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Maggie O’Grady  
Program Manager  
Institute for Clinical and Economic Review  
2 Liberty Square, 9th Floor  
Boston, MA 02109

Submitted Electronically: [mogrady@icer-review.org](mailto:mogrady@icer-review.org); [publiccomments@icer-review.org](mailto:publiccomments@icer-review.org)

Dear Ms. O’Grady,

Thank you for the opportunity to provide feedback to ICER on its draft evidence report for assessing the comparative clinical effectiveness and value of inclisiran (Novartis) and bempedoic acid (Nexleto™, Esperion Therapeutics, Inc.) for treatment of high cholesterol in the setting of heterozygous familial hypercholesterolemia (HeFH) and for secondary prevention of atherosclerotic cardiovascular disease (ASCVD). We appreciate your willingness to review comments and recommendations from the National Forum’s Value & Access Steering Committee and partners working on these issues.

The Value & Access (V&A) Steering Committee and partners operate under the consensus goal to enhance health and well-being by supporting people’s access to evidence-based care that is appropriate for them by:

- Identifying evidence-based strategies for determining appropriateness of care
- Supporting the implementation of evidence-based care that aligns incentives for patients, providers, payers, other stakeholders

The (V&A) Steering Committee and partners jointly offer the following feedback for ICER’s consideration in the development of the draft evidence report.

**Positives**

The Steering Committee and partners appreciate ICER’s inclusion in the draft evidence report of our recommendations on the draft scoping document :

- That ICER’s value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms (e.g., health disparities and access to care issues) are evaluated. We encourage ICER to continue increasing patient advocacy groups’ involvement in the process through direct outreach to groups with expertise in areas of focus, opportunities for meetings with ICER and its experts, and enhanced explanation of ICER’s processes.

- The clear identification of the populations of interest for this review including all patients with HeFH and patients with established ASCVD (secondary prevention).
- The inclusion of people with statin intolerance.
- The separate evaluation of data for the subpopulations.
- The review of both bempedoic acid alone and in combination with ezetimibe.
- The inclusion of health-related quality of life among Patient-Important Outcomes.
- The inclusion of important information about the designation of adults with HeFH having a high-risk equivalent of developing ASCVD even though they have not yet had an event, and that FH remains an underdiagnosed and undertreated subpopulation.

Additionally, the V&A Steering Committee and partners appreciate the following:

- Acknowledgements throughout the report of disparities in LDL-treatment goals for people with HeFH, the overall burden of ASCVD, and under-representation by race/ethnicity and sex in clinical trials. We encourage ICER to identify strategies to address the disproportionate burden on members of populations underrepresented in clinical trials.
- The inclusion of the patient perspective, including patient statements.
- The outline describing the type of input received from patients, caregivers, and advocacy organizations that informed ICER's research approach.
- Acknowledgements addressing the lack of data regarding:
  - relatively fewer injections (for inclisiran) and administration in the clinical setting, and whether that will translate into better real-world adherence and outcomes, and
  - the effect of recurrent events on quality of life

The Steering Committee and partners appreciate that ICER is open to stakeholders providing evidence to support alternative assumptions.

- Clear notation to caution readers against assuming values provided in the threshold analysis results section will approximate the health benefit price benchmarks (HBPBs) that will be presented in the next version of the report because results may change substantially due to input.
- Clear notation regarding uncertainty and controversies to help better understand the model and assumptions.

### **Opportunities**

- Patient Perspectives
  - There are additional opportunities for even more inclusivity of input from patients, caregivers, and advocacy organizations (noted above).
  - ICER's data inputs are focused on randomized controlled trials (RCT), which do not proportionately reflect real world demographics.<sup>1</sup> Studies have shown that the patient populations that are underrepresented in RCTs are often those with the highest risk and lower access to treatments<sup>2,3,4</sup> and additional data show that when step therapy is signaled, these populations are disproportionately left out.<sup>5</sup> We encourage ICER to find a way address this in its modeling.

- Comparator Populations
  - Despite having good outcomes, being low-cost, and being included as a step through before adding a PCSK9 inhibitor (per the 2018 ACC/AHA guidelines for the management of blood cholesterol) ezetimibe use among patients with ASCVD and HeFH is low ( $\leq 7\%$  in the U.S.).<sup>6,7,8</sup> Between 2007 & 2017 (except for a small increase in 2014), the number of ezetimibe prescriptions has consistently declined.<sup>9</sup>
    - In ICER’s key population characteristics estimation (pg. 60) from the National Health and Nutrition Examination Survey (NHANES), only 4.2% of people with prior ASCVD, and an LDL-C level  $>70$  mg/dL on statin therapy were taking ezetimibe. The model assumed that all patients would take ezetimibe, which is not a real-world scenario. Furthermore, this runs counter to the FDA-approved labeling for Nexletol/Nexlizet (both of which are approved as adjuncts to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C), and do not include the step through of ezetimibe.
  - Using consistent base cases would enable users of ICER reviews to make meaningful comparisons across therapies. For example, in its 2015 review and 2019 update,<sup>10</sup> “PCSK9 Inhibitors for Treatment of High Cholesterol,” ICER used maximally dosed statins as the base case. Using ezetimibe as another layer of therapy in the bempedoic acid/inclisiran base case makes this assessment incongruous with the one on PCSK9i’s.
  - Many patients, particularly those who require more than 20% LDL-C reduction, will fail to reach LDL-C targets on ezetimibe alone. For these patients, initiating a more potent LDL-C lowering agent than ezetimibe after statin therapy has been maximized may be preferred. Moreover, inertia and the time it takes to get patients’ therapy properly titrated will mean that high-risk patients will be at prolonged risk.
  - There are large numbers of FH and/or ASCVD patients with uncontrolled LDL-C. Inclisiran and/or bempedoic acid may provide an additional line of therapy for people who are not currently adequately treated.
  
- Base Case Results
  - The report states that, “...*This resulted in savings in downstream cardiovascular costs, but these savings were offset by increased costs of lipid-lowering therapy and background health care costs (due to additional years of life). Assuming that any improvements in survival were at perfect quality-of-life (per the evLYG approach) improved the cost-effectiveness of the intervention in every subgroup studied.*” (pg. 60). We urge ICER to note that improvements in health and survival are the aims of health care. As presently stated, it suggests the offset of savings due to additional years of life is a negative. This is particularly important for individuals who have premature coronary artery disease and HeFH with no further events because of effective LDL-C lowering on combination therapy.

- **Baseline Population Characteristics**
  - The baseline LDL-C level among patients on maximally tolerated statin and ezetimibe used in the model is  $88.8 \pm 1.2$  mg/dL (pg. 46) is significantly lower than baseline LDL-C levels in Phase III trials.<sup>11</sup> The goal for cholesterol treatment is significant, absolute lowering of LDL-C levels. Therefore, health impact and cost-effectiveness are minimized if using the lower number.
- **Sensitivity Analysis Results**
  - Major Adverse Cardiovascular Events (MACE) rates observed in real-world studies are substantially higher than those reported in randomized clinical trials, suggesting that the secondary MACE burden and potential benefits of effective CVD management in ASCVD patients may be underestimated if real-world data are not taken into consideration.<sup>12</sup> We suggest that ICER review this real-world data.
- **Statin Intolerance**
  - Statin use among patients with ASCVD remains suboptimal because of various patient- and clinician-related factors.<sup>13</sup>
  - Additional treatments, such as inclisiran and bempedoic acid, could help increase access and adherence to treatments in patients who are otherwise at risk for not taking and/or adhering to medications and therefore, at higher risk for adverse events.
- **Cost-effectiveness**

Some payers currently have bempedoic acid on Tier 2 formularies without restrictions. With an estimated cost of approximately \$10/day, they deem it cost-effective. In its report, ICER has stated that bempedoic acid at current prices is unlikely to achieve the commonly cited cost-effectiveness threshold of \$150K/QALY gained or the \$150K/evLYG thresholds. There is concern that some payers who currently have bempedoic acid on formulary as a cost-effective option may read ICER's report and make incorrect assumptions. We advocate for finding middle ground in the language that is used, as bempedoic acid is an inexpensive therapy already covered by some payers.
- **Voting Questions**
  - The economic analysis looks at four populations. We suggest the same approach be applied for clinical effectiveness and for the voting questions.
    - Adults with ASCVD
    - Adults with ASCVD and HeFH
    - Adults with ASCVD and statin intolerance
    - Adults with ASCVD and recent ACS

The V&A Steering Committee and partners would like to see how the recommendations we have provided impact the cost-effectiveness score. We know that there are additional data that come into consideration. It is important that model assumptions about the uptake of these medications

be informed by real world-evidence of uptake of other therapies. We support the right treatment to the right patient at the right time.

The V&A Steering Committee and partners recommend that ICER comment on/evaluate payer restrictions, namely the specialty restriction and step therapy considerations for bempedoic acid. Those restrictions would severely limit access to a medication that is easy to monitor, has few adverse effects, and does not require specialty training to decide whether to use it or not. In its report, ICER mentions that one payer has such specialty restrictions and also comments on the current step therapy restrictions for multiple plans.

Again, thank you for your consideration. We look forward to reviewing and providing additional comments once the evidence report is released.

Sincerely,

Members of the Value & Access Steering Committee and Partners representing the following organizations:

*National Forum for Heart Disease & Stroke Prevention (convener)*

*American Association of Heart Failure Nurses*

*American Heart Association*

*American Pharmacists Association Foundation*

*American Society for Preventive Cardiology*

*Association of Black Cardiologists*

*Association of State and Territorial Health Officials*

*BallengeRx Consulting*

*The FH Foundation*

*Global Healthy Living Foundation*

*Independent Health*

*Institute for Patient Access*

*Mended Hearts*

*National Alliance of Healthcare Purchaser Coalitions*

*National Lipid Association*

*Partnership to Advance Cardiovascular Health*

*Partnership to Improve Patient Care*

*Preventive Cardiovascular Nurses Association*

*University of Michigan Center for Value-Based Insurance Design*

## References

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