PATIENTS RISING NOW

September 23, 2020

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

RE: Draft Evidence Report "Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A"

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with serious and chronic conditions and diseases for have access to life-improving and life-saving therapies and services. Access to such treatments and services is essential, and it spans affordability, insurance coverage and physical access. To support improved access, we are committed to engaging patients, caregivers, physicians, media, health policy experts, payers, providers and others to foster people-centered discussions about the entire U.S. health care system. Our goal is a balanced dialogue that illuminates the truth about health care innovations and advancements in a transparent and equitable way.

We appreciate the opportunity to provide our comments on ICER's August 26th Draft Evidence Report "Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A." After some introductory observations, our comments about the draft report are organized below into the following sections: People-Centered Perspectives; Value Viewpoints about Cures for Serious Diseases; ICER's Budget Impact Assessment Process; and Additional Points.

We have previously submitted comments to ICER about emicizumab concerning its 2018 review about the use of that medicine for people with hemophilia A with inhibitors.[i] We would like to note that ICER's current draft report addresses the use of emicizumab for people with hemophilia A who do not have inhibitors, and that the trials of the gene therapy valoctocogene roxaparvovec were also conducted in people with hemophilia A without inhibitors.

The FDA approved emicizumab for use in people with hemophilia A without inhibitors on October 4, 2018.[ii] We point this out because we believe that in discussing the clinical situation for people with hemophilia A it should be made more explicitly clear that the current draft report: 1) Is addressing a different subset of patients with hemophilia A than ICER's 2018 report;[iii] 2) Is reviewing a second FDA-approved indication for emicizumab; and 3) People with hemophilia A develop inhibitors after receiving factor VIII. For example, the draft report notes that "the development of inhibitors has very important implications for management, costs, and quality of life."[iv] But simply referencing ICER's 2018 report here is inadequate. We strongly feel that the draft report should contain more extensive discussions of the differences between the two groups of people with hemophilia A, the natural course and history of how people with hemophilia develop inhibitors and what that means for their treatment and care options, costs,

and lives.[v] An updated and complete discussion of those matters is important not only for patients and clinicians to assess ICER's work, but also for policy makers and payers to be able to determine the utility of ICER's reporting for their internal health technology assessments and related practices and policies. In addition, to parallel ICER's 2018 report, we believe the report's title should include the phrase "without inhibitors," i.e., "Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A Without Inhibitors."

People-Centered Perspectives

As noted above, the current draft report focuses on people with hemophilia A without inhibitors. From the perspective of people with hemophilia A – and their family and caregivers – the goal is to achieve as normal a life as possible, which the draft report reasonably presents by discussing the many challenges and life limitation people with hemophilia currently face.

We are again somewhat dismayed that ICER proceeded with examining valoctocogene roxaparvovec even after the FDA declined to advance its own review, which essentially pushes back the earliest approval date to late 2021 or sometime in 2022. Given that the remainder of the review concerns emicizumab, which was originally approved in November 2017,[vi] we fundamentally question the utility of the draft report: Is the purpose to review data about an approved indication that is now two years old, i.e., for hemophilia A without inhibitors? Or to review data that will be updated in about a year with additional information before any potential decision could be made by the FDA? Either of those scenarios has limited utility to patients, clinicians, payers or policy makers. Specifically, policy decisions about additional uses for emicizumab have already been established, and clinical decision makers should already be familiar with the information. Similarly, it is premature to make any clinical or policy decisions about valoctocogene roxaparvovec. Thus, the draft report's assessments and "findings" are inherently unactionable for those audiences.

Similarly, the report is not actionable for payers and policy makers, who work on an annual or biannual timeframe that corresponds to benefit plan years. For them, emicizumab's second approved indication should already be incorporated into their processes, and while valoctocogene roxaparvovec should be on their radar, it is not a factor they need to consider now. In fact, they cannot evaluate it until the additional research required by the FDA has been conducted and analyzed. ICER's review seems premature at best.

The draft report also minimizes the real patient implications of having to receive treatments or prophylaxis intravenously versus subcutaneously. This difference between emicizumab and factor VIII is important, particularly for people with hemophilia A who have transportation or mobility limitations or live in geographic areas where access to clinical facilities for intravenous treatments may require many hours of travel.

Those differences in route of administration can also make the real-life benefits and utility very different from what is reported in clinical studies, particularly as they may be calculated in a meta-analysis of multiple studies. We noted that the draft report includes the sentiments of patients that support this real-world benefit, "98% of patients favored emicizumab over factor VIII prophylaxis,"[vii] and "all caregivers [in the HOEHEMI trial] indicated the lower frequency of treatment and easier route of administration as the major reasons for their preference for emicizumab."[viii] And as the draft report states, "If reductions in adherence outside of trials are not

similar for the two therapies [clinical trial data] could incorrectly characterize the relative benefits of the therapies in the real world. Emicizumab prophylaxis is substantially less burdensome than factor VIII prophylaxis, and so real world adherence is likely to be more similar to clinical trial adherence with emicizumab than with factor VIII."[ix] Similarly, such real-world adherence differences could translate into great benefits for people, particularly because the draft report found that "Emicizumab appears to have lower bleeding rates (of all types) compared with factor VIII."[x] If ICER's goal is to affect real-life policies and actions rather than to provide guidance for future research studies, we urge ICER to expand its recognition and discussion of such people-centered factors.

Value Viewpoints about Cures for Serious Diseases

Because the draft report includes information about valoctocogene roxaparvovec as a potential gene therapy despite the FDA's decision to defer action, we believe it is appropriate to comment on the meaning of such treatments. While it seems from the currently available data that valoctocogene roxaparvovec may have some waning of effectiveness after several years, it also needs to be viewed through the lens of how medical progress actually occurs. Similar to how biplanes were not directly or immediately replaced by jets, improvements in treatments occurs incrementally – sometimes with small steps, and sometimes in larger leaps. Clearly the development of a gene therapy that is effective for several years is a leap over injections that must be given every few weeks. However, valoctocogene roxaparvovec should also not be viewed as the finish to the race for gene therapies. Indeed, improvements will be made upon that very large step, with the ultimate goal of having reliable, stable, and permanent cures. Thus, the initial leap – in this case valoctocogene roxaparvovec – needs to be viewed in its context as part of a process of treatment advancements. For example, in viewing the advancement that valoctocogene roxaparvovec potentially represents, the variability of individual responses to treatment as depicted in Figure 4.1 in the draft report is illuminating. Such individual variability indicates that there is much still to be learned about the use of such gene therapies, and how to customize or adjust their use for individual patients, which – again – is part of the process of innovation and the advancement of scientific knowledge to improve care and outcomes.

For patients, such significant leaps represent hope in concept – as well as in reality – that better treatments will be developed while they are benefiting from those that are small steps or significant leaps, but that still leave them with some impairment, limitation or dependence upon ongoing treatments. This value of hope is real for patients even if payers, policy makers, and quantitative modelers are unable or unwilling to incorporate that reality for patients into their cognition and conclusions. We hope that as ICER continues to refine its processes and practices it will be able to better include that value and similar perspectives of real patients.

ICER's Budget Impact Assessment Process

ICER correctly determined that because valoctocogene roxaparvovec is not yet approved and more research is ongoing, the draft report should not include a Budget Impact analysis for this potential gene therapy. We applaud this decision, as such hypothetical exercises can do more harm than good.

However, in the past we have expressed concern about certain technical and procedural components of ICER's Budget Impact analyses, and with the current draft report there is an additional confusing aspect. Specifically, the draft report includes a Budget Impact analysis for emicizumab, even though it is not a newly approved compound; FDA approved this medicine in

November 2017. We find this inconsistent with ICER's potential Budget Impact analysis formula that includes the number of newly approved medicines as a fundamental factor. This is problematic because to anyone familiar with the reality of the U.S. health care system, off-label uses of approved medicines is both common and an expected and necessary part of quality health care, except in very rare circumstances. Thus, ICER's conducting a Budget Impact analysis on a 3-year-old medicine presents a murky analytical rationale within ICER's theoretical Budget Impact evaluation process.

We would appreciate ICER clarifying how it will consistently conduct potential Budget Impact analyses based upon original versus subsequently approved indications. We eagerly await ICER's insights about how it can be more consistent and coherent in this particular facet of its activities.

In addition, as we discussed in our comments to ICER's 2018 draft report about the use of emicizumab,[xi] people with hemophilia are not evenly distributed among all the different payers in the U.S. Specifically, data indicates that people with hemophilia are much more likely to be insured by Medicaid, and less likely to be insured by Medicare or the Veterans Health Administration. (It is not unreasonable to postulate that they are also very unlikely to be covered by the Department of Defense's health system.) However, when a curative gene therapy for hemophilia is available, those differences may disappear. We are not advocating that ICER attempt to include such forward, evolutionary modeling into its work – since our impression is that ICER prefers to view the future as a static situation – but we believe it must be part of broader discussions concerning how budget impact should be conducted, and modeling of potential future scenarios could be constructed.

Lastly, we would be remiss if we did not point out that ICER's style of global budget impact assessments don't account for the patient perspective: what matters to patients and their families is their actual costs, not some aggregate for the entire country. And further, regarding health system or payor budgets and spending, people with serious and chronic conditions have intense concerns about how any budget or access restrictions will impair innovations that could help treat or cure their health problems, and improve or prolong their lives – real-world implication that are generally missing from ICER's work and activities.

As we've stated before, and continue to maintain, presenting a "budget impact" analysis for the health care spending across the entire United States is essentially a fictional story.

<u>Additional Points</u>

- We are confused by the lack of inclusion of Serious Adverse Events in the Long-Term Cost Effectiveness Model inputs[xii] since in ICER's 2018 report SAEs were included in the model at a rate of 3%.[xiii] If there is a difference in clinically observed SAEs in people with and without inhibitors then this certainly should be presented and discussed by ICER.
- ICER's SST framework that arbitrarily picks caps of $150,000/patient/year or 50% over a lifetime for the amount of "cost savings" that a company might receive from a new treatment in this category[xiv] continues to be puzzling. We are particularly concerned about treatments – such as gene therapies – that could be very expensive to produce and administer, and as such if either the $150,000 number or a 50% threshold of "cost savings" were somehow

implemented, it could result in net losses for the company, leading to the discontinuation of the treatment or service.

- Reference #13 should be updated to the link for the most current label for emicizumab since the text refers to both the initial approval for hemophilia with inhibitors and the subsequent approval for hemophilia without inhibitors.
- The year for the World Federation of Hemophilia Guidelines should be 2020 not 2012.[xv]
- There is reference in the text to an economic model in a 2017 ICER report,[xvi] but there is no citation or footnote.

Conclusions

Patients Rising Now is pleased that people with hemophilia A have access to different treatment options, and that other new and better treatments and cures appear to be on the horizon. However, we are concerned that access to current and future treatments may be limited or barred by insurance plans and their agents through formulary design, cost-sharing structures, or prior authorization requirements because of ICER's activities, which may at the same time expand administrative burdens for clinicians and patients.

Sincerely,

Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

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[i] http://icerwatch.org/wp-content/uploads/2018/10/02232018-Patients-Rising-Comments-to-ICER-RE-HemophiliaA-FINAL-1.pdf
[ii] https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-emicizumab-kxwh-hemophilia-or-without-factor-viii-inhibitors
[iii] https://icer-review.org/material/hemophilia-a-final-evidence-report/
[iv] Draft report, p. 39
[v] For example, from the CDC: https://www.cdc.gov/ncbddd/hemophilia/inhibitors.html; from the Hemophilia Federation of America: https://www.hemophiliafed.org/understanding-bleeding-disorders/complications/inhibitors/; and from UpToDate: https://www.uptodate.com/contents/inhibitors-in-hemophilia-mechanisms-prevalence-diagnosis-and-eradication
[vi] https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-emicizumab-kxwh-prevention-and-reduction-bleeding-patients-hemophilia-factor-viii
[vii] Draft report, p. 28
[viii] Draft report, p. 29
[ix] Draft report, p 39
[x] Draft report p. 42
[xi] http://icerwatch.org/wp-content/uploads/2018/10/02232018-Patients-Rising-Comments-to-ICER-RE-HemophiliaA-FINAL-1.pdf
[xii] Draft report, p. 52
[xiii] "Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value" Final Evidence Report, April 16, 2018, p. 45, Table 4.8
[xiv] Draft report, p. 58
[xv] Draft report, p. 17 and reference #25
[xvi] Draft report, p. 67