Genentech
A Member of the Roche Group

February 23, 2018

Institute for Clinical and Economic Review (ICER)
Two Liberty Square, 9th Floor
Boston, MA 02109

RE: Response to ICER's Hemophilia A: Draft Evidence Report from January 26, 2018

Dear ICER Review Panel:

Thank you for the opportunity to respond to the Hemophilia A: Draft Evidence Report. Genentech, a member of the Roche Group, appreciates the significant effort that ICER has undertaken to evaluate emicizumab-kxwh (hereinafter referred to as emicizumab) in hemophilia A with factor VIII (FVIII) inhibitors. Genentech also acknowledges the partnerships that ICER developed with patient, payer, physician and manufacturer communities to ensure the unique considerations of an ultra-rare condition are accounted for when conducting the value framework assessment.

Genentech is dedicated to improving the lives of patients through scientific innovation and discoveries. Approximately 20-30% of patients with hemophilia A develop inhibitors to FVIII, resulting in greater risk of life-threatening bleeds and joint damage.[1] Emicizumab represents an important therapeutic advancement as the first new medicine in nearly 20 years to treat people with hemophilia A with FVIII inhibitors. Based on data from two of the largest pivotal clinical studies conducted, emicizumab was FDA approved to prevent or reduce the frequency of bleeds for adults and pediatric patients with hemophilia A with FVIII inhibitors.

We hope our comments will strengthen ICER's evaluation of hemophilia A with FVIII inhibitors. Our feedback is focused on the following priorities:

1. Model validity will be enhanced by greater use of HAVEN 1 data to better represent efficacy outcomes of treatment with BPAs compared to emicizumab in patients with hemophilia A with FVIII inhibitors, as well as the use of consistent cost sources.
2. Adverse events associated with the treatments of interest should be accurately represented in the evidence report in order to prevent misinterpretation of safety profiles.

3. Patient-centric outcomes and considerations should be expanded to better capture the impact of emicizumab to patients, caregivers and communities.

1. Model validity will be enhanced by greater use of HAVEN 1 data to better represent efficacy outcomes of treatment with BPAs compared to emicizumab in patients with hemophilia A with FVIII inhibitors, as well as the use of consistent cost sources.

1a. The efficacy of emicizumab compared to prophylaxis with bypassing agents (BPAs) should be based on the intra-patient comparison for patients from the non-interventional study (NIS; NCT02476942) who switched to emicizumab (Arm C - HAVEN 1)

The intra-patient comparison (comparing NIS data to Arm C of HAVEN 1) is the only data source that compares the efficacy of BPAs to emicizumab. As communicated in prior responses, we believe that the NIS is the most current and relevant source of data to inform model assumptions around the utilization and outcomes in patients with hemophilia A with FVIII inhibitors for the following reasons:

- The NIS is the largest and most recent clinical study of patients with hemophilia A with FVIII inhibitors to date.
- The intra-patient comparison captures the treatment comparisons of emicizumab versus the class of BPAs that ICER seeks to evaluate.
- The NIS has greater generalizability to a real-world population.

The current model is limited by the assumption that all BPAs are equivalent based on the PROOF trial. However, only activated prothrombin complex concentrate (aPCC) was evaluated in the PROOF trial.[2] The assumption that all BPAs are equivalent when used for prophylaxis in patients with hemophilia A with FVIII inhibitors is not supported by head-to-head clinical trials. We strongly encourage ICER to consider the above points around efficacy assumptions in order to more comprehensively represent the treatment interventions of interest.

1b. Consistent sources for drug price must be used to ensure fair and balanced comparisons.

The current model uses different pricing sources by comparing the wholesale acquisition cost (WAC) of emicizumab with the average sales price (ASP) of recombinant activated factor VII (rFVIIa) and aPCC. ASP is a discount of WAC, and combining these different prices biases the comparison of one intervention over the other. Currently, WAC is the only available price for emicizumab. We recommend that ICER conservatively assume WAC for all treatments in order to maintain consistency in its comparisons.

1c. ICER should ensure consistency by using efficacy measures based on the same statistical approach.

As acknowledged in the draft report, the statistical approach to calculate bleed outcomes varies significantly in hemophilia trials. ICER's model uses two different values to characterize the efficacy of treatment comparators by comparing the median treated annualized bleed rate (ABR) for patients receiving aPCC prophylaxis with the adjusted mean ABR for emicizumab. The median and mean ABR calculations estimate different rates of bleed events and should not be compared unless it's known the cohort distributions are symmetrical. Adjusted mean and median ABRs for emicizumab are presented in table 1.

Table 1. ABR with no prophylaxis vs emicizumab prophylaxis in HAVEN 1.[3]

Endpoint	Arm A: emicizumab prophylaxis (n=35)	Arm B: no prophylaxis (n=18)	Arm C: emicizumab prophylaxis (n=49)
Median (range) duration of efficacy period	29.29 (0.1-48.9)	24.14 (23-26)	19.14 (6.9-45.3)
Treated bleeds (with BPAs; primary endpoint)			
ABR* (95% CI)	2.9 (1.69, 5.02)	23.3 (12.33, 43.89)	5.1 (2.28, 11.22)
Median (IQR)ABR¶	0 (0, 3.7)	18.8 (13, 35.1)	0 (0, 1.7)
All bleeds (treated with BPAs/not treated)			
ABR* (95% CI)	5.5 (3.58, 8.6)	28.3 (16.79, 47.76)	6.5 (3.43, 12.43)
Median (IQR) ABR¶	2 (0, 9.9)	30.2 (18.3, 39.4)	0 (0, 6)
Treated spontaneous bleeds			
ABR* (95% CI)	1.3 (0.73, 2.19)	16.8 (9.94, 28.3)	3.1 (1.2, 8.02)
Median (IQR) ABR	0 (0, 3.3)	15.2 (6.6, 30.4)	0 (0, 0)
Treated joint bleeds			
ABR* (95% CI)	0.8 (0.26, 2.2)	6.7 (1.99, 22.42)	0.6 (0.21, 1.48)
Median (IQR) ABR	0 (0, 0)	1 (0, 14.4)	0 (0, 0)
Treated target joint bleeds			
ABR* (95% CI)	0.1 (0.03, 0.58)	3 (0.96, 9.13)	0.3 (0.1, 0.95)
Median (IQR) ABR	0 (0, 0)	1 (0, 6.5)	0 (0, 0)

Notes: * The comparison of the number of bleeding events over time among study arms was performed using a negative binomial regression model (adjusted mean). The model accounted for different follow-up times, with the number of bleeding events (for each patient) as a function of randomization and the time that each patient stayed in the study included as an offset in the model. The model also included the number of bleeds (<9 or ≥9) in the last 24 weeks prior to study entry. ¶ Calculated median ABR.
Abbreviations: ABR=annualized bleeding rate; BPA(s)=bypassing agent(s); IQR=interquartile range; RR=risk ratio.

2. <u>Adverse events</u> associated with the treatments of interest should be accurately represented in the evidence report in order to prevent misinterpretation of safety profiles.

2a. 'Thrombotic microangiopathy' should be used throughout the report to accurately reflect the adverse events reported in HAVEN 1.

Increased specificity of adverse event reporting will result in a more accurate representation of emicizumab's safety profile. The Draft Evidence Report often refers to 'thrombotic and microangiopathic events'. This inaccurately represents the serious adverse events observed in HAVEN 1 because microangiopathy is a broad term that refers to <u>any</u> small vessel disease. In HAVEN 1, only <u>thrombotic</u> microangiopathy, which results in thrombosis in capillaries and arterioles, was reported. We suggest aligning with the terminology used in the ICER report to

that used in the HAVEN 1 publication (thrombotic microangiopathy or thrombosis) or the Hemlibra prescribing information (thrombotic microangiopathy and thrombotic events).

3. <u>Patient-centric outcomes</u> and considerations should be expanded to better capture the impact of emicizumab to patients, caregivers and communities.

Genentech acknowledges the importance of capturing outcomes that are important to patients. We are committed to investing in patient-centric research to fully characterize the benefit of emicizumab in the real-world setting. We suggest expanding section 5.1 in the Draft Evidence Report by including additional patient-centric considerations available in published literature.

3a. Burden of treatment administration and impact to adherence is an important consideration for patients and caregivers.

Genentech appreciates ICER's discussion of the burden of treatment administration, particularly given the life-long duration of hemophilia. In Section 5.1 of the report, we suggest that ICER include a statement acknowledging that intravenous administration has been identified in the published literature as a key barrier to starting and adhering to prophylactic therapies in patients with hemophilia.[4,5]

3b. Consider including recently-presented, patient-centric data from the HAVEN 1 and HAVEN 2 clinical trials.

In response to the report's statement that no published data are available on the impact of emicizumab prophylaxis on missed work or school days and hospitalization, we provide exploratory data that was recently presented at the 11th Annual Congress of the European Association of Haemophilia and Allied Disorders (EAHAD) in Tables 2, 3 and 4.[6,7] Adults and adolescents treated with emicizumab prophylaxis had numerically fewer missed work and school days when compared to those on episodic BPAs in HAVEN 1.[6] Additionally, school and daycare attendance numerically improved after children began receiving emicizumab.[7]

Table 2. Proportion of work/school days missed from start of HAVEN 1 through Week 25.[6]

	Arm A: emicizumab	Arm B: no prophylaxis	Arm C: emicizumab
Missed work days	7%	14%	3%
Missed school days	4%	33%	5%

Table 3. Percentage of patients with no missed school or daycare days - HAVEN 2.[7]

	Baseline (n=51)	Emicizumab Week 13 (n=22)	Emicizumab Week 25 (n=18)
Percentage of patients with no missed school/daycare days*	27.5%	81.8%	83.3%
*Calculated at each time point for previous 4 weeks			

Patients treated with emicizumab prophylaxis had numerically fewer hospitalization days when compared to adults and adolescents on episodic and prophylaxis BPAs in HAVEN 1.[6] The number of days hospitalized from start of HAVEN 1 through Week 25 are presented in Table 4.

Table 4. Number of days hospitalized from start of HAVEN 1 through Week 25.[6]

	Arm A: emicizumab	Arm B: no prophylaxis	Arm C: emicizumab
Mean (SD) number of days hospitalized	1.9 (8.9)	4.2 (9.5)	0.7 (2.8)

Genentech also requests the following minor corrections/suggestions:

Page #	Entry	Correction Requested	Rationale/Comments
At first mention	emicizumab	emicizumab-kxwh	Suggest using FDA-approved generic name
21	Table 3.1 – HAVEN 1 period 24 weeks	Change to: At least 24 weeks	Study period was a minimum of 24 weeks[3]
30	Table 3.2 - p-value for treated joint bleeds is reported as <0.0001	Change to: p=0.0050	Per HAVEN 1 supplement, p=0.0050 for treated joint bleeds[3]
39	Patients had to have at least 6 bleeding events on BPA prophylaxis prior to study entry	Change to: Patients had to have at least 2 bleeding events on BPA prophylaxis prior to study entry.	Patients were eligible for HAVEN 1 if they experienced **2 bleeding events on <u>prophylactic</u>** BPA in the 24 weeks prior to the study[3]

We hope these comments will contribute to improvements to the value framework assessment of emicizumab. We welcome the opportunity to provide clarification should ICER have any questions.

Sincerely,

Jan Hansen, PhD
Vice President, Evidence for Access
Genentech U.S. Medical Affairs

References

1. DiMichele DM. The North American immune tolerance registry: contributions to the thirty-year experience with immune tolerance therapy. Haemophilia. 2009; 15: 320-328.
2. Antunes SV, Tangada S, Stasyshyn O, et al. Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors. Haemophilia. Jan 2014;20(1):65-72.
3. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N Engl J Med. Aug 31 2017;377(9):809-818. (supplement and protocol appear online)
4. Thornburg CD and Duncan NA. Treatment Adherence in Hemophilia. Patient Prefer Adherence 2017; 11:1677-1686
5. Ono O, Suzuki Y, Yosikawa K et al. Assessment of haemophilia treatment practice pattern in Japan. Haemophilia 2009; 15(5): 1032-1038.)
6. Oldenburg J, Mahlangu JN, Bujan W, et al. Emicizumab Prophylaxis and Health-Related Outcomes in Persons with Haemophilia A (PwHA) with Inhibitors: HAVEN 1 Study. Presented at the 11th Annual Congress of the European Association of Haemophilia and Allied Disorders in Madrid, Spain; 2018 Feb 7-9. EAHAD Poster P120.
7. Mancuso ME, Mahlangu J, Sidonio R, et al. Emicizumab Prophylaxis in Paediatric Persons With Haemophilia A (PwHA) With Inhibitors: Impact on Health-Related Outcomes and Caregiver Burden in the HAVEN 2 Study. Presented at the 11th Annual Congress of the European Association of Haemophilia and Allied Disorders in Madrid, Spain; 2018 Feb 7-9. EAHAD Oral Presentation.

GRIFOLS

Grifols Shared Services of North America
79 T.W. Alexander Drive
4101 Research Commons
Research Triangle Park, NC 27709
www.grifols.com

February 21, 2018

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Review Team:

Thank you for the opportunity to comment on the Draft Evidence Report entitled "Emicizumab for Hemophilia A: Effectiveness and Value." Please see our comments below. They will be noted by page number from the report.

1) 2.2 Clinical Guidelines, at top of page 14 – the report acknowledges the difficulty with high-titer inhibitors, but only refers to use of by-passing agents (BPAs). In the report's reference #50, National Hemophilia Foundation's (NHF) Medical and Scientific Advisory Council (MASAC) makes the statement: "For high-titer inhibitors, immune tolerance induction is the best option for inhibitor eradication."[1] While the report does not address immune tolerance induction (ITI), we think that ICER should acknowledge that NHF's MASAC has stated that ITI is the best option to eradicate FVIII inhibitors.
2) 3.1 Overview, Harms, at top of page 17 – the report lists "Thrombolytic events." We think that you mean "Thrombotic events."
3) 3.3 Results, 4th paragraph down, page 32 – We are not sure why there is a statement (concerning ITI) made that is unrelated to the model used in the evaluation. It is pure speculation that emicizumab may be used to defer or replace ITI. Because the efficacy and safety of such an approach is unknown at this time, we recommend deleting this paragraph.
4) 4.2 Methods, Key Model Characteristics and Assumptions, entire section – we applaud ICER for the use of both a lifetime time horizon and costs and outcomes over a 5-year time horizon. Lifetime costs are not always considered when making treatment decisions that can have such a life-long and significant impact.
5) 5.1 Other Benefits, page 64 – each of these areas of potential benefit are reasonable given the concept of a once-a-week subcutaneous administration. However, one area that is not addressed in the draft report is that of bleeding and discerning between a true bleed and an injury that causes pain without significant bleeding. According to MASAC guidance, patients have been instructed on home administration of BPAs whenever they experience a bleed.[2] However, MASAC has issued interim guidance on the use of emicizumab that describes the need for reassessment of bleeds and pain in patients who are receiving emicizumab, since the bleeding phenotype will likely be changing to a milder one.[3] Additionally, 30+ percent of

patients in the HAVEN-1 study had bleeds while taking emicizumab.[4] Because of this, and the fact that there is little long term data or experience with emicizumab, it seems purely speculative at this time that the changes in the quality of life that have been concluded by ICER will be so transformative.

6) 5.2 Contextual Considerations, last bullet on page 64 – While this statement is true, it appears "out of context" with the report. None of the products currently in the market today were in the market at the time of this tragedy in the blood supply and in the hemophilia community specifically. There have been significant improvements in therapeutics since that time, including improved screening of plasma donors, enhanced manufacturing processes and the development of recombinant factor products. The report is a comparative effectiveness report of current treatments for patients with inhibitors, not a comparative effectiveness report with treatments for hemophilia from the 1970s and 1980s. We recommend deleting this bullet.
7) 7.3 Results, bottom of page 69 – It is clear that the report is "…applicable to a specific population (i.e., those with hemophilia A with inhibitors to factor VIII who will not be treated with ITI or for whom ITI has been unsuccessful)…" but the report ignores another segment of the population – those who will be treated with ITI. We suggest revising this sentence to read:

> "As stated in earlier sections of this report, the results of this analysis are applicable to a specific population (i.e., those with hemophilia A with inhibitors to factor VIII who will not be treated with ITI or for whom ITI has been unsuccessful), and not to those who may be treated with ITI or to the broader population of patients with hemophilia A who do not have inhibitors."

Again, thank you for the opportunity to review and comment on the draft evidence report concerning emicizumab for hemophilia A.

Sincerely,

Jeffrey B. Spears, PharmD
Medical Director, Hematology
Global Medical Affairs

References:

[1] https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/MASAC-Recommendations-Concerning-Products-Licensed-for-the-Treatment-of-Hemophilia-and-Other-Bleeding-Disorders. Accessed February 20, 2018.

[2] https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/MASAC-Recommendation-on-Administration-of-Inhibitor-Bypassing-Agents-in-the-Home-for-Patients-with-Hemophilia-and-Inhibitors. Accessed February 21, 2018.

[3] MASAC Update on the Approval and Availability of the New Treatment: Emicizumab (Hemlibra), for Persons with Hemophilia A with Inhibitors to FVIII: Interim Guidance on Acute Bleed Management and Use of Laboratory Assays, Approved by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF), November 24, 2017.

[4] J Oldenburg et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. New England Journal of Medicine 2017; 377:809-818.

February 23, 2017

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Emicizumab for Hemophilia A: Effectiveness and Value, Draft Evidence Report

To Whom It May Concern:

The National Hemophilia Foundation (NHF) and the Hemophilia Federation of America (HFA) are national non-profit organizations that represent individuals with bleeding disorders across the United States. Our missions are to ensure that individuals affected by hemophilia and other inherited bleeding disorders have timely access to quality medical care, therapies, and services, regardless of financial circumstances or place of residence. Both organizations accomplish this through advocacy, education, and research. We appreciate the opportunity to provide comment to the Institute for Clinical and Economic Review (ICER) on its draft evidence report concerning Emicizumab for Hemophilia A. Our comments follow by section of the report:

2.1 Coverage Policies

On page 13 of the draft report, ICER states: "Since BPAs are covered as a medical benefit, patient groups expressed concern about patient out-of-pocket costs in the form of co-insurance and deductibles, although patients with inhibitors already regularly reach their annual out-of-pocket maximums." HFA would like to clarify this statement. Data from Project CALLS shows that many BPAs are covered under the medical benefit AND that patients are worried about increased out-of-pocket costs. Patients with hemophilia, particularly inhibitor patients, are consistently worried about the cost of treatment, wherever the benefit is covered. CALLS data shows an even split between BPAs being covered under the pharmacy benefit, the medical benefit, and patients not knowing which benefit (although our understanding is that BPAs are most commonly covered under the medical benefit).[1]

3.3 Results - Health-Related Quality of Life and Other Outcomes

In the draft report, ICER indicates that it was unable to find clinical studies in published or unpublished form that discuss the impact of Emicizumab on various aspects of patient and caregiver quality of life. We wish to highlight two additional publications that have been released since ICER began its review, which provide additional data not previously available:

- The *Emicizumab Prophylaxis and Health-Related Outcomes in Persons with Haemophilia A (PwHA) with Inhibitors: HAVEN 1 Study* poster *presentation* from the 11th Annual

Congress of the European Association of Haemophilia and Allied Disorders found that study participants on Emicizumab on prophylaxis had higher quality of life scores – as measured by the Haemophilia-specific quality of life (QoL) instrument in adults (Haem-A-QoL) – than did individuals not on prophylaxis, specifically in the "school and work" and "family" domains. These individuals also reported fewer missed days of school and work. The poster cites "substantial and meaningful differences in the daily lives" of people with hemophilia and inhibitors.[2]

- *The Emicizumab Prophylaxis in Paediatric Persons with Haemophilia A (PwHA) with Inhibitors: Impact on Health-Related Outcomes and Caregiver Burden in the HAVEN 2 Study* oral presentation at the 11th Annual Congress of the European Association of Haemophilia and Allied Disorders also provides additional data regarding the impact of Emicizumab on children and caregivers. This study found that children reported improvements in their physical health and feelings using the Haemophilia-Specific Quality of Life Assessment for Children Short Form. Caregivers reported marked improvements regarding several aspects of the caregiver burden, especially with their perception of the child's hemophilia and the impact of the condition on the family life. They also reported significant, sustained improvements in school/daycare attendance.[3]

4.3 Summary and Comment – Limitations

It is challenging to anticipate the real-world adherence to Emicizumab outside of the structure of the clinical trial setting. Accordingly, it will be important to monitor adherence over time.

5.1 Other Benefits and Contextual Considerations

Finally, we wish to emphasize the points made in prior comment letters that the "other benefits and contextual considerations" should remain a primary consideration in ICER's value calculations. While the ultra-rare size of the patient population, combined with the longer time period necessary to fully assess the effects of prophylaxis with Emicizumab on education, employment and careers, we believe that Emicizumab brings a number of other long-term benefits to affected individuals and their families.

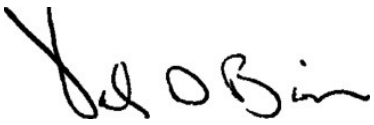
Personal communications from patients and families who have participated in the Emicizumab trials, along with the data reported in the HAVEN 1 and 2 studies referenced above, suggest that Emicizumab transforms the way people with hemophilia and an inhibitor may now live their lives. Data suggest that Emicizumab has the potential to reduce caregiver and family burden and that it will have a significant impact on improving patients' ability to attend school and work. The subcutaneous administration is also meaningful in terms of reducing complexity associated with treatment, treatment burden and improving patient outcomes. Moreover, it is clear that the

intervention is intended for the care of individuals with a condition of high-severity in terms of impact on quality of life, morbidity and mortality.

We reiterate our request that ICER prominently discuss these other benefits and contextual considerations in the final report. If not suitable for inclusion within the economic model, we encourage ICER to prominently discuss the added patient-relevant outcomes in any executive summary it produces, rather than leave them to recommendations for future research.

We appreciate the opportunity to provide these comments. Thank you for your consideration.

Sincerely,



Val Bias
Chief Executive Officer
National Hemophilia Foundation

Kimberly Haugstad
President & CEO
Hemophilia Federation of America

---

[1] Hemophilia Federation of America (2018). [Project CALLS survey.] Unpublished raw data.

[2] M. E. Mancuso, J. Mahlangu, R. F. Sidonio Jr. et al. (2018). Emicizumab prophylaxis in paediatric persons with haemophilia A (PWHA) with inhibitors: Impact on health-related outcomes and caregiver burden in the HAVEN 2 study. Oral Presentations. *Haemophilia*, 24: 23–31. doi:10.1111/hae.13392.

[3] J. Oldenburg, J. N. Mahlangu, W. Bujan et al. (2018). Emicizumab prophylaxis and health-related outcomes in persons with hemophilia a (PwHA) with inhibitors: HAVEN 1 study (2018), Poster Presentations. *Haemophilia*, 24: 32–135. doi:10.1111/hae.13393.

February 23, 2018

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: ICER Draft Hemophilia A Evidence Report

Dear Dr. Pearson:

Patients Rising Now analyzes and advocates on behalf of patients for *all patients with life-threatening and chronic diseases* to have *access to vital therapies and services.* We believe that if a patient needs treatments to survive and live a better and more productive life – access to those treatments is warranted and essential – and access spans affordability, insurance coverage, and physical access.

In our work, we are committed to engaging patients, caregivers, physicians, the media, health policy experts, payers, providers and other allied health professionals to develop realistic, solution-oriented discussions so that those impacted with critical medical needs can amplify their collective voice and create lasting impact on the future of health care in the United States. That is, our goal is advancing a balanced dialogue and national conversation that illuminates the truth about health care.

Our sister organization, Patients Rising, has previously written to you about our concerns with ICER's work and processes, and specifically, the lack of meaningful patient engagement, inadequate attention to aspects of therapeutic choices that go beyond strict "clinical value", problems with evaluating Quality Adjusted Life Years (QALYs), and new information not being included in updates to ICER's analyses in a timely and meaningful fashion.

While all those areas are critically important to patients – and should be part of how patient perspectives are considered by researchers, regulators, and payers – we are focusing our comments about the draft evidence report "Emicizumab for Hemophilia A: Effectiveness and Value" on the section titled "Potential Budget Impact."

Budget Impact from a Patient's Perspective

We are very aware that the Potential Budget Impact section of ICER's reports has long received considerable attention, but in our view, ICER's process and presentation have not undergone significant nor positive revisions. For example, the concept that it is possible or reasonable to evaluate "the budget" for health care spending in the United States is dubious. That is, while others (CMS, Altarum) routinely evaluate spending on health care in the United States, and they and others (such as CBO or the Federal Reserve) model future or expenditures, the inherent

reality of the multi-payer structure of financing of health care in the United States means that there is no specific budget. Of course, there are specific programs and payers that do have budgets for various sectors or populations in the United States: The National Institutes of Health (NIH) has a budget; The Center for Disease Control and Prevention (CDC) has a budget; and the Veterans Health Administration (VHA) has a budget. Other programs have projected expenditures and either draw on trust funds for those payments (such as Medicare Part A), or manage themselves based upon those projections of spending and revenues, such as individual hospitals, health systems, and insurers.

It is critical to realize that patient's perspectives involve their costs and their access to care. Thus, regarding budgets and spending, their concerns about the implications of any innovation, or legal or regulatory change, are how such innovations or changes would affect their insurance program, benefits plan, affordability, or access to care.

Specific to the Potential Budget Impact section in ICER's draft evidence report concerning hemophilia, there are many, many deficiencies because it treats all health care spending in the United States as one uniform bucket. However, for many diseases, and particularly for hemophilia, this is not true. For example, as an inherited disorder predisposing people to bleeding (and significant complications such as joint damage), it is extremely unlikely that people with hemophilia would pass the physical tests necessary to join the armed services. Thus, the prevalence of people with hemophilia who are patients in the VHA is likely to be very, very small, and certainly much lower than in the general population. Therefore, for the VHA to apply ICER's Potential Budget Impact estimate to their system for veterans would be irrational. Similarly, the prevalence of people with hemophilia who are Medicare beneficiaries is less than the national average. This was shown by the GAO in an older report that found about 6% of Medicare beneficiaries have hemophilia, which is less than half the rate of enrollment in Medicare for the entire population.[i] Similar data shows that by age, hemophilia prevalence skews considerably towards younger segments of the population. (See chart below.[ii])

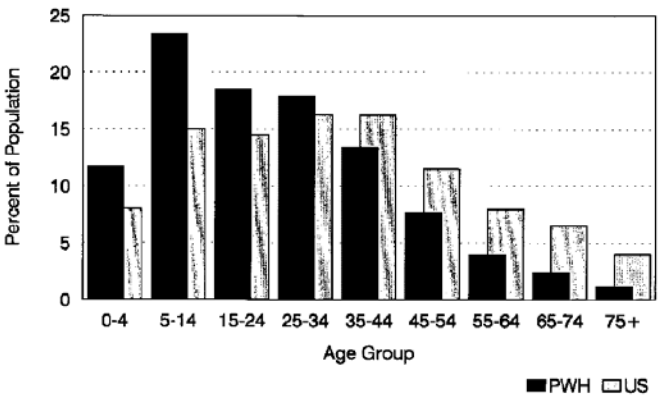


Fig. 1. Distribution by age of the male population for persons with hemophilia (PWH) and for residents of the United States (US) in 1994.

This skewing of the age distribution makes sense because hemophilia is a genetic condition, and thus, it would also be expected that Medicaid programs would have a higher prevalence of people with the condition. This is reflected in a study of Medicaid and hemophilia that found "30–40% of male patients with hemophilia were covered by Medicare or Medicaid"[iii] indicating that about 24-34% are covered by Medicaid,[iv] a percentage that is at least twice that of the non-elderly population enrolled in Medicaid.

What this means in term of financial consequences for patients concerned about rising costs and access to care is that any changes in treatment options or payment paradigms, need to be viewed in the context of their individual insurance coverage and clinical situation. Similarly, managers, administrators, and leaders of health care payers and care delivery organizations need to have parallel perspectives. Therefore, in the case of new treatments for hemophilia (such as emicizumab), the financial implications for Medicaid programs (before considering any rebates or discounts) should be greater than any average "budget impact," while the financial implications for Medicare would be less than the average, and the implications for the VHA are essentially negligible.

The bottom line is that presenting a "budget impact" analysis for the health care spending across the entire United States is essentially a fictional story. Rather, appropriate assessments of financial implications need to be done from the perspective of the individual health plan or insurance company. An extreme (and currently hypothetical) example would be for a health insurance plan that only covered women, e.g., "WomenHI Plan of the US." Since hemophilia is an X-linked genetic disorder, it is rare for a female to have hemophilia. Thus the "budget impact" of new treatments for hemophilia for the "WomenHI Plan of the US" would be very negligible, while the "budget impact" for their brothers' male only plan could be very significant.

Analyzing Budget Impact v. Modeling Financial or Spending Estimates

As discussed above, there is a significant difference between budgeting (which is done by all sorts of organizations – from families to corporations – to help them plan their activities based upon expected revenues and expenses), and macro-economic modeling that encompasses multiple organizations or entities, such as annual spending on hospital in-patient services.

Another very problematic aspect of the methodology ICER uses in its "Budget Impact" section is to assume that a fixed percentage of spending on biopharmaceutical therapies is appropriate. This presumption fails to recognize the perspectives of many, many patients who are suffering with chronic illnesses that severely impair or shorten their lives, and for whom there are no or inadequate treatments. For them, a new treatment may represent not just a dramatic improvement in function, quality of life, or longevity, but also hope – hope that even if the new treatment has modest benefits it will bridge them until the next clinical breakthrough becomes available. The history of HIV infection and AIDS therapies is very illustrative of this concept: In the early 1990s there were only a few antivirals that helped slow the progression of AIDS, and while certainly not adequate, they did provide time for people infected with HIV. That time enabled many to live until the protease inhibitors became available in the mid-1990s, which then provided the basis for combination therapies that offered the first opportunity for controlling HIV infection and significantly longer life. Of course, since then, there have been even more advances making treatment of HIV infection much easier, and with fewer and milder

complications. (There are similar examples of this concept in oncology and serious chronic conditions.)

We recognize that in the draft evidence report, the budget impact section attempts to model costs foregone when using a new treatment, however, the update to ICER's framework states concerning increased spending for a new treatment includes: "A good discussion might indeed lead to decisions to take further resources from hospitals, nursing homes, physicians, or other dimensions of health care."[v] This statement implies that decisions about resource allocations (i.e., drugs v. hospitalizations) are "made" on a national or even health system-wide basis, but the reality is extremely different. Rather, such substitutions (to use an economists' term) reflect clinical and other benefits rather than management decisions. For example, again using the example of HIV and AIDS, with the advent of the reverse transcriptase inhibitors in the 1990s, the rate of hospital admissions for complications of HIV (such as opportunistic infections) dropped very dramatically. This had significant financial implications (i.e., "budget impact") for hospitals – particularly academic institutions with specialized infectious disease units – causing many of them to reassess their operations and cut back their spending because their revenues from patient care declined significantly. This was <u>not</u> a "a decision to take resources from hospitals," it was a reality of how an innovation improved patient care, reduced morbidity, and extended the lives of many patients with HIV and AIDS, and dramatically reduced the need for inpatient care.

An additional point we would like to note is that using FDA's approval numbers for NMEs and BLAs as some sort of appropriate benchmark is curious at best since the actual number can vary significantly from year to year. For example, ICER shows an average of 33.5 approvals in the years 2015-16. However, in 2017 there were 46 approvals, so the 3-year average would be 37.7, and including 2014 data raises the 4-year average to 38.5. We recognize that these higher numbers would reduce the "Annual threshold for average cost growth per individual new molecular entity," but that is the point – from patients' perspectives, more new treatments are a good thing, so building into ICER's Potential Budget Impact model a penalty for more new treatments is completely opposite to patients interests and the movement towards "patient-centered" perspectives in the U.S. health care system, and thus ICER's modeling methodology, is directly anti-patient-centric. For example, if hypothetically 71 new treatments were approved by the FDA in 2019, and 70 of them were for diabetes and one was for Alzheimer's, according to ICER's modelling process, the acceptable budget impact for each of them would be the same – even though it is very questionable that they truly would all result in the same level of spending, particularly since many of the 70 new diabetes treatments would be expected to compete with each other and ICER's model explicitly does not "attempt to estimate the uptake of a new intervention."[vi] If such a budget impact analyses were blindly used by payer or health system administrators, they would likely severely restrict access to the one new treatment for Alzheimer's – clearly not in the best interests of patients or society.

Conclusions & Recommendations

Patients Rising Now believes that ICER's work continues to inadequately reflect patients' perspectives about quality of life, functionality, heterogeneity of patient choices and goals. The reality of differential financial implications of new therapies – specifically regarding potential budget impacts derived from a model that has so many methodological problems – needs to be

reflected more accurately in ICER's work, and specifically any financial projections or estimates should be as granular and relevant as possible so that they can be useful for individual health programs, payers, or groups of patients. Our very high-level recommendation on this last point is for ICER to either completely remove the "Potential Budget Impact" section of its reports, or to make them more relevant and useful by providing more specific projected financial implications for the major health financing sectors in the United States, e.g., Medicare, Medicaid, VA, DoD, commercial. In addition, for some new treatments and related interventions, it would also be appropriate to assess the spending implications for other programs or groups of providers, such as CDC and public health programs for a new treatment for an SDI, or hospitals and surgical centers for new antiseptics or antibiotics used in procedures.

While we do not expect ICER to act on these recommendations, we hope that others will take up the task to the extent that it will help health system managers and policy makers with their work, and thus promote more patient-centered insights and improvements for health care in the United States.

Sincerely,

Terry Wilcox
Co-Founder & Executive Director, Patients Rising

---

[i] "Payment for Blood Clotting Factor Exceeds Providers' Acquisition Cost", GAO-03-184, January 2003.
[ii] "Occurrence of Hemophilia in the United States," American Journal of Hematology 59:288–294
[iii] "Health care expenditures for Medicaid-covered males with haemophilia in the United States, 2008", *Haemophilia* (2012), 18, 276–283
[iv] Census Bureau Estimated 13.2% of population covered by Medicare in 1996, and HFCA (now CMS) reported that 14.3% of the population was covered by Medicare in 1996.
[v] "Overview of the ICER value assessment framework and update for 2017-2019"
[vi] "Overview of the ICER value assessment framework and update for 2017-2019"

300 Shire Way
Lexington
Massachusetts
02421
USA
www.shire.com

February 23, 2018

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA
Submitted electronically via: publiccomments@icer-review.org

RE: Shire's Response to the Draft Evidence Report Representing the Institute for Clinical and Economic Review (ICER) Evaluation of Emicizumab for Hemophilia A with Inhibitors

Shire respectfully appreciates the opportunity to provide comments on the draft evidence report "Emicizumab for Hemophilia A: Effectiveness and Value" released on January 26, 2018. Most of the suggestions Shire provided following the review of the preliminary draft model were not incorporated into the base case model, including one key assumption of the model that, if changed, would lead to model results that we believe would be more useful for the hemophilia and payer community. The purpose of this letter is to share Shire's reservations concerning the evaluation, especially given the potential for the findings to be considered by physicians and payers for therapy decision-making.

The title of the report "Emicizumab for Hemophilia A: Effectiveness and Value" is inaccurate, as the evaluation is specific to Hemophilia A patients with inhibitors. The value and affordability of emicizumab in non-inhibitor patients has not yet been evaluated.

Many new products brought to market to address patients' needs in a disease area can be proven safe and effective for FDA approval, but still be in the process of developing more data needed for value assessment.

This is particularly true in the case of rare diseases such as hemophilia A with inhibitors. In cases where products show great promise for treating rare disease in which they may have limited data, ICER should cautiously review these technologies until adequate information is available and outcomes in real-world practice become more widely available. It is not appropriate to pass judgement on a new technology with limited data. Patient safety remains Shire's first priority. In addition to clinical studies, we support the use of real world evidence in the ICER value assessment. FEIBA has a well-established safety profile developed over 40 years and spontaneous reporting rate of thromboembolic events (TEEs) of less than 0.005%[1]. In 103 patients in the emicizumab Phase III trial, 2 (1.9%) TEEs and 3 thrombotic microangiopathy (2.9%) were observed with 1 of the TMA event leading to a fatal rectal hemorrhage[5]. Due to the limited clinical data and lack of real world experience, the rate of these serious adverse events

with emicizumab in a larger, heterogeneous population for longer durations is unknown. To our knowledge, there has been no TMAs related to FEIBA use alone.

We reassert that lack of sufficient evidence precludes conclusive comparative effectiveness analysis and economic modeling.

Unlike more common diseases, value assessment in rare diseases, such as hemophilia A with inhibitors, is challenging due to the small and heterogeneous patient population, leading to a dearth of scientifically robust data. The small population also results in a lack of randomized study designs across products, requiring indirect comparison among small individual product studies where endpoints and populations can be different. These limitations for rare diseases can lead to greater uncertainty when applying the cost per QALY threshold for treatments.

There are 4 published randomized controlled clinical trials for the prophylaxis treatment of hemophilia A with inhibitors[2-5]. These trials have substantial differences in trial design, patient population, comparators, endpoints and supportive care, making it extremely challenging to conduct conclusive clinical effectiveness analysis, and subsequently meaningful cost-effectiveness analysis. Hemophilia A with inhibitors is an orphan condition in which treatment decisions require complex and personalized clinical, safety, and ethical considerations. It would be inappropriate to consider the current base case model results as a part of therapy decision-making without understanding how variable the results can be based on clinical assumptions made.

To reflect normal clinical practice, we reassert that this evaluation should compare emicizumab to aPCC and rFVIIa as separate bypassing agent (BPA) comparator arms rather than combining them together as a BPA arm.

The BPA arm of the model should be separated into distinct aPCC and rFVIIa treatment arms. While aPCC and rFVIIa are both categorized as BPAs, there are substantial and well-recognized differences in mechanism of action, prophylaxis efficacy, dosing, and unit cost between the two[2-4,6,7]. Importantly, while aPCC is indicated for prophylaxis, rFVIIa is not. Comparing emicizumab to a generic BPA prophylaxis grouping does not provide an adequate level of evidence necessary for practical use of the analysis results, as evaluation of treatments are made based on individual product benefits and risks. For a payer, given that the cost of aPCC prophylaxis is half that of rFVIIa prophylaxis based on dosing used in the model, a combined BPA grouping inappropriately links aPCC with a high cost.

Particularly for complex conditions such as hemophilia A with inhibitors, assessment of treatments should be left to clinical experts, who can be expected to provide guidance on the continual evolution of the standard of care and the nuance of individual clinical decision making. The complexity of tailoring different treatment options for different population under various treatment settings should be directed by the clinical community through guidelines and peer-reviewed publications.

Elements of the "BPA-favoring scenario" are more reflective of real-world hemophilia care and outcomes and should be included in the base case model.

ICER has considered the cost of aPCC prophylaxis only in a separate "BPA-favoring scenario" which results in an overall **53% lower estimate of BPA costs**. In addition to eliminating the use/cost of rFVIIa, this scenario considers:

1. All bleeds on emicizumab are treated with rFVIIa and all bleeds on aPCC prophylaxis are treated with aPCC.
2. Emicizumab adherence is 100% and aPCC adherence is 88% (applied to cost only)
3. The disutility applied to bleed events is limited to 2 days and the "No Bleed" utility is applied for the remaining 5 days of each model cycle.
4. The rate of thrombotic and microangiopathic events is as reported in HAVEN-1.

We strongly believe that compared to the base case model, the "BPA-favoring scenario" is a closer representation of how hemophilia is managed with aPCC and generally how hemophilia impacts patients. We ask that these assumptions be incorporated into the base case model, rather than its current position as a scenario included on page 122 of a 124-page document.

The wording for voting questions 4d and 4e should reflect a comparison to "currently used bypassing agents" instead of "supportive care".

The current wording of the voting question is:

4. Are any of the following contextual considerations important in assessing emicizumab's long-term value for money? (yes, no, uncertain)

    d. Compared to supportive care, there is significant uncertainty about the long-term risk of serious side effects of this intervention.

    e. Compared to supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.

Since bypassing agents, rather than supportive care, are considered the standard of care for Hemophilia A patients with inhibitors, the comparison of long-term risk and magnitude or durability of long-term benefits should be relative to bypassing agents, not supportive care.

Product discounts presented in the model do not accurately reflect manufacturer discounts. Table 4.6 (p.44) incorrectly minimizes actual product discounts, as the actual ASPs are lower than what was represented.

Shire appreciates the challenge of modelling outcomes in a condition like hemophilia A with inhibitors, where there are few patients and high variability in patient response to therapy. We believe that the wide variability in cost outcomes encountered between the ICER base case model and the BPA favoring scenario depending on some basic clinical assumptions highlights the difficulty in conducting meaningful cost effectiveness analysis. Shire is committed to understanding and responding to the unmet needs of patients, their families and caregivers. It is

our intent to ensure that hemophilia A patients with inhibitors continue to receive the therapy that is best for them.

Respectfully submitted,

Kathleen Gondek, PhD
Vice President, Global Outcomes Research & Epidemiology
Phone: (781) 482-2748
Mobile: (617) 893-2058
Email: kagondek@shire.com