December 10, 2020

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Draft evidence report for high cholesterol therapies

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide comments regarding ICER's draft evidence report titled: "Bempedoic Acid and Inclisiran for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD: Effectiveness and Value," dated November 12, 2020.

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality health care. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient-centered care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of policy-minded health care providers committed to shaping a patient-centered health care system. IfPA is a 501(c)(3) public charity nonprofit organization.

Draft Evidence Report Comments

The prevalence of high low-density lipoprotein cholesterol (LDL-C), which is a major risk factor for atherosclerotic cardiovascular disease (ASCVD), remains alarmingly high in the United States. According to the Centers for Disease Control and Prevention, "93 million U.S. adults age 20 or older have total cholesterol levels higher than 200 mg/dL. Nearly 29 million adult Americans have total cholesterol levels higher than 240 mg/dL."[1]

Untreated ASCVD imposes substantial financial costs on the health care sector and broader economy. These costs include direct costs of higher health care expenditures and the indirect

[1] "High Cholesterol Facts" *Centers for Disease Control and Prevention*; https://www.cdc.gov/cholesterol/facts.htm#:~:text=95%20million%20U.S.%20adults%20age,higher%20than%20240%20mg%2FdL.&text=7%25%20of%20U.S.%20children%20and,19%20have%20high%20total%20cholesterol.

costs that include lost productivity and decreased quality of life. Cardiac events are also responsible for serious illnesses, permanent disability and nearly 1 million deaths annually.

Effectively managing high LDL-C mitigates many of these health implications; therefore, treatments that sufficiently lower patients' LDL-C offer great value. Statins are widely available in low-cost generic formulations and help many patients lower their LDL-C, but they do not adequately reduce LDL-C for all patients. The novel treatments inclisiran and bempedoic acid are designed to help these patients, and the emerging medical literature substantiates that these medicines are meeting this goal.[2] Thus, these treatments can provide a high-value treatment to the targeted patient population.

The draft evidence report recognizes that these medicines benefit patients who cannot use statins. As noted, clinicians view bempedoic acid and the bempedoic acid/ezetimibe combination therapy as "most helpful in patients with statin intolerance" (page 11).

Despite recognizing the therapies' value for patients who are not well treated by statins, however, the draft evidence report employs several assumptions and methodologies that bias the analysis toward undervaluing these treatments. They are as follows.

The Draft Evidence Report Relies on Cost Thresholds That are Inconsistent with the Systemic Cost of ASCVD

The annual threshold prices estimated in the report range between $920 and $5,480, depending on the dollar-per-QALY benchmark and drug. These values are low relative to the direct medical costs associated with heart disease.

Consider that the total annual costs of heart disease in 2030 will reach $1.1 trillion, adjusted for inflation.[3] Of these costs, $818 billion are direct medical costs. Patients with unmanaged risk factors, including the roughly 26.7 million Americans whose cholesterol levels are not well maintained by statins, will bear a disproportionate share of these costs.[4] For example, one-third of the total direct medical costs would average $10,334 per patient annually. Looking at the full scope of direct medical costs, that figure would average $30,626 per patient annually.

These high annual costs suggest that the cost thresholds used in the model are too low, too stringent. The excessively stringent thresholds could translate into inappropriate access barriers

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[2] Jia, Xiaoming et al. (2019) "Post Statin Lipid Therapeutics: A Review" *Methodist DeBakey cardiovascular journal* vol. 15,1: 32-38. doi:10.14797/mdcj-15-1-32; Laufs U. et. al. "Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance" Journal of the American Heart Association, March 29, 2019, https://doi.org/10.1161/JAHA.118.011662.

[3] Heidenreich PA, et al. (2011) "Forecasting the Future of Cardiovascular Disease in the United States A Policy Statement From the American Heart Association" *Circulation*, Vol. 123, No. 8, https://www.ahajournals.org/doi/full/10.1161/cir.0b013e31820a55f5.

[4] Akyea RK, et al. (2019) "Sub-optimal cholesterol response to initiation of statins and future risk of cardiovascular disease" *Heart*; 105:975–981. doi:10.1136/heartjnl-2018-314253. (emphasis added); Laufs U, et al. "Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance" Journal of the American Heart Association, March 29, 2019, https://doi.org/10.1161/JAHA.118.011662.

that block patients from efficacious treatments that could improve patient outcomes and decrease overall health care costs.

ICER's Preferred Base Case Doesn't Reflect Clinical Practice and Will Delay Patients from Reaching their Target

The base-case analysis makes assumptions that are inconsistent with actual clinical practice.[5] The draft evidence report assumes that all of the patients were treated with ezetimibe and a maximally tolerated statin (page 46). According to the National Health and Nutrition Examination Survey, however, only *4.2%* of the relevant patient population was treated in this manner. As a consequence, the base case in the draft evidence report rests on a distorted LDL baseline of 89 mg/dl, which is significantly lower than the observed LDL values of the relevant population (110 mg/dl).

The distortions created by this base case could also lead to access obstacles that delay patients from receiving efficacious treatments. As a consequence, it may take longer for many patients to reach their target LDL-C goals, with some never reaching their target. These delays increase the risks for cardiovascular events and mortality. They also will lead to avoidable increases in overall health care costs.

The Base-case Analysis Should Include Indirect Costs, Not Simply a "Health Care Sector Perspective"

Consistent with past reports, the draft evidence report relies on a "health care sector perspective" for the base-case analysis. The health care sector perspective ignores the indirect costs imposed by ASCVD that harm patients, diminish their quality of life and create other health risks. Since patients' welfare improves when indirect costs are reduced or, ideally, eliminated, these costs should be included in the base-case scenario.

Disregarding these costs by assumption means that the base case analysis ignores $276 billion in lost productivity and other indirect costs, causing the draft evidence report to underestimate the costs of untreated LDL-C by 33% of the actual total cost.[6]

The Indirect Cost Estimates in the Modified Societal Perspective are Undervalued

The draft evidence report accounts for indirect costs in its "modified societal perspective" by valuing the number of lost work hours based on the average earnings of all employees. These assumptions result in an estimate for indirect costs of $4,810 annually. Yet productivity losses are only one part of the indirect costs of cardiovascular disease, which also include premature

[5] The NHANES is a cross-sectional survey that is conducted every two years by the National Center for Health Statistics. ICER often uses this survey to provide nationally representative estimates of risk factors and disease prevalence.
[6] Heidenreich PA, et al. (2011) "Forecasting the Future of Cardiovascular Disease in the United States A Policy Statement From the American Heart Association" *Circulation*, Vol. 123, No. 8, https://www.ahajournals.org/doi/full/10.1161/cir.0b013e31820a55f5.

mortality and long-term disability. As a result, the proxy used in the draft evidence report is small relative to the current estimates for the indirect costs of heart disease.

To provide a sense of how significant the underestimate is, the annual indirect costs of ASCVD are estimated to reach $276 billion by 2030. Relative to the number of patients who experienced a cardiac event last year (1.06 million), the per-patient indirect costs equals $261,611. Relative to the 26.7 million patients estimated to be statin intolerant, the indirect cost burden equals $10,334 per statin intolerant patient.

The gap between these figures and the $4,810 in lost productivity costs used in the draft evidence report is substantial. By defining indirect costs solely in terms of lost productivity, the report significantly undervalues the magnitude of the indirect costs that patients are enduring. For the sake of accuracy, the final evidence report should re-evaluate its assumptions regarding the indirect costs of ASCVD and incorporate a more realistic estimate of these impacts.

The Base Model Does Not Examine Key Subgroups

The value of inclisiran and bempedoic acid is to provide an efficacious medicine to key subgroups. These subgroups include: (a) patients who have already experienced a cardiovascular event and must reach more aggressive LDL-C targets, (b) patients that do not respond well to statins, and (c) key demographic groups, such as African Americans, who bear a disproportionate burden from cardiovascular disease.

The base-case analysis does not incorporate the unique costs and benefits that the therapies offer these key subgroups. Therefore, the model contains an unacceptable amount of uncertainty regarding the estimated value that inclisiran and bempedoic acid offers the very patients these medicines are intended to help.

The Long-term Cost Effectiveness Model Should be Based on the Evaluated Drugs, Not Statins

The draft evidence report "assumed that the relationship between LDL-C lowering with each drug and the subsequent reduction in MACE rates would be identical to that observed with statins" (page 43). This is an inappropriate assumption.

The purpose of the model is to discover the cost effectiveness of the medicines under review – inclisiran and bempedoic acid – for the relevant patient group, which is patients who are statin intolerant. Consequently, the relevant relationship is the reduction in LDL-C caused by inclisiran and bempedoic acid for patients who are statin intolerant.

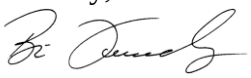
Basing the model on the relationship observed with statins introduces uncertainty into the results and undermines their reliability. And while the inclisiran relationship is used in a sensitivity analysis, this subsequent analysis does not correct the errors inherent in the base model.

Conclusion

Effective treatments that reduce the risk factors associated with ASCVD offers tremendous value to the patient community. IfPA urges ICER to account for the considerations outlined above before finalizing its evidence review.

If IfPA can provide further detail or aid the Institute for Clinical and Economic Review in incorporating any of the above recommendations into its final draft, please contact us at 202-499-4114.

Sincerely,



Brian Kennedy
Executive Director