply promulgated through press releases showing top line results.

Manufacturers and Researchers

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

To adequately assess prophylactic therapies for hemophilia, randomized trials need to be performed comparing therapies to each other with outcomes including quality of life and pain. Use of validated measures for quality of life that are sensitive to patient experiences and can be translated into patient utilities would help patients, clinicians, and health technology agencies in

assessing therapies. When evaluating gene therapies, the coreHEM outcome set developed with input from multiple stakeholders, including patients and patient groups, is an appropriate starting point; more extensive capture of patient-important outcomes will enhance value assessment.

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

Evidence on development of factor VIII inhibitors is critically important. Until this evidence is available, it will be difficult to accurately value emicizumab.

Payers

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

All payers should be aware of the widespread consensus among clinical experts and patient organizations that a trough factor VIII level of 3%-5% should be viewed as a minimum target for the vast majority of patients. Clinical experts highlighted that many patients may require higher trough levels depending on their life activities and because individual patients can exhibit different bleeding tendencies at the same factor level. Flexibility is therefore necessary in implementing coverage criteria related to trough levels.

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 evaluate patterns of care and reach out to talk with clinicians who do not recommend emicizumab for eligible patients. The goal should be to share perspectives on the rationale for the use of emicizumab versus factor VIII.

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

Management of hemophilia is both complex and expensive, and HTCs provide consolidated expertise and care through a network of centers of excellence funded by the Federal Government.

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

Small employers are at risk for severe financial toxicity if one or two of their covered employees/families require a gene therapy, even if that gene therapy may be highly cost-effective over the long term. Payers should therefore consider offering programs that protect plan sponsors (and their employees) by mechanisms such as carved out PMPM coverage plans for cell and gene therapies.

Prior authorization criteria should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

Clinical Considerations for Emicizumab

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.
b. **Patient Population**: Patients eligible for prophylaxis are typically all patients with severe hemophilia A (factor activity level <1%) and some patients with moderate hemophilia A (factor activity level between 1% and 5%) based on clinical phenotype. Patients both with and without inhibitors to factor VIII typically benefit from prophylaxis. For patients who do not meet criteria for severe hemophilia A, payers will likely want to defer to clinicians as to which patients are appropriate for prophylaxis.
c. **Exclusions**: Payers should not exclude patients who have never bled from receiving prophylaxis and should not require a specific number or location of bleeds. A goal of management is to prevent bleeding in patients with severe hemophilia. Additionally, patients who are receiving emicizumab will continue to require access to factor VIII preparations in the event they bleed; emicizumab cannot be used to treat acute bleeds.

Step Therapy

Emicizumab will be preferred by many patients for prophylaxis, and it is a lower cost option from the payer perspective. Payers considering implementing formal step therapy, however, should recognize the heterogeneity of patient experience with factor VIII and its different delivery mechanism. In lieu of formal step therapy, payers may wish to contact clinicians at the time of initiation of prophylaxis if the initial prescription is for factor VIII instead of emicizumab to discuss the clinical situation.

Provider Qualification Restrictions

a. **Payers may wish to require that management of factor VIII be done by or in consultation with a Hemophilia Treatment Center.** Management of hemophilia is expensive, and HTCs provide consolidated expertise and care on a national level. In any case, patients with severe hemophilia A should be managed by, or in consultation with, a hematologist with expertise in clotting disorders.

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 recognize that high prices contribute to financial toxicity for the patients they represent, for other patients with other illnesses, and for all of society.

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

Patient groups should take pride in making it easy to find information on which drug companies and other health industry sources provide funding, and at what levels. This information should not be relegated to the dense forests of IRS forms or small print in annual reports. Hemophilia patient groups have much to be proud of in their independent voice, but they should match that heritage with a renewed commitment to purposeful transparency on their potential conflicts of interest.

Regulators

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

We heard from payers and clinical experts that real world costs of emicizumab can be substantially higher than the average net price because of vial wastage. We additionally heard that many countries outside the US require packaging that prevents substantial wastage of expensive medications.

All Stakeholders and Policy Makers

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

As life science companies get closer to bringing a wide range of gene therapies and other potential cures into clinical practice, the celebration that ensues will be shadowed by growing concerns about the affordability of these types of high-impact treatments. Traditional methods for value-based pricing recommendations shift money saved by a cure into the price given to the manufacturer. All stakeholders and policymakers should engage in an open dialogue on the extent to which society wishes to reward innovators more handsomely just because their cure is for a condition that is more expensive to treat. Should a cure arrive for hemophilia A, should the drug maker recoup all the money saved from prevented factor VIII use over decades of time? What proportion of those cost savings should be retained by the health system and used to reduce health insurance costs or pay for other new treatments? 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.

Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the New England CEPAC public meeting on October 30, 2020.

Table A1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Foluso Agboola, MBBS, MPH,* Director, Evidence Synthesis, ICER	**Cat Koola, MPH**, * Program Manager, ICER
Pamela Bradt, MD, MPH,* Chief Scientific Officer, ICER	**Steven D. Pearson, MD, MSc**,* President, ICER
Rick Chapman, PhD, MS,* Director of Health Economics, ICER	**David M. Rind, MD, MSc**,* Chief Medical Officer, ICER
Monica Frederick,* Program and Event Coordinator, ICER	**Danny Quach, PharmD**,* University of Illinois at Chicago College of Pharmacy
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*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.

Table A2. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Leslie Fish, RPh, PharmD, Vice President of Clinical Pharmacy, IDP Analytics	No financial conflicts to disclose.
Richard Ko, MD, MHS, MS, Head of Rare Blood Disorders, US Medical Affairs, Genentech, Inc.	Dr. Richard Ko is a full-time employee of Genentech, Inc.
Brian O'Mahony, Chief Executive, Irish Haemophilia Society, Patient Advocate	Brian O'Mahony has received fees for participation in advisory boards or educational activities from Bayer, BioMarin, Freeline, Roche and Uniqure.
Steven Pipe, MD, Pediatric Medical Director, Hemophilia and Coagulation Disorders Program, University of Michigan	Dr. Steven Pipe has received consulting fees from Apcintex, Bayer, BioMarin, Catalyst Biosciences, CSL Behring, HEMA Biologics, Freeline, Novo Nordisk, Pfizer, Roche/Genentech, Sangamo Therapeutics, Sanofi, Takeda, Spark Therapeutics, uniQure.
Margaret Ragni, MD, MPH, Professor of Medicine and Clinical and Translational Medicine, University of Pittsburgh	Dr. Margaret Ragni receives research funding (through the University of Pittsburgh) for gene therapy trials with SPARK, a gene therapy trial with BioMarin, and past gene therapy trial funding with Sangamo.
Mark Skinner, JD, President & CEO, Institute for Policy Advancement Ltd, Patient Advocate	*
Wing Yen Wong, MD, Group Vice President, Global Medical Affairs, BioMarin Pharmaceutical Inc	Dr. Wing Yen Wong is a full-time employee of BioMarin Pharmaceuticals.
John Watkins, PharmD, MPH, BCPS Formulary Manager, Premera Blue Cross	Dr. John Watkins is a full-time employee of Premera Blue Cross.
Todd Williamson, PhD, MSc, Vice President, Data Generation & Observational Studies, Bayer	Dr. Todd Williamson is a full-time employee of Bayer Pharmaceuticals.

*Mr. Skinner has received fees and honoraria of more than $5,000 for educational presentations and advisory board participation from F. Hoffman-La Roche / Genentech, Bayer Healthcare, BioMarin, and the Blue Cross Blue Shield Association. Mr. Skinner's household has or held equity interests in the following companies in the health sector: Cryosport, CVS Health, Editas Medicine, Horizon discovery, Illumina, Intellia Therapeutics, Intuitive Surgical, Johnson & Johnson (Sold), Novartis, Regeneron (Sold) and Teladoc Health. These holdings are independently managed by a financial advisor with instructions not to invest in companies with a known interest in therapies for bleeding disorders. Mr. Skinner is a member of the ICER Governing Board; Board of Directors of the World Federation of Hemophilia USA, which receives product and monetary donations for a global humanitarian aid program; serves as a consultant for the US National Hemophilia Foundation, and is a member of the NHF Scientific Advisory Council. Mr. Skinner is a Principal investigator for the Patient-Reported Outcomes and Burdens and Experiences (PROBE) study, which has received fees and grant support from Bayer, BioMarin, CSL-Behring, Freeline Therapeutics, Novo Nordisk, F. Hoffman-La Roche, Sanofi, Sobi, Takeda, uniQure. The PROBE study is an independent, investigator-led research project led by patients and patient advocacy organizations. Mr. Skinner is a person with severe hemophilia A.

Table A3. New England CEPAC Panel Member Participants and COI Disclosures

Participating Members of New England CEPAC	
Robert H. Aseltine, Jr., PhD (Chair)* Professor and Chair, Division of Behavioral Sciences and Community Health Director, Center for Population Health	**Kimberly Lenz, PharmD (ex-officio)*** Clinical Pharmacy Manager MassHealth
Rena Conti, PhD* Associate Research Director of Biopharma and Public Policy, Institute for Health System Innovation and Policy; Associate Professor, Questrom School of Business	**Greg Low, RPh, PhD*** Program Director, MGPO Pharmacy Quality and Utilization Program
Megan Golden, JD** Co-Director, Mission:Cure	**Eleftherios Mylonakis, MD, PhD, FIDSA*** Chief of the Infectious Diseases Division and Dean's Professor of Medicine, Warren Alpert Medical School of Brown University
Claudia B. Gruss, MD, FACP, FACG* Gastroenterologist and Internist, Western Connecticut Medical Group	**Stephanie Nichols, PharmD, BCPS, BCPP, FCCP*** Associate Professor of Pharmacy Practice University of New England College of Pharmacy
Claudio W. Gualtieri, JD* Advisor, Center to Champion Nursing in America	**Leslie Ochs, PharmD, PhD, MSPH*** Associate Professor of Social and Administrative Pharmacy, University of New England College of Pharmacy
Rebecca Kirch, JD* Executive Vice President, Health Care Quality and Value for the National Patient Advocate Foundation (NPAF)	**Jeanne Ryer, MSc, EdD*** Director, NH Citizens Health Initiative
Stephen Kogut, PhD, MBA, RPh* Professor of Pharmacy Practice University of Rhode Island College of Pharmacy	**Jason L. Schwartz, PhD*** Assistant Professor Department of Health Policy and Management, Yale School of Public Health
Tara Lavelle, PhD* Assistant Professor Center for the Evaluation of Value and Risk in Health at Tufts Medical Center	**Jason H. Wasfy, MD, MPhil*** Director, Quality and Outcomes Research, Massachusetts General Hospital Heart Center Medical Director, Massachusetts General Physicians Organization

*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.

** Mission: Cure has received grants from AbbVie for patient education and charitable support.