

Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value

Revised Background and Scope
February 25, 2020

Background

ICER reviewed emicizumab for hemophilia A in patients with factor inhibitors in 2018 ([Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value](#)). Much of the background information in this draft scoping document is reproduced from that report.

Hemophilia A is a condition of increased tendency to bleed due to an inherited deficiency of factor VIII, which disrupts the clotting cascade (Figure 1). Hemophilia A has X-linked recessive inheritance, and so predominately affects males. It is the most common of the hemophilias with an incidence of one in 5,000 male births.¹ The exact prevalence of hemophilia in the United States (US) is not known, but is estimated to be around 20,000.² Approximately 77% of all hemophilia patients in the US have hemophilia A.³

Patients with hemophilia A, 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 can lead to substantial disability.⁴ Hemarthroses cause ongoing joint inflammation and damage and also increase the likelihood of further bleeding into the same joint.

Severity of hemophilia A has generally been defined by factor levels (the percentage of normal factor that a patient has).⁵ However, severity based on factor levels does not perfectly correlate with actual clinical severity.⁶ Despite this, other severity classifications are not yet widely accepted, and factor levels define severity in most clinical trials. Using factor level classifications, severe disease is defined by factor VIII levels below 1% of normal.⁵ Patients with severe disease who are not receiving prophylactic treatment experience an average of 20 to 30 episodes of spontaneous bleeding or excessive bleeding after minor trauma per year.¹ Patients with moderate disease (factor VIII levels of 1% to 5% of normal) typically have delayed bleeding episodes after minor trauma several times per year, but only occasionally have spontaneous bleeding.⁷ Individuals with

mild disease (factor VIII levels between 5% to 40% of normal) typically have bleeding after procedures such as tooth extractions or surgery, or after significant injuries.

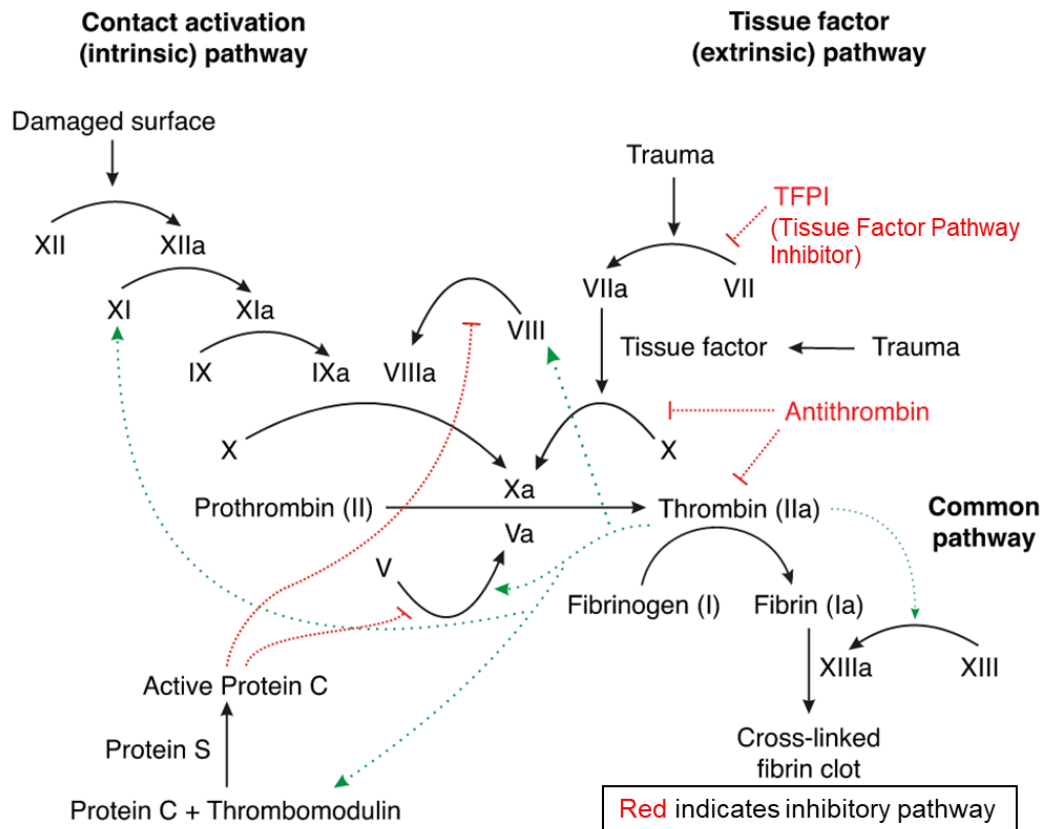
To reduce the risk of bleeding, patients with severe hemophilia A have typically administered factor VIII concentrate intravenously multiple times per week.^{7,8} The use of factor concentrates both as treatment and prophylaxis has dramatically altered the management and clinical course of patients with hemophilia A. However, prophylaxis with factor replacement is burdensome and does not maintain patients at normal levels of factor VIII. A number of factor VIII preparations are available for prophylaxis, some with modifications to extend the half-life of the therapy, some prepared from human plasma, and some prepared using recombinant technology.

Emicizumab-kxwh (Hemlibra[®], Genentech, referred to as “emicizumab” in this draft scope) is a monoclonal antibody with dual targets (“bispecific”) that allow it to bridge activated factor IX and factor X, the role normally played by activated factor VIII in the clotting cascade (Figure 1).⁹ Emicizumab was approved by the US Food and Drug Administration (FDA) as a prophylactic treatment for hemophilia A in patients who have inhibitors to factor VIII in 2017 and in those without inhibitors in 2018.¹⁰ Emicizumab is administered subcutaneously and may be dosed weekly, every two weeks, or every four weeks based on provider and patient preference.

ICER found in 2018 that in patients with factor inhibitors, prophylaxis with emicizumab was cost saving ([Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value](#)), even though the wholesale acquisition cost (WAC) of emicizumab was approximately \$482,000 for the first year of treatment and \$448,000 for subsequent years at the time.

Valoctocogene roxaparvovec is an adeno-associated virus serotype 5 (AAV5) mediated gene therapy for hemophilia A.¹¹ It delivers a B-domain-deleted gene to cells in the liver, resulting in production of an active variant of factor VIII. Published information is available on a limited number of patients who received therapy with valoctocogene roxaparvovec, with up to three years of follow-up. BioMarin submitted a biologics license application for valoctocogene roxaparvovec to the FDA in December 2019.

Figure 1. Illustration of Activated Factor VIII in the Clotting Cascade



Source: Joe Dunckley, own work. Adapted with permission under the conditions of CC BY-SA 3.0, <https://commons.wikimedia.org/w/index.php?curid=1983833>.

Review Modifications

ICER performs certain modifications to its assessments of therapies intended for ultra-rare conditions ([Modifications to the ICER VAF for treatments for ultra-rare diseases](#)). Criteria to qualify for these modifications include:

- An eligible patient population for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.
- There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals.

There are estimated to be approximately 15,500 individuals with hemophilia A in the US.^{3,12} Valoctocogene roxaparvovec is intended for the treatment of adults with severe hemophilia A. It is possible that the treatment could be used for older teenagers (ages 16 and older) and for those with moderate hemophilia with a more severe phenotype. Approximately 60% of patients with hemophilia A have severe disease. Including some patients with moderate disease could raise this

total above 10,000 patients, but once the population is restricted to adults it will be well below 10,000 individuals. As such, valoctocogene roxaparvovec is a therapy for an ultra-rare condition.

ICER also has modifications to its assessments of high impact single or short-term therapies (SSTs) (e.g., potential cures) ([Adapted Value Assessment Methods for High Impact SSTs](#)). Valoctocogene roxaparvovec as a one-time gene therapy for hemophilia A is a prototypical example of an SST and will be evaluated under this framework.

Emicizumab was evaluated under the ultra-rare framework for patients with inhibitors in ICER's previous review ([Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value](#)). The current potential population for emicizumab exceeds 10,000 patients and so emicizumab will not be assessed under the ultra-rare framework in this review. Emicizumab is not an SST.

Stakeholder Input

This scoping document was developed with input from diverse stakeholders, including patients and advocacy groups, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during calls with stakeholders, open input submissions from the public, and public comments on the draft scope. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of treatments.

Report Aims

This project will evaluate the clinical and economic outcomes of valoctocogene roxaparvovec and emicizumab for patients with hemophilia A. The ICER value framework includes both quantitative and qualitative comparisons to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as public health effects, reduction in disparities, innovation, and patient experience – are considered in the judgments about the clinical and economic value of the interventions.

Scope of the Assessment

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be collected from randomized controlled trials as well as high-quality systematic reviews; observational studies and case series will be considered for inclusion as well, given the limited evidence base for valoctocogene roxaparvovec. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards

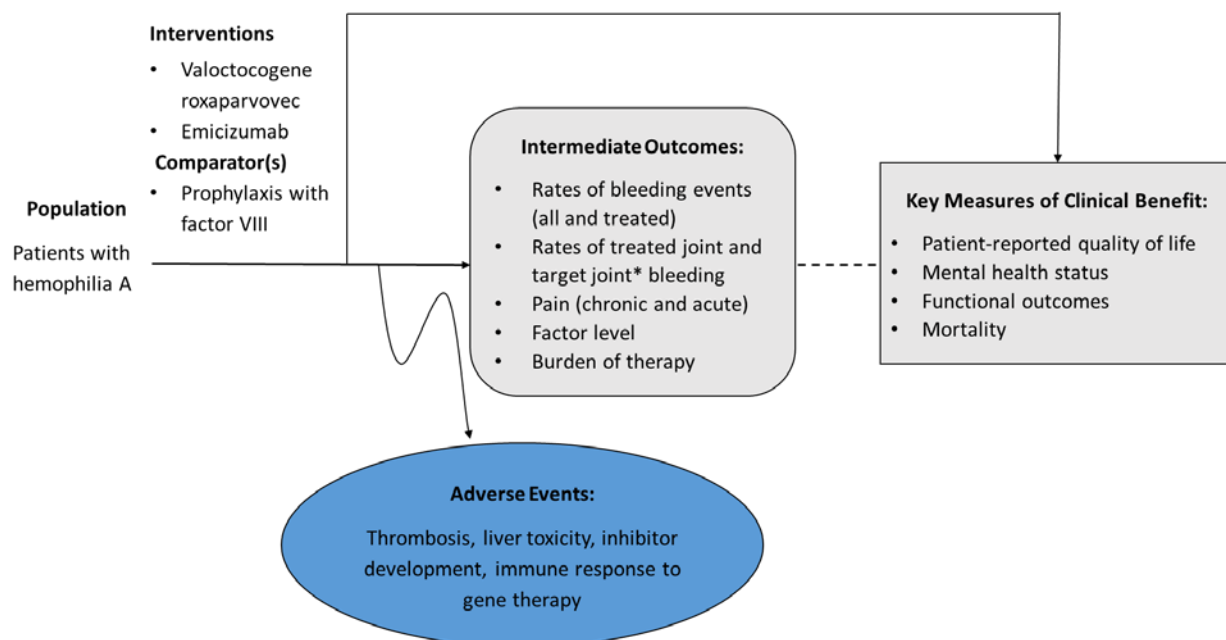
(for more information, see <https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/>).

Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided in a forthcoming Research Protocol to be published on the Open Science Framework website.

Analytic Framework

The analytic framework for this assessment is depicted in Figure 2.

Figure 2. Analytic Framework



*A *target joint* may be defined as a joint that had three or more bleeds in the 24 weeks before the intervention period, however the definition has changed over time and will vary across studies

Populations

The population of focus for this review will be people with hemophilia A without inhibitors to factor VIII who would be appropriate for routine prophylaxis with factor VIII. For valoctocogene roxaparvovec, we will limit the review to an adult population.

For the clinical review, as discussed below, we will examine outcomes in infants and children around the development and management of inhibitors. The economic review is expected to focus

on individuals who do not develop inhibitors to factor VIII for reasons that are discussed further below.

Interventions

The interventions of interest for this review are listed below:

- Valoctocogene roxaparvovec
- Emicizumab

Comparators

Data permitting, we intend to compare the interventions to each other and to prophylaxis with factor VIII preparations.

Outcomes

Patients and patient groups directed us to review the core outcome set established through coreHEM, an international multi-stakeholder project that convened 49 experts (patients, clinicians, researchers, drug developers, methodologists, regulators, health technology assessors and payers) to identify a core set of outcomes for hemophilia gene therapy trials.¹³ Specifically, the coreHEM project identified six core outcomes as crucial for evaluating the effectiveness of gene therapy: frequency of bleeds, factor activity level, duration of expression, chronic pain, mental health status, and utilization of the healthcare system (direct costs).¹³ The coreHEM outcomes have been integrated in our outcome list below.

For this review, we will look for evidence on the following outcomes of interest:

- Patient Important Outcomes:
 - Patient-reported quality of life
 - Rates of bleeding events
 - Rates of treated bleeding events
 - Rates of treated joint bleeding and treated target joint bleeding
 - Pain (chronic and acute)
 - Mental health status
 - Burdens of therapy
 - Mortality
 - Adverse events including:
 - Thrombosis
 - Liver toxicity

- Other outcomes:
 - Factor level (factor activity level)
 - Duration of expression of the clotting factor gene
 - Utilization of healthcare system
 - Adverse events including:
 - Immune response to FVIII (Inhibitor development)
 - Immune response to gene therapy

Of particular note, factor level is an extremely important surrogate/intermediate outcome when thinking about gene therapy, but it is not, in itself, a patient-important outcome. This distinction can be clarified by considering emicizumab. Emicizumab does not increase factor levels but dramatically improves patient-important outcomes when compared with no prophylaxis. Additionally, patients with identical factor levels can have important differences in their experience of disease. However, over certain broader ranges it is clear that factor level is an excellent surrogate, and that a therapy that resulted in normal sustained factor VIII levels in the absence of significant harms or burdens would be expected to achieve normal thrombosis in patients with hemophilia A.

A review suggested that rate of bleeding events is a less-useful outcome, as it acts as a surrogate for more significant patient-centric outcomes.¹⁴ With regard to potential effects of gene therapy, we received patient input that even the coreHEM Core Outcomes Set does not adequately capture the implications of being cured of a serious disease.

We also heard from patients and patient groups that hemophilia can restrict:

- Career choices for the patient and caregivers
- Educational choices for the patient
- Decisions about where to live for the patient and caregivers
- Recreational activities
- Family structure (marriage, divorce, etc.) and employment choices because of concerns about the need to maintain insurance

Over time, joint injury from bleeding can further restrict activities.

We will also look for evidence on additional patient-reported outcomes, such as employment, disability status, social engagement, overall well-being, mobility (activity), anxiety, and depression, as available, as well as outcomes for family and caregivers, particularly for younger children with hemophilia A.

Timing

Evidence on intervention effectiveness will be derived from studies of any duration, as long as they meet the study design criteria set forth above and measure the outcomes of interest.

Settings

Evidence from all relevant settings will be considered, including inpatient, outpatient/clinic, office, and home settings.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the interventions to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Table 1. Potential Other Benefits and Contextual Considerations

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|---|
| Potential Other Benefits |
| This intervention offers reduced complexity that will significantly improve patient outcomes. |
| This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories. |
| This intervention will significantly reduce caregiver or broader family burden. |
| This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed. |
| This intervention will have a significant impact on improving return to work and/or overall productivity. |
| Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention. |
| Potential Other Contextual Considerations |
| This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life. |
| This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness. |
| This intervention is the first to offer any improvement for patients with this condition. |
| Compared to “the comparator,” there is significant uncertainty about the long-term risk of serious side effects of this intervention. |
| Compared to “the comparator,” there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention. |
| There are additional contextual considerations that should have an important role in judgments of the value of this intervention. |

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a simulation model to assess the cost-effectiveness of using valoctocogene roxaparvovec versus prophylaxis using emicizumab and prophylaxis using Factor VIII preparations. A detailed economic model analysis plan with proposed methodology, model structure, parameters, and assumptions is forthcoming. At this time, we propose that the model structure will take the form of a Markov model, with time in each state tabulated from the time since entry into that state. The model structure will be derived as appropriate from previously published economic evaluations,^{15,16} as well as clinical trials and observational studies of hemophilia A treatment. The population entering the model will consist of patients with hemophilia A requiring prophylaxis. The proposed model will consider four mutually exclusive bleed states, including: 1) no bleed (origination state), 2) untreated bleed, 3) treated bleeds not into a target joint, 4) treated target-joint bleed, and death as the absorbing state. In addition, the model will consider the lifetime risk and consequences of arthropathy. The model will be developed from a health-care system perspective over a lifetime time horizon. In addition, a societal perspective will be explored in a scenario analysis, as data allow.

As mentioned above, we currently expect to model patients not at risk for the development of inhibitors to factor VIII. This will apply to nearly all adult patients (who are candidates for all the therapies being considered), and to about three quarters of infants and children who would be initiating prophylaxis. We are limiting the review in this way given the lack of data, and the lack of expert consensus, on the implications for inhibitor development of starting prophylaxis with emicizumab rather than factor VIII. Additionally, for patients who do develop inhibitors, there is no current consensus on how to use emicizumab as part of immune tolerance induction. If, during the review, we find more information and consensus on these issues we may reconsider.

Data permitting, key model inputs will include the relevant transition rates for each health state (e.g., treated and untreated bleed rates, arthropathy rates, symptom improvement, mortality), treatment-related adverse events, and health utilities. Model cost inputs will include those of the prophylaxis and treatment regimens, non-drug costs, costs of treating adverse events, and costs of ongoing care that are essential to the current paradigm of treatment. Data permitting, sub-group scenario analyses varying patient age and factor level upon initiation of therapy will be constructed. Results from the model will include the estimated mean life expectancy, quality-adjusted life expectancy, health outcomes such as number of additional bleeds prevented, and health care costs. These results will be used to estimate the incremental cost per bleed prevented and the incremental cost per life-year gained, per equal value life-year gained (evLYG), and per quality-adjusted life-year (QALY) gained. Our model will present results using thresholds extending from \$50,000 per QALY up to \$150,000 per QALY gained.

In separate analyses, we will explore the potential health system budgetary impact of treating hemophilia A patients in need of prophylaxis with valoctocogene roxaparvovec over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This potential budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of the potential for needing to manage the cost of the intervention. More information on ICER's methods for estimating potential budget impact and calculating value-based price benchmarks can be found on [ICER's website](#).

Identification of Low-Value Services

As described in its Value Assessment Framework for 2020-2023, ICER will include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/wp-content/uploads/2019/05/ICER_2020_2023_VAF_013120-2.pdf). These services are not ones that would be directly affected by gene therapy or emicizumab (e.g., fewer bleeds), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of hemophilia beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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