Emicizumab for Hemophilia A:
Effectiveness and Value

Draft Background and Scope
September 11, 2017

Background

Hemophilia A, due to an inherited deficiency of factor VIII, is the most common of the hemophilias with an incidence of 1 in 5,000 male births.[1] Hemophilia A has X-linked recessive inheritance, and so affects mainly males. The exact prevalence of hemophilia in the United States is not known, but is estimated to be around 20,000.[2] The degree of factor deficiency determines the severity of the condition, with severe disease typically defined by factor levels below 1% of normal.[3] Without prophylactic treatment, patients with severe disease have an average of 20 to 30 episodes per year of spontaneous bleeding or excessive bleeding after minor trauma.[1] Patients with moderate disease (factor VIII levels of 1% to 5%) typically have delayed bleeding episodes after minor trauma several times per year, but only occasionally have spontaneous bleeding.[4] Those with mild disease (factor levels of >5% to 40%) typically have bleeding after procedures such as tooth extractions or surgery, or significant injuries.

Patients with hemophilia A, particularly those with severe disease, are at risk for life-threatening bleeding, including intracranial bleeding, but bleeding into joints (hemarthroses) and muscles is more common and can lead to substantial disability.[5] 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 A are typically administered factor VIII concentrate intravenously multiple times per week.[4,6] The use of factor concentrates both as treatment and prophylaxis has dramatically altered the management and clinical course of patients with hemophilia A.

Approximately 27% of patients with severe disease who receive factor VIII concentrates develop neutralizing antibodies known as "inhibitors."[7] As discussed below, inhibitors can resolve with treatment.[8] The overall prevalence of inhibitors across severity levels appears to be about 5-7%,[9] suggesting a total population of patients with inhibitors in the US of around 1,400; however, the exact prevalence is unknown.[10] Patients with low levels of inhibitors who develop bleeding can often be treated with higher doses of factor VIII, while those with high levels of inhibitors are treated with "bypassing agents" such as activated prothrombin complex concentrate (aPCC) or

activated factor VII (FVIIa).[8] Treatment of a single bleeding episode can cost $50,000 or more, and some patients are treated prophylactically with bypassing agents, which can be extremely expensive, with cost estimates for factors in such patients of around $300,000 to $2.5 million per year.[11,12] In some patients, inhibitors can be eradicated by inducing immune tolerance with high and then continual doses of factor VIII, which is also expensive but allows for prophylactic and episodic therapy with factor VIII alone when successful.[13]

Emicizumab is a monoclonal antibody with dual targets 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).[14] Emicizumab is currently being evaluated by the US Food and Drug Administration (FDA), with orphan and breakthrough designations, as a prophylactic treatment for hemophilia A in patients with factor VIII inhibitors.[14,15] It is administered subcutaneously, and is dosed weekly or less frequently, and is also being studied as a potential alternative for prophylaxis even in patients without inhibitors. For patients with severe hemophilia who have inhibitors, an effective prophylactic therapy could be life changing. Emicizumab is expected to be expensive, but may reduce the need for other costly therapies. The FDA is expected to issue a decision on approval by February 23, 2018.[14]

Figure 1. Illustration of Activated Factor VIII in the Clotting Cascade
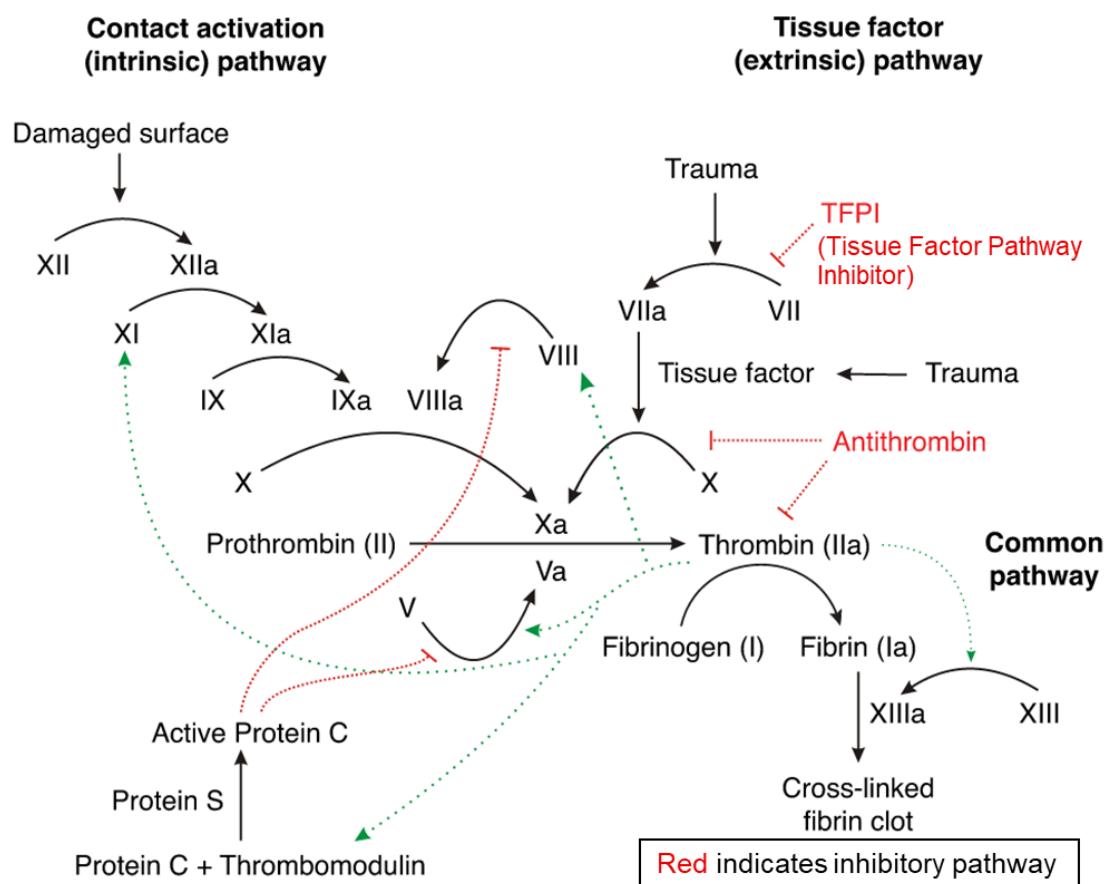
Source: Joe Dunckley, own work. Adapted with permission under the conditions of CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=1983833.

Potential Major Advance for a Serious Ultra-Rare Condition

ICER has posted and asked for public comment on proposed changes to its value assessment framework for treatments of certain ultra-rare conditions (https://icer-review.org/material/odaps-proposed-changes/). While awaiting those comments, we are considering whether emicizumab should be evaluated under these proposals, recognizing that public comments received and further reflection may lead to some revisions to this modified set of methods and procedures.

The proposed criteria are:

- *The treatment is envisaged for a patient population of fewer than 10,000 individuals*
- *There is little chance of future expansion of indication or population that would extend the size of the treated population above 20,000 individuals*
- *The treatment potentially offers a major gain in improved quality of life and/or length of life*

While the population of hemophilia A patients in the US with inhibitors is likely much less than 10,000,[9] and treatment with emicizumab offers potential major gains in quality of life, future expansion of use to the broader population of patients with hemophilia A could extend the size of the treated population to above 20,000 individuals.[1] As such, we plan to evaluate emicizumab under the usual ICER value assessment framework.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services used in the management of patients with hemophilia that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). ICER encourages all stakeholders to suggest services that could be reduced or eliminated in their responses to this draft scoping document.

Report Aims

This project will evaluate the clinical and economic outcomes of emicizumab for patients with hemophilia A with factor VIII inhibitors. 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; high-quality comparative cohort studies will be considered, particularly for comparisons, measures, and

time horizons that have not been featured in randomized trials. 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 (see below for further detail).

Analytic Framework

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

Figure 2. Analytic Framework
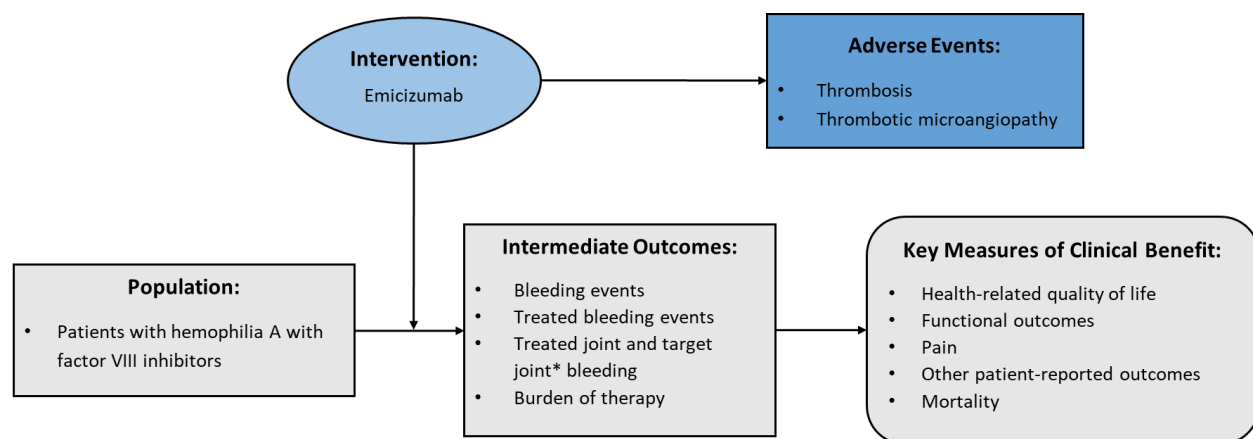
* A target joint is a joint that had three or more bleeds in the 24 weeks before the intervention period

Populations

The population of focus for this review will be patients with hemophilia A with inhibitors to factor VIII who have either failed immune tolerance induction (ITI) or are not going to be treated with ITI. We will plan to evaluate the following three subgroups by age:

1. Adolescents and adults (ages 12 and older)
2. Children (ages 2-12)
3. Younger children (ages 0-2)

Interventions

The intervention of interest will be subcutaneous injection of emicizumab for prophylaxis.

Comparators

We will compare prophylaxis with emicizumab to two alternatives:

1. No prophylactic therapy; patients will be treated with bypassing agents (recombinant FVIIa [NovoSeven®; Novo Nordisk] or aPCC [FEIBA; Shire]) when they bleed, as would occur in patients who bleed while receiving emicizumab or prophylactic bypassing agents
2. Prophylaxis with a bypassing agent

Outcomes

Outcomes of interest from clinical trials will include:

- Rates of bleeding events
- Rates of treated bleeding events
- Rates of treated joint bleeding and treated target joint bleeding
- Pain
- Mortality
- Patient-reported quality of life
- Harms and burdens of therapy

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

We 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.

Patients and patient groups further directed us to a review that identified patient-important outcomes that included mortality, missed days of school or work, number of emergency department visits and number of inpatient days, quality of life, joint damage, educational attainment, patient knowledge, and adherence.[16] The last is an important issue as, even in adult patients who can receive prophylaxis with factor VIII, adherence is only about 50%.[17] The review suggested that rate of bleeding events is a less-useful outcome, acting as a surrogate for more significant patient-centric outcomes.[16]

Evidence tables will be developed for each selected study and results will be qualitatively summarized; pairwise meta-analysis may be used to quantitatively synthesize study results for each intervention of interest versus each comparator. In addition, we will conduct network meta-analyses to combine direct and indirect evidence of effectiveness if available data permit.

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.

Simulation Models Focusing on Long-term Value for Money

As a complement to the evidence review, we will develop a simulation model to assess the cost-effectiveness of emicizumab prophylaxis relative to prophylaxis with bypassing agents or no prophylaxis (i.e., treating bleeding events only). 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,[18,19] as well as clinical trials and observational studies of hemophilia A treatment. The population entering the model will consist of patients in two age categories (12 years and older, and 2 to 12 years) with hemophilia A and inhibitors to factor VIII who have either failed ITI or are not going to be treated with ITI. We do not plan to model children younger than 2 years old as we do not expect to have adequate evidence for this group. Model health states proposed include 1) no bleed, 2) treated bleed, 3) untreated bleed, 4) treated target-joint bleed, 5) arthropathy, 6) and death. The model will be developed from a health-care system perspective over a lifetime horizon.

Key model inputs 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. If sufficient data are available, we will include productivity costs and associated offsets for patients and their caregivers as a scenario analysis. Results from the model will include the estimated mean life-expectancy, quality-adjusted life-expectancy, health outcomes such as number of additional bleeds prevented, health care costs, the incremental cost per bleed prevented, the incremental cost per life-year gained, and the incremental cost per quality-adjusted life-year (QALY) gained.

In separate analyses, we will explore the potential health system budgetary impact of emicizumab treatment 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 any need for managing the cost of such interventions.

Finally, we will develop a "value-based price benchmark" for emicizumab reflecting prices aligned with long-term cost-effectiveness thresholds.

More information on ICER's methods for estimating potential budget impact and calculating value-based price benchmarks can be found on ICER's website.

References

1. Mannucci PM, Tuddenham EG. The hemophilias--from royal genes to gene therapy. *The New England journal of medicine.* 2001;344(23):1773-1779.
2. CDC. https://www.cdc.gov/ncbddd/hemophilia/data.html. Accessed September 8, 2017.
3. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: communication from the SSC of the ISTH. *Journal of thrombosis and haemostasis : JTH.* 2014;12(11):1935-1939.
4. Konkle BA, Huston H, Nakaya Fletcher S. Hemophilia A. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews(R).* Seattle (WA): University of Washington, Seattle; 1993.
5. Hoyer LW. Hemophilia A. *The New England journal of medicine.* 1994;330(1):38-47.
6. Ljung R. Aspects of prophylactic treatment of hemophilia. *Thrombosis journal.* 2016;14(Suppl 1):30.
7. Rota M, Cortesi PA, Steinitz-Trost KN, Reininger AJ, Gringeri A, Mantovani LG. Meta-analysis on incidence of inhibitors in patients with haemophilia A treated with recombinant factor VIII products. *Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis.* 2017.
8. Witmer C, Young G. Factor VIII inhibitors in hemophilia A: rationale and latest evidence. *Therapeutic advances in hematology.* 2013;4(1):59-72.
9. Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. *Haemophilia : the official journal of the World Federation of Hemophilia.* 2003;9(4):418-435.
10. Soucie JM, Miller CH, Kelly FM, et al. A study of prospective surveillance for inhibitors among persons with haemophilia in the United States. *Haemophilia : the official journal of the World Federation of Hemophilia.* 2014;20(2):230-237.
11. Leissinger C, Gringeri A, Antmen B, et al. Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. *The New England journal of medicine.* 2011;365(18):1684-1692.
12. Guh S, Grosse SD, McAlister S, Kessler CM, Soucie JM. Healthcare expenditures for males with haemophilia and employer-sponsored insurance in the United States, 2008. *Haemophilia : the official journal of the World Federation of Hemophilia.* 2012;18(2):268-275.
13. Rocino A, Cortesi PA, Scalone L, Mantovani LG, Crea R, Gringeri A. Immune tolerance induction in patients with haemophilia a and inhibitors: effectiveness and cost analysis in an European Cohort (The ITER Study). *Haemophilia : the official journal of the World Federation of Hemophilia.* 2016;22(1):96-102.
14. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. *The New England journal of medicine.* 2017.
15. US FDA. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/. Accessed August 29,2017.
16. Pai M, Key NS, Skinner M, et al. NHF-McMaster Guideline on Care Models for Haemophilia Management. *Haemophilia : the official journal of the World Federation of Hemophilia.* 2016;22 Suppl 3:6-16.
17. Ragni MV. Targeting Antithrombin to Treat Hemophilia. *The New England journal of medicine.* 2015;373(4):389-391.
18. Knight C, Paisley S, Wight J, Jones ML. Economic modelling of different treatment strategies for haemophilia A with high-responding inhibitors. *Haemophilia : the official journal of the World Federation of Hemophilia.* 2003;9(4):521-540.

19. Hay JW, Zhou ZY. Economical comparison of APCC vs. rFVIIa for mild-to-moderate bleeding episodes in haemophilia patients with inhibitors. *Haemophilia : the official journal of the World Federation of Hemophilia.* 2011;17(5):e969-974.