ESPERION The Lipid Management Company

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July 23, 2020

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
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RE: Draft Scope for the Assessment of Treatments for High Cholesterol

Dear Dr. Pearson,

Esperion appreciates the opportunity to submit comments regarding the Institute for Clinical and Economic Review (ICER) draft scope on inclisiran and bempedoic acid for lipid lowering in patients with atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH).[1]

Bempedoic acid (BA) and the fixed dose combination of BA with ezetimibe (BA+EZE) are FDA-approved oral non-statin therapies indicated for ASCVD and HeFH patients who require additional LDL-C lowering as an adjunct to diet and maximally tolerated statins, which may mean no statin at all. BA is a first-in-class ATP citrate lyase inhibitor. Because BA acts on the same cholesterol biosynthesis pathway as statins, the efficacy of BA is pronounced in statin intolerant (SI) patients, a population with high unmet need for non-statin therapies. Additionally, in Phase 3 studies BA was associated with reductions in hemoglobin A1c (HbA1c) and high sensitivity C-reactive protein (hsCRP), important markers of glycemic control and inflammation, respectively, which have been associated with increased microvascular (HbA1c) and macrovascular (hsCRP) cardiovascular (CV) event risks.

Regarding the draft scope, Esperion would like to comment on the following topics:

1. **Populations**

Esperion recommends that ICER <u>quantitively</u> assess the cost-effectiveness of BA and BA+EZE in patients with SI as a dual base-case given that BA has greater lipid lowering effect in SI populations (BA reduces LDL-C by an average of 24.5% overall, and by 27.2% among patients on no statin at all).[2]

BA 180 mg was evaluated for efficacy and safety across 4 Phase 3 randomized controlled clinical trials of at least 12 weeks duration involving over 3600 patients.[2] Two studies focused on patients with ASCVD and/or HeFH receiving maximally tolerated statins[3,4] and two studies were conducted in patients with statin intolerance where maximally tolerated statin was no more than the lowest approved starting dose of a statin.[5,6] A fifth trial investigated the efficacy and safety of BA+EZE.[7] The 5 trials in the Phase 3 program are summarized in Table 1. A summary of pooled efficacy of BA by patient population as well by background statin therapy can be found in Table 2. Table 3 contains efficacy data for BA+EZE.

The published data in SI patients can inform a quantitative assessment of BA and BA+EZE in patients with SI.[2] Given the high CV risk and unmet need for non-statin treatments among SI patients[8,9] and the availability of data specific to SI in the phase 3 trials, Esperion recommends that ICER consider evaluating this population as a dual base case analysis for BA and BA+EZE. This approach is consistent with feedback ICER received from clinical experts during the draft scope period regarding the anticipated role of BA and BA+EZE in the treatment paradigm.

2. CV Event Rates

Esperion recommends that ICER use the most recent available real-world estimates of the baseline risk of CV events in the US population for model calibration.

Baseline CV event risk is an important driver in the model. We recommend that ICER use recent registry or other real-world data to assess baseline risk of CV events in the US population.

3. Timing

Esperion agrees with ICER's plan to "consider evidence from studies with at least 12 weeks of follow-up" and recommends using Phase 3 Week 12 LDL-C lowering data as the primary efficacy measure.

The Phase 3 trials of BA and BA+EZE were specifically powered to detect changes in LDL-C at Week 12, the primary endpoint. In the two 52 week BA studies, beginning after Week 24, the study protocols specified that blinded laboratory personnel would notify the investigator if a patient had met pre-specified LDL-C criteria (>170 mg/dL and ≥25% increase from the patient's baseline LDL-C value) to provide an opportunity for the blinded investigator to adjust the patient's background lipid-lowering regimen, therefore deviating from the pre-specified trial design used to estimate the expected net benefit of BA on LDL-C. For modeling analyses, we recommend that ICER use the Week 12 primary endpoint and account for patient disposition through discontinuation estimates from trial evidence.

4. Contextual Considerations

Esperion suggests that ICER consider BA's reductions in HbA1c, the risk of new onset diabetes (NOD), and hsCRP, as well as BA and BA+EZE's oral route of administration as important distinguishing contextual considerations for this evaluation.

a) **Impact on HbA1c and risk of NOD**
Statins have been associated with a small risk of NOD, especially in patients with a body mass index >30 kg/m^2, fasting blood glucose >100 mg/dL, metabolic syndrome, HbA1c>6% or those on a high intensity statin.[10] Despite the fact that the majority of patients in our Phase 3 trials had either prediabetes (51.6%) or diabetes (31.3%), treatment with BA did not worsen measures of glycemic control or increase NOD, and in fact was associated with a statistically significant improvement in HbA1c.[11] Diabetes is a major cardiovascular risk factor and, while statins are still the standard of care, improvement in glycemic parameters is a critical distinction between statins and BA. Improvement in measures of glycemic control are associated with decreases in CV events and health care expenditures, and increases in quantity and quality of life; these improvements in patient outcomes would increase the benefit of BA beyond LDL-C lowering and ultimately increase its value.

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b) Impact on hsCRP

Inflammation is a well-documented component of atherosclerosis[12] and the recent Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) demonstrated that reductions in hsCRP are associated with significantly reduced CV events in patients with stable atherosclerosis and elevated hsCRP ≥ 2 mg/L in the absence of any effects on lipids.[13] In the Phase 3 trials of BA and BA+EZE, median % change from baseline in hsCRP was significantly decreased at Week 12 in both ASCVD/HeFH patients and in patients with statin intolerance ($p<0.001$).[2]

c) **Oral route of administration**

BA and BA+EZE are effective oral, non-statin, once-a-day options for patients needing additional LDL-C lowering, especially among those who prefer to avoid injectable therapies. Studies suggest that oral therapies are preferred over injections by the majority of patients in the absence of serious side effects.[14,15,16,17,18]

In conclusion, we agree with many of ICER's planned approaches outlined in the draft scoping document (i.e., comparing each intervention with their respective placebo arm, evaluating hsCRP as an outcome of interest, and considering evidence from studies with at least 12 weeks of follow up) and appreciate ICER's thoughtful approach to this evaluation. Esperion recommends that ICER consider the key issues outlined above. Specifically, we urge ICER to quantitively evaluate statin intolerant patients in a dual base case analysis for both BA and BA+EZE, as this is a population with high CV risk and unmet need for non-statin treatment options. In addition, we recommend that ICER use the pre-specified LDL-C primary endpoint at 12 weeks for determination of efficacy. Finally, there are important contextual considerations that are relevant in this population, including impact of the interventions on glycemic control and inflammation, as well as route of administration.

Esperion appreciates the opportunity to share our recommendations with ICER on the Draft Scope. We look forward to working with ICER and providing additional comments throughout the remainder of this evaluation process. Please feel free to contact me should you wish to discuss in further detail.

Sincerely,

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APPENDIX

Table 1: Summary of the Bempedoic Acid Phase 3 Program Controlled Clinical Studies

Study	N	Randomization Ratio (BA:placebo)	Patient Population/Pool	Duration	Primary Efficacy Endpoint	Background Statin Use
Bempedoic Acid Program						
Study-040[3]	2330	2:1	ASCVD/HeFH on max tolerated statin	52 weeks	Week 12 % change LDL-C	99.9%
Study-047[4]	779	2:1	ASCVD/HeFH on max tolerated statin	52 weeks	Week 12 % change LDL-C	89.6%
Study-046[5]	345	2:1	Statin Intolerant	24 weeks	Week 12 % change LDL-C	8.4%*
Study-048[6]	269	2:1	Statin Intolerant	12 weeks	Week 12 % change LDL-C	31.2%**
Bempedoic Acid + Ezetimibe						
Study-053[7]	301	2:2:2:1	High CV risk (no pooled analysis)	12 weeks	Week 12 % change LDL-C	63%

*Only very low dose (below the lowest approved starting dose) statin allowed
**Only up to low dose statin allowed

Table 2: Summary of Mean Percent Change in LDL-C at Week 12 Compared to Baseline in the BA Phase 3 program[2]

Treatment	N*	Least-Square Mean (SE)	Difference (SE)	95% CI of the Difference	P value
Overall Results: ASCVD/HeFH Patients (Pooled data from 2 maximum tolerated statin RCTs included 97.2% on statin with 91% moderate or high intensity statin)					
BA	1922	-16.0 (0.48)			
Placebo	978	1.8 (0.74)	-17.8 (0.88)	(-19.5, -16.0)	<0.001
Overall Results: Statin-Intolerant Patients (Pooled data from 2 SI RCTs included 18% on statin that was no more than lowest approved starting dose, 82% on no statin)					
BA	399	-23.0 (1.11)			
Placebo	189	1.5 (1.30)	-24.5 (1.72)	(-27.8, -21.1)	<0.001
Pooled SI data: Percent Change from Baseline to Week 12 in LDL-C by Statin Use at Baseline					
Treatment	**N**	**Least-Square Mean (SE)**	**Difference (SE)**	**95% CI of the Difference**	**P value**
Background Statin (no more than lowest approved starting dose)					
BA	73	-10.5 (2.81)	-19.0 (4.82)	(-28.7, -9.4)	<0.001
Placebo	32	8.5 (3.91)	-	-	-
No Background Statin					
BA	326	-27.1 (1.12)	-27.2 (1.69)	(-30.6, -23.9)	<0.001
Placebo	157	0.2 (1.26)	-	-	-

* Number of subjects with data at week 12

Table 3: Summary of Mean Percent Change in LDL-C at Week 12 Compared to Baseline in the BA+EZE Phase 3 program[7]

Treatment	N*	Least-Square Mean (SE)	Difference (SE)	95% CI of the Difference	P value
Overall Results					
BA+EZE	86	-36.2 (2.56)			
Placebo	41	1.8 (3.49)	-38.0 (4.32)	(-46.5, -29.6)	P<0.001

* Number of subjects with data at week 12

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July 24, 2020

Submitted electronically to: publiccomments@icer-review.org

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Re: Scoping document comments

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide comments regarding ICER's Draft Background and Scope Document,"Inclisiran and Bempedoic Acid for Lipid Lowering in Patients with ASCVD or Heterozygous Familial Hypercholesterolemia: Effectiveness and Value," dated July 6, 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 health care providers committed to shaping a patient-centered health care system. IfPA is a 501(c)(3) public charity nonprofit organization.

Scoping Document Comments

Atherosclerotic cardiovascular disease (ASCVD) impacts a significant share of the U.S. population. According to the American Heart Association, more than 92 million Americans, around one-third of the total population, has some form of heart disease.[1]

Cardiac events associated with heart disease, such as strokes and heart attacks, cause nearly 1 million deaths annually in the United States. They also lead to adverse health outcomes, including serious illnesses and permanent disability. People with heart disease can mitigate many serious health implications by effectively managing their risk factors.

One major risk factor for ASCVD is a high low-density lipoprotein cholesterol (LDL-C) level. According to data from the Centers for Disease Control and Prevention, "95 million U.S. adults age 20 or older have total cholesterol levels higher than 200 mg/dL. Nearly 29 million adult

[1] (2017) "Heart failure projected to increase dramatically, according to new statistics" *American Heart Association;* https://www.heart.org/en/news/2018/05/01/heart-failure-projected-to-increase-dramatically-according-to-new-statistics.

Americans have total cholesterol levels higher than 240 mg/dL."[2] Current cholesterol management guidelines cite a target of less than 100 mg/dL for primary prevention of ASCVD and less than 70 mg/dL for secondary prevention. Given the risk of elevated cholesterol, treatments that sufficiently lower a patient's LDL-C level offer great value.[3]

Statins, widely available in low-cost generic formulations, serve this purpose for many patients. There is growing evidence, however, that statins cannot adequately reduce LDL-C values for some patients. In fact, a study in BMJ Heart concluded that "over half of the patients in the large general population studied did not experience an optimal reduction in their LDL-C, months after starting statin therapy. These patients had a significantly increased risk of future CVD (coronary artery disease, stroke/TIA, PVD) compared with those with an optimal cholesterol response."[4] Applied to the United States, these results indicate that more than 47.5 million Americans may not experience an optimal reduction in their LDL-C with a statin regimen alone. Those people may continue to live with elevated risks of cardiac events that could lead to permanent disability or even death.

The novel treatments discussed in the scoping document, inclisiran and bempedoic acid, are designed to help patients who remain at a high risk for cardiac events. As highlighted by a review of post-statin medications conducted by Jia et al. (2019), the current evidence supports the efficacy and safety of both of these medications.[5] These treatments have the potential to provide the targeted patient population with high-value benefits. To accurately assess whether these treatments provide their expected value, ICER's evaluation should reflect several considerations.

(1) The relevant cost comparisons should be to patients with untreated cardiac risk factors.

If inclisiran and bempedoic acid sufficiently lower LDL-C values for patients who cannot reach target with statin treatments, then patients who previously had an uncontrolled risk factor for cardiac events will now have access to efficacious medicines. Thus, the value of these medicines should be benchmarked to untreated/poorly treated patients, not to patients whose LDL-C values are well maintained by low-cost generic statins.

(2) Relevant health, economic and quality-of-life costs should be incorporated in the base case analysis.

According to the scoping document, "productivity changes and other indirect costs will be included in a separate analysis as available data allow." With respect to ASCVD, the impact on

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[2] "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.

[3] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. Circulation. 2019 Jun 18;139(25):e1082–e1143.

[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.

[5] Jia, Xiaoming et al. (2019) "Poststatin Lipid Therapeutics: A Review" *Methodist DeBakey cardiovascular journal* vol. 15,1: 32-38. doi:10.14797/mdcj-15-1-32

productivity and other indirect costs are important contributors to the value of the medicine for many patients living with heart disease. Relegating important life considerations to a separate analysis will significantly undervalue these medicines in the base model. From a patient perspective, such an undervaluation could undermine access to medicines that provide significant benefit.

(3) Key subgroups should be incorporated into the base case analysis.

The scoping document notes that, "data permitting," the analysis will evaluate the impact on patient subgroups that include higher risk ASCVD patients and patients with statin intolerance. The caveats are disconcerting.

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 consequently require medicines that will help them reach more aggressive LDL-C targets, (b) patients who experience statin-associated side effects, and (c) key demographic groups, such as African Americans, who bear a disproportionate burden of cardiovascular disease.

Unless the base case analysis incorporates the unique costs and benefits that the therapies offer these key subgroups, the models will contain an unacceptable amount of uncertainty regarding the estimated value that inclisiran and bempedoic acid offers patients.

(4) The analysis should explicitly account for the long-term budget impact of these treatments.

Managing elevated LDL-C levels is a long-term endeavor. Therefore, value assessments of inclisiran and bempedoic acid should also take a long-term budget perspective. If the value assessment uses an inappropriately short-term timeframe, then the results of the analysis may fail to account for the drugs' full health benefits. The failure to incorporate these longer-term benefits will, by definition, bias the analysis toward undervaluing the drugs' benefits for patients.

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 when performing its clinical evidence review.

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

Sincerely,

Brian Kennedy
Executive Director

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July 24, 2020

Maggie O'Grady
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Submitted Electronically: mogrady@icer-review.org, publiccomments@icer-review.org

Dear Ms. O'Grady,

Thank you for the opportunity to provide feedback to ICER on its draft scoping document for assessing the comparative clinical effectiveness and value of inclisiran (Novartis) and bempedoic acid (Nexletol™, Esperion Therapeutics, Inc.) for treatment of high cholesterol in the setting of heterozygous familial hypercholesterolemia or secondary prevention of 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 Steering Committee and partners reviewed the draft scoping document and jointly offer the following feedback for ICER's consideration.

Positives:

The Steering Committee and partners affirm the inclusion of the following key points in the draft scoping document:

- Consideration of the HeFH and ASCVD populations separately
- Inclusion of people with statin intolerance
- Review of both bempedoic acid alone and in combination with ezetimibe
- Inclusion of health-related quality of life among Patient-Important Outcomes

Opportunities:
The Steering Committee and partners identified the following opportunities for the review.

- As mentioned in the section above, we appreciate the examination of data related to patients with HeFH with and without established ASCVD (secondary and primary prevention).
  - High ASCVD event rates suggest that adults with FH warrant designation as having an ASCVD risk equivalent even though they have not had an event. Earlier and more aggressive therapy of FH is needed to prevent ASCVD events.[1] Importantly, evidence suggests that health disparities

contribute to undertreatment of FH patients in the US.[2] Increased efforts are warranted to raise awareness and treatment of these patients.

- Health system utilization was not included among outcomes. Based on the increased healthcare resource utilization by people with ASCVD, including these costs is important to gain a complete understanding of the cost-effectiveness of the treatments being reviewed.

- We recommend that future reviews focus on cost and clinical effectiveness in which ICER has demonstrated strength, and not include budget impact analysis. However, if this review includes a budget impact analysis, we recommend using realistic estimates of the actual use of medications and the cost of non-utilization and non-adherence. Data show that the overall non-utilization /non-adherence rate can be up to 50%.[3] In patients with hyperlipidemia, data show between 44.4% and 52.7% non-adherence.[4] Leaving out the non-utilization rate would distort the overall budget impact.

- We appreciate your inclusion of information on wasteful or lower-value services and recommend that you interview Dr. Mark Fendrick, Director of the University of Michigan's Center for Value-Based Insurance Design whose work centers around these issues. Dr. Fendrick is a member of the Value & Access Steering Committee. We would be happy to introduce you to him.

Again, thank you for your consideration. We would like to have the opportunity for representatives from the Steering Committee to meet with your team to further the conversation.

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
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
WomenHeart

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[2] Amrock SM, Duell PB, Knickelbine T, et al. Health disparities among adult patients with a phenotypic diagnosis of familial hypercholesterolemia in the CASCADE-FH™ patient registry. Atherosclerosis. 2017;267:19-26. doi:10.1016/j.atherosclerosis.2017.10.006

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[4] Gillespie CW, Morin PE, Tucker JM, et. al. Medication Adherence, Health Care Utilization, and Spending Among Privately Insured Adults With Chronic Conditions in the United States, 2010-2016. Am J Med. 2020;133:690-704. DOI:https://doi.org/10.1016/j.amjmed.2019.12.021

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Executive Summary

The Novartis Pharmaceuticals Corporation (Novartis) appreciates the opportunity to provide feedback on the Institute of Clinical and Economic Review's (ICER) draft scoping document for the assessment of treatments for high cholesterol. In summary, Novartis respectfully offers the following suggestions for consideration:

- Standard of care (as defined in the ORION-10 trial) should be the primary comparator of the assessment.
- The economic evaluation of inclisiran should include the expected benefits of better compliance to therapy associated with the inclisiran treatment regimen.
- There are benefits associated with the health care professional (HCP) administration of inclisiran that should be noted in the assessment.
- Novartis is open to discuss specific sub-groups of relatively higher risk of cardiovascular events, although the trials are not adequately powered to address these.
- Clearance of inclisiran is not a concern, and long-term safety data shows that inclisiran is well-tolerated.
- Clarity on how biomarker outcomes (e.g., apolipoprotein B, lipoprotein (a), high-sensitivity C-reactive protein, etc.) will be utilized in the assessment would be helpful.
- Clarification around the definition of "maximally tolerated lipid-lowering therapies" is needed.

The remainder of this letter provides a more detailed discussion of these points.

Standard of care (as defined in the ORION-10 trial) should be the primary comparator of the assessment.

Inclisiran is the first and only cholesterol-lowering small interfering ribonucleic acid (siRNA) that delivers durable, potent, and safe reduction of LDL-C levels (Raal et al, 2020; Ray et al, 2020). The standard of care in the management of LDL-C in US atherosclerotic cardiovascular disease (ASCVD) patients is based on the utilization of statins (Grundy et al, 2018); additionally, this is the basis of the placebo arm in the inclisiran clinical development program. Real-world studies have shown utilization of PCSK9 inhibitor monoclonal antibodies (PCSK9i mAbs) to lower LDL-C levels remains low. One real-world study using data from the National Patient-Centered Clinical Research Network of >3.6 million patients with dyslipidemia, coronary artery disease, coronary heart disease, or untreated LDL-C ≥130 mg/dL found that approximately half of patients had been prescribed lipid-lowering medication but <1% were being prescribed PCSK9i mAbs (Chamberlain et al, 2019). Additionally, PCSK9i mAbs are not considered as part of standard of care treatment for high cholesterol (Grundy et al, 2018). Given the lack of inclusion of PCSK9i mAbs in standard of care treatment for high cholesterol and the low real-world utilization of PCSK9i mAbs, Novartis believes the most relevant comparator for this ICER assessment is maximally tolerated statin regimens.

The economic evaluation of inclisiran should include the expected benefits of better compliance to therapy associated with the inclisiran treatment regimen.

Novartis recommends that ICER incorporate compliance in the cost-effectiveness model. Given the variation in dosing schedule and routes of administration of treatments, there may be significant differences in compliance across treatments that may impact the achievement of LDL-C goals and long-term cost-effectiveness results. Studies have shown that statin discontinuation rates increase

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over time due to poor adherence and side effects, ranging from 12% to 15% after 6 months of starting therapy (Booth et al, 2017; Colantonio et al, 2017), and rising to 50% to 70% after 1 and 2 years, respectively (Maddox et al, 2014; Hirsch et al, 2015). Additionally, a retrospective study of PCSK9i mAbs found that 52% of patients experienced an interruption in PCSK9i mAb therapy in the first year after treatment initiation (Rymer et al, 2020).

There are benefits associated with HCP administration of inclisiran that should be noted.

Inclisiran is administered via subcutaneous injection into the abdomen by a HCP. The recommended administration schedule is an initial single subcutaneous injection, again at 3 months, followed by every 6 months thereafter. Given the twice-yearly dosing schedule, the burden of administration is lower than other injectable treatments that are administered more frequently and oral treatments that need to be taken daily.

The HCP administration of inclisiran biannually is a significant advantage over current therapies and can circumvent typical adherence issues associated with patient self-administration (e.g. self-injection anxiety, delayed doses). There are several benefits of administration by a HCP, including increased adherence and proper administration technique. With the HCP-administered regimen, physicians have certainty that the patient has taken the medication and is able to follow-up with the patient twice a year. Furthermore, research in other asymptomatic conditions has shown that patients have better adherence to treatment when receiving a therapy administrated by an HCP. A study of postmenopausal women with osteoporosis found that patients receiving subcutaneous denosumab injections every 6 months were more adherent, compliant, and persistent compared to patients receiving once-weekly alendronate tablets (Freemantle et al, 2012).

Unlike complex infusion therapies, inclisiran will be considered for reimbursement purposes, a simple HCP administered subcutaneous therapy. Costs for outpatient administration of inclisiran compared to other treatments for high cholesterol are not significantly higher. For inclisiran, patients would incur a cost of $14.44 for the administration, based on Healthcare Common Procedure Coding System (HCPCS) codes (CMS 2020).

Novartis is open to discuss specific sub-groups of relatively higher risk of cardiovascular events.

Data permitting, sub-group analyses of more severe patients could be explored. Nonetheless, it should be noted that the inclisiran clinical program did not focus on patients with recent MI as a subgroup, and therefore, this sub-group was not pre-specified for analyses. Similarly, there were very few patients (approximately 5-10%) with statin intolerance in ORION-10 and ORION-11. Novartis is open to discussing specific sub-groups of relatively higher risk of cardiovascular events, although the trials are not adequately powered to address these. ORION-10 and ORION-11 did conduct sub-group analyses, with the evidence indicating consistent results across various sub-groups (e.g., demographic and baseline clinical factors; Ray et al, 2020).

Clearance of inclisiran is not a concern, and long-term safety data shows that inclisiran is well-tolerated.

Novartis would like to clarify the clearance and safety/tolerability data for inclisiran. Page 2 of the draft scoping document states: “Some clinicians said they would be cautious about adoption of inclisiran given its slower clearance from the body and its relatively limited safety experience. A patient started on inclisiran could theoretically be at risk for some side effects for a much longer period of time compared to patients started on PCSK9s [mAbs] or other shorter-acting

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medications." After administration, inclisiran is predominantly taken up by the liver and cleared by the kidney (Fitzgerald et al, 2017). Inclisiran has a short plasma half-life (5-10 hours), regardless of renal impairment, and systemic exposure to inclisiran is much more limited in duration than the duration of the pharmacodynamic effects, as inclisiran is not detected in plasma 24 to 48 hours after administration (Wright et al, 2020).

The safety of inclisiran has been established through 18-month pivotal trial data. This is a longer follow-up duration than the registration trials from other LDL-C lowering therapies and accounts for the longer duration of effect of inclisiran. Interim 3-year follow-up results (N=290) from the ongoing ORION-3 (ClinicalTrials.gov Identifier: NCT03060577) open-label extension study of ORION-1 (ClinicalTrials.gov Identifier: NCT02597127) showed that inclisiran was well-tolerated (Kastelein 2019). Over 3 years, injection site reactions were infrequent, of mild to moderate severity, and transient. Additionally, there were no liver function test (LFT) elevations, myalgias or creatinine phosphokinase (CPK) elevations, or renal adverse events or thrombocytopenia considered related to inclisiran. There was one cerebrovascular accident death that was related to underlying ASCVD (Kastelein et al, 2019). Overall, the long-term safety and tolerability results were consistent with trials of shorter duration. Therefore, concerns related to the persistence of side effects are not currently supported by trial data. Patients who completed the 18-month trials of inclisiran were eligible to continue receiving inclisiran in another open-label extension study (ORION-8; ClinicalTrials.gov Identifier: NCT03814187) that is currently ongoing. Novartis will continue to closely monitor the safety in patients on inclisiran and report this data when available.

Clarity on how biomarker outcomes (e.g., apolipoprotein B, lipoprotein (a), high-sensitivity C-reactive protein, etc.) will be utilized in the assessment would be helpful.

Novartis recommends that ICER provide more clarity on how information on biomarker outcomes will be utilized in the comparative clinical evidence review and cost-effectiveness model.

Clarification around the definition of "maximally tolerated lipid-lowering therapies" is needed.

Novartis recommends that ICER provide clarity on the definition of maximally tolerated lipid-lowering therapies. It is unclear whether the term "maximally tolerated lipid-lowering therapies" refers to only maximally tolerated statins. Novartis recommends that ICER focus on maximally tolerated statin therapies, as this aligns with the inclusion criteria used in the inclisiran clinical trials (Raal et al, 2020; Ray et al, 2020).

We appreciate the opportunity to provide comments for this assessment and feel that consideration should be given to the points we have made to ensure a scientifically sound assessment.

Sincerely,
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