



**Bempedoic Acid and Inclisiran for Patients
with Heterozygous Familial
Hypercholesterolemia and for Secondary
Prevention of ASCVD:
Final Policy Recommendations**

March 2, 2021

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the February 5, 2021 Midwest CEPAC public meeting on the use of bempedoic acid with or without ezetimibe and inclisiran for the treatment of HeFH and for secondary prevention of ASCVD. At the meeting, ICER presented the findings of its revised report on these treatments and the Midwest CEPAC voting council deliberated on key questions related to their comparative clinical effectiveness, potential other benefits and contextual considerations, and long-term value for money at current prices. Following the votes, ICER convened a Policy Roundtable of two patients, two clinical experts, two payers, and two representatives from pharmaceutical manufacturers to discuss how best to apply the evidence and votes to real-world practice and policy. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed [here](#), and a recording of the voting portion of the meeting can be accessed [here](#). More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's report on these treatments, which includes the same policy recommendations, can be found [here](#).

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

All Stakeholders

All stakeholders should ensure that the introduction of new therapies for high cholesterol do not exacerbate existing health inequities and should strive to decrease inequity in the health care system by decreasing cost and access barriers for patients to access effective therapies.

In particular:

- Manufacturers should price new therapies according to value to lower initial barriers to accessing therapy. Race and ethnicity have been shown to be a significant predictor of medication underuse, and disparities exist even with health insurance, in part due to drug costs. Pricing in alignment with and in reasonable proportion to the benefits for patients provides ample rewards for innovation while assuring greater affordability to the health care system. Responsible pricing fosters improved affordability and thus better access for patients.

- Payers can help reduce health inequities by recognizing the distinctive access barriers that disadvantaged communities can face and taking steps to assure that coverage criteria take into consideration challenges patients may have with transportation, family support, and greater comorbidity. Allowing greater choice among options of similar effectiveness with different modes of administration and side effect profiles can be one way to help remove barriers that may disproportionately affect communities of color.
- Clinicians and professional societies should take steps to improve outreach to patients in racial/ethnic minority populations, as these populations both bear a higher burden of ASCVD and, along with women, are more likely to be undertreated. This should include outreach strategies tailored to diverse populations (e.g., partnering with established community-based organizations for outreach, developing linguistically and culturally appropriate messaging, encouraging lipid-lowering treatment as part of preventive care messaging, and seeking non-clinical venues including, but not limited to, barbershops and salons, places of worship, community centers, and health fairs, to encourage screening and education regarding ASCVD).
- Researchers should work to increase recruitment and retention of minority populations for clinical trials to ensure that there is adequate data for analysis regarding efficacy and safety in racial/ethnic subpopulations. Researchers should also seek to use large, population-based data sources to elucidate populations in which underuse of effective therapies occurs.

All stakeholders should act to help increase awareness about the diagnosis and treatment of high cholesterol and, in particular, address the underdiagnosis and undertreatment of familial hypercholesterolemia (FH).

In particular:

- Clinicians should align their lipid screening protocols with clinical guidelines to ensure that all patients are being screened appropriately for lipid disorders.
- Payers should ensure that appropriate coverage is provided for diagnostic tests for FH but should also work with clinical experts to guide approaches to accepting clinical diagnosis based on obvious signs of early ASCVD in the setting of extremely high LDL-C cholesterol
- Manufacturers may consider direct-to-consumer advertising about FH and ASCVD to encourage consumers to seek testing for these conditions.

Along with encouraging steps to improve diet and exercise, all stakeholders should seek to increase utilization of effective therapies such as statins and ezetimibe for patients with

established ASCVD and HeFH. These therapies are backed by extensive evidence, are safe for the vast majority of patients, and are far less expensive than other treatment options.

In particular:

- Payers should minimize barriers to obtaining effective therapies such as statins and ezetimibe. For ezetimibe, its current low level of utilization is in part due to barriers to prescribing that clinicians experienced in the past due to the drug's high price at launch and substantial prior authorization barriers. Today, backed by long-term evidence of clinical benefit, support in clinical guidelines, and a lower price for the generic version, use of ezetimibe is inappropriately low and should be encouraged by all stakeholders for appropriate patients.
- Health systems should provide clinicians the time and support to implement shared decision-making to help patients make appropriate choices about lipid-lowering therapy. Some underuse of statins may be due to misconceptions about statin therapy and the importance of lifelong medical therapy for the treatment of ASCVD and HeFH. Shared decision-making can be effective in improving patient knowledge of the relative benefits and harms of treatment, in improving patient activation in the decision-making process, and potentially in improving patient adherence to therapy.
- Clinicians, health systems, and payers should seek ways to increase appropriate screening for lipid disorders and identify and reach out to eligible patients who are not currently on appropriate lipid-lowering therapy or at their LDL-C goal. This may include using electronic health record data or registries to identify and track patients, using clinical staff or other ancillary health providers (e.g., pharmacists) to assist in counseling patients about the importance of lipid-lowering therapy, and identifying and implementing effective methods for increasing uptake of statins.
- Professional societies should seek ways to increase uptake of effective therapies for lowering cholesterol at the population level, including working with clinicians and patient advocacy groups to develop evidence-based messaging around the benefits and harms of statin therapy, developing evidence-based patient education materials, and supporting research to identify underuse.
- Patient advocacy organizations should seek to increase awareness around effective therapies and frame the benefits and harms of statin therapy objectively so that patients can engage in shared decision-making with their clinicians and make decisions based on evidence rather than anecdotal experiences often amplified through social media.

Payers

Payers should develop consistent prior authorization criteria for lipid-lowering drugs and assure that the documentary burden and other administrative elements of prior authorization do not create an unreasonable burden on clinicians and patients.

One of the barriers to access to effective lipid-lowering therapies are the varied prior authorization criteria among payers. Although health plans are not legally able to collaborate to create common prior authorization criteria, they should seek forums with professional societies, guideline authors and patient groups, and use publicly available materials to establish norms and standards around the approach to prior authorization, including whether step therapy on clinical grounds is appropriate. Doing so could streamline work for clinicians and increase access for patients.

Payers should also ensure that they take steps to implement prior authorization through administrative procedures that are transparent and efficient. Even the most clinically reasonable set of prior authorization criteria can be implemented in a way that creates an unreasonable burden through excessive requirements for prior medical records, labyrinthine algorithms, paper-based applications, and spotty responsiveness of payer representatives through phone or email. For example, prior authorization should be available through electronic formats not requiring fax or printed material; and re-authorization of coverage should be streamlined to reduce burden on clinicians and patients, given that ASCVD and HeFH are lifelong conditions and the need for therapy is not likely to change over the patient's lifetime. In considering how to design prior authorization content and procedural policies, payers should be aware of and seek to implement standards developed by ICER and other independent groups that help assure the appropriate implementation of prior authorization and step therapy policies.¹

Payers should work with clinical experts and patient groups to develop consistent criteria and procedures for demonstrating drug intolerance due to statin associated side effects (SASE).

Statin associated side effects (SASE) are among the most common reasons to seek use of newer non-statin therapies such as PCSK9 inhibitors. Criteria for establishing SASE vary amongst health plans. For example, some health plans will look for claims for two trials of statin drugs with an initial denial if not found, requiring clinician appeal; others accept initial clinician attestation of SASE. Furthermore, periodic re-authorization is often required, adding to provider and patient burden and presenting an additional barrier to access of effective non-statin therapies.

Payers should work with clinical specialty societies and patient groups to establish a more consistent operational definition for the threshold of SASE that will qualify patients for coverage for additional therapies. This definition should then be implemented in an efficient manner. For initial prior authorization, payers may accept clinician attestation, or they may design an efficient algorithm based on claims data and/or medical records, but the latter option should be tested to

ensure that it does not ensnarl clinicians and patients trying to gain appropriate treatment. Furthermore, if claims data or medical record data are required, payers should ensure that patients who are switching plans and may not have ready access to previous records are not required to re-try statins. One way to operationalize this safeguard for new-to-plan patients would be to institute a “transition of care” period during which clinician attestation is accepted for all patients during a time frame long enough to allow discussion and review of the patient’s situation.

Payers should ensure that coverage criteria reflect the status of higher-risk subpopulations for whom therapies may be both more clinically effective and cost effective.

For certain populations in need of additional lipid lowering, some therapies may be more clinically and cost effective than in the general population. For example, bempedoic acid gives a greater degree of LDL-C lowering in patients with SASE, and so those patients may derive particular benefit from this treatment. In such cases, consideration should be given to broader coverage criteria (e.g., skipping step therapy with ezetimibe).

Drug-Specific Considerations for Bempedoic Acid with or without Ezetimibe

Bempedoic acid with or without ezetimibe represents an additional option for oral lipid-lowering therapy for patients with established ASCVD and/or FH. Bempedoic acid may be of greatest utility clinically in patients who have SASE or who are unwilling or unable to take injectable therapies, and consideration should be given to decrease barriers to treatment in these populations. Additionally, in particularly high-risk populations such as patients with FH or a recent cardiovascular event, steps to decrease barriers to treatment – such as more permissible criteria for skipping step therapy – should be considered to ensure timely access to treatment and avoid delays in care.

Patient Eligibility Criteria

- a. **Diagnosis/patient population:** The FDA labeled use for bempedoic acid with or without ezetimibe is “as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia [HeFH] or established atherosclerotic cardiovascular disease [ASCVD] who require additional lowering of LDL-C.” Diagnosis of HeFH can be established either by genetic testing for an LDL-C-raising gene defect or by clinical criteria (LDL-C \geq 190 mg/dL with premature CAD or 1 first-degree relative similarly affected). Payers may choose to accept clinician attestation of these criteria or may institute a requirement for documentation. Diagnostic criteria for “established ASCVD” includes any evidence of coronary artery disease, peripheral artery disease, or cerebrovascular disease. Patients may qualify through cardiovascular events, symptoms, or abnormal testing (e.g., cardiac catheterization). For patients requesting coverage without established ASCVD or FH, some payers may wish to consider providing

coverage for patients with LDL-C > 100 mg/dl who are at “high risk” for future ASCVD by means of a documented 10-year ASCVD risk of $\geq 20\%$ and/or the presence of diabetes.

- b. **Clinical eligibility criteria:** Current clinical guidelines establish 70 mg/dl as the threshold for LDL-C among patients with established ASCVD, so coverage criteria are likely to deny coverage initially for patients who are already below that level. The primary consideration for clinical eligibility will often be whether patients have had a reasonable trial of “maximally tolerated statin therapy.” As noted earlier, criteria for establishing SASE vary amongst health plans. Following clinical guidelines, many health plans require two trials of statin drugs that have been halted because of side effects, but others require trials with more than two statins. Patient advocates and clinical experts suggest that requiring more than two trials is counterproductive.

Some payers will accept clinician attestation to document adequate trials of statins with SASE, whereas other payers will require documentation of both. Payers should be aware, however, that patients may have had unsuccessful trials on statins many years previously, making it challenging or impossible to obtain past records in all cases.

- c. **Exclusion:** Approximately 10% of patients with a history of gout had a gout event during the trial of bempedoic acid, but neither hyperuricemia nor history of gout were included as contraindications in the FDA label.

Step Therapy

Prior to the initiation of bempedoic acid with or without ezetimibe, patients should be on maximally tolerated statins or have documented SASE and not have reached their LDL-C goal according to clinical guidelines. Payers may wish to consider step therapy with ezetimibe prior to bempedoic acid, as some patients may reach their LDL-C goal with the combination of statin and ezetimibe, both of which are generic drugs and have been shown to improve cardiovascular outcomes. This would be consistent with the 2018 AHA/ACC clinical guidelines.² However, if patients are not on ezetimibe and are unlikely to reach their LDL-C goal with the addition of ezetimibe alone (e.g., $\geq 25\%$ above their LDL-C goal with adherence to their maximally tolerated statin dose), payers should allow coverage for the combination pill of bempedoic acid with ezetimibe without requiring a first step through ezetimibe. Direct access for these patients to the combination pill would be consistent with appropriateness criteria for step therapy that step therapy should only be used when patients have an excellent chance to achieve treatment goals with the first-step therapy.¹

Renewal Criteria

As ASCVD and FH are lifelong conditions, once approval has been given for therapy, barring new

safety concerns, renewal of prior authorization should either not be necessary or be automatic to minimize burden on clinicians, pharmacists, and patients and prevent disruptions or delays in care.

Provider Qualification Criteria

Any provider should be able to prescribe bempedoic acid with or without ezetimibe; specialist consultation should not be necessary.

Drug-Specific Considerations for Inclisiran

Inclisiran will be considered as an option for patients also eligible for PCSK9 inhibitors. Until inclisiran has completed trials demonstrating its clinical effects, payers may choose to prefer PCSK9 inhibitors. However, if clinical outcomes data for inclisiran confirm assumptions of comparable effectiveness to PCSK9 inhibitors, either payers or manufacturers may suggest a lower price for one option if it is made the only option in the formulary. This approach to negotiating lower prices in return for exclusive formulary placement can be appropriate under certain circumstances, but payers and manufacturers should be aware that the very different delivery schedule and administration of inclisiran and the PCSK9 inhibitors may offer distinct advantages for some patients based on their living situation and other factors beyond mere preference. These factors should be carefully weighed with input from patient groups and clinical experts if excluding inclisiran or PCSK9 inhibitors from a formulary is ever under consideration.

Patient Eligibility Criteria

- a. **Diagnosis/patient population:** Inclisiran has not been approved yet and therefore has no FDA labeled indication, but all of its trials enrolled adults with ASCVD, with some trials including patients with ASCVD equivalents. All trials required patients to be on maximally tolerated lipid lowering therapy. The ORION 9 trial enrolled patients with HeFH and/or untreated LDL-C >190 mg/dL and a family history of FH, elevated cholesterol, or early heart disease on maximally tolerated statin therapy ± ezetimibe. It seems likely that the FDA will consider a label broadly inclusive of these patient groups and one that may even be worded more broadly than the label for PCSK9 inhibitors (adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol (LDL-C).

As with bempedoic acid, payers may wish to design coverage criteria that bring more specificity to the diagnostic criteria for these conditions. Diagnosis of HeFH can be established either by genetic testing for an LDL-C-raising gene defect or by clinical criteria (LDL-C \geq 190 mg/dL with premature CAD or 1 first-degree relative similarly affected). Payers may choose to accept clinician attestation of these criteria or may institute a requirement for documentation. Diagnostic criteria for “established ASCVD” includes any evidence of

coronary artery disease, peripheral artery disease, or cerebrovascular disease. Patients may qualify through cardiovascular events, symptoms, or abnormal testing (e.g., cardiac catheterization). For patients requesting coverage without established ASCVD or FH, some payers may wish to consider providing coverage for patients with LDL-C > 100 mg/dl who are at “high risk” for future ASCVD by means of a documented 10-year ASCVD risk of $\geq 20\%$ and/or the presence of diabetes.

- b. **Clinical eligibility criteria:** Current clinical guidelines establish 70 mg/dl as the threshold for LDL-C among patients with established ASCVD, so coverage criteria are likely to deny coverage initially for patients who are already below that level. The primary consideration for clinical eligibility will often be whether patients have had a reasonable trial of “maximally tolerated statin therapy.” As noted earlier, criteria for establishing SASE vary amongst health plans. Following clinical guidelines, many health plans require two trials of statin drugs that have been halted because of side effects, but others require trials with more than two statins. Patient advocates and clinical experts suggest that requiring more than two trials is counterproductive.

Some payers will accept clinician attestation to document adequate trials of statins with SASE, whereas other payers will require documentation of both. Payers should be aware, however, that patients may have had unsuccessful trials on statins many years previously, making it challenging or impossible to obtain past records in all cases.

- c. **Exclusion:** There are no specific contraindications or risks uncovered in the pivotal trials to suggest specific clinical exclusion criteria.

Step Therapy

Prior to the initiation of inclisiran, patients should be on maximally tolerated statins or have documented SASE and not reached their LDL-C goal according to clinical guidelines. Payers may wish to consider step therapy with ezetimibe prior to inclisiran or PCSK9 inhibitors, as some patients may reach their LDL-C goal with the combination of statin and ezetimibe, both of which are generic drugs and have been shown to impact cardiovascular outcomes. This would be consistent with clinical guidelines. However, if patients are not on ezetimibe and are unlikely to reach their LDL-C goal with the addition of ezetimibe alone (e.g., $\geq 25\%$ above their LDL-C goal with adherence to their maximally tolerated statin dose), payers should allow coverage for inclisiran without requiring a step through ezetimibe. A required step through bempedoic acid plus ezetimibe may be considered for patients close to their LDL-C threshold, but patient experts and clinical experts have suggested that for some patients the risk of poor adherence to additional oral treatment will create an important clinical opportunity for inclisiran to help patients reach LDL targets. Under such circumstances, direct access for these patients to inclisiran would be consistent with

appropriateness criteria for step therapy that require that patients have an excellent chance at treatment success with the first-step therapy.¹

Renewal Criteria

As ASCVD and FH are lifelong conditions, once approval has been given for therapy, barring new safety concerns, renewal of prior authorization should either not be necessary or be automatic to minimize burden on clinicians, pharmacists, and patients and prevent disruptions or delays in care.

Provider Qualification Criteria

If inclisiran is to be given in a healthcare setting, consideration should be given to allow prescribing by primary care clinicians who have access to consultation with lipid-lowering specialists (e.g., cardiology, endocrinology, or other lipidologists). Although inclisiran does not present significant known risks, many patients with ASCVD or HeFH are likely to benefit if inclisiran administration is integrated into a broader care approach that is designed with input from a specialist. Allowing primary care prescribing with access to consultation would help address access concerns for patients in rural areas or those who have other challenges getting to specialty care centers.

Manufacturers

Manufacturers should seek to set prices that will foster affordability and good access for all patients by aligning prices with independent assessments of the therapeutic value of their treatments. In particular, until cardiovascular outcomes data are available from ongoing trials, Novartis should fulfill its stated intent to set the price of inclisiran at or below the cost-effective range of pricing for PCSK9 inhibitors.

Drug prices that are set well beyond the cost-effective range for a drug or drug class can impact uptake and adherence. This was the case for the PCSK9 inhibitors evolocumab and alirocumab, where the initial pricing contributed to cumbersome prior authorization criteria by payers, which in turn led to slower than expected uptake and patient discontinuation of the drug due to high out-of-pocket costs. Furthermore, although inclisiran decreases LDL-C in the same range as PCSK9 inhibitors, cardiovascular outcomes data are not yet available and thus it is not clear whether the degree of LDL-C lowering will translate to MACE reduction that is similar to that of statins or PCSK9 inhibitors, which could affect inclisiran's ultimate value. Finally, inclisiran is expected to be delivered in a healthcare setting and thus could be classified under a drug plan's medical benefit rather than pharmacy benefit, which may affect administration costs for healthcare systems and out-of-pocket costs for patients. The manufacturer should take this into consideration when evaluating what a fair price is for inclisiran.

Manufacturers should include measurement of a broad set patient-important outcomes in clinical trials.

Current clinical trials are focused on measuring the degree of LDL-C lowering and the prevention of cardiovascular events. While these are appropriate primary outcomes to establish the clinical effectiveness of the drug, other patient-important outcomes such as quality of life play a role in patient and clinician choice of therapy and adherence to therapy. Therefore, inclusion of these outcomes in clinical trials will give patients and clinicians more information to consider during the treatment decision-making process and improve the quality of inputs into cost-effectiveness models.

Researchers

Researchers should seek to standardize definitions of ASCVD, major adverse cardiovascular events (MACE), and SASE (statin intolerance) in clinical trials to facilitate comparison of drugs and assist payers, clinicians, and patients in understanding which groups may benefit from a particular drug therapy.

A major challenge in interpreting clinical trial results is a lack of standardization of populations and outcomes. For example, ASCVD is variably defined as including coronary artery disease, peripheral vascular disease, cerebrovascular disease, but also certain conditions such as diabetes mellitus (so-called “ASCVD risk-equivalent” condition). This leads to heterogeneity in clinical trial populations and makes it difficult to compare the effectiveness of similar drugs and to identify subpopulations where a drug may be more effective. As more lipid-lowering therapies are developed, it is important to standardize definitions to assist payers with operationalizing coverage decisions, and clinicians and patients with choosing the right treatment for the right patient.

Researchers should use real world data to standardize definitions of “adherence to therapy” as part of trials that evaluate adherence and its impact on clinical outcomes.

In the future, the increase in availability of real-world data (e.g., electronic medical records, all-payer claims databases, clinical registries) will assist researchers in studying adherence to medication. However, there is currently no standard method of measuring adherence, and thus the external validity and applicability of such study findings are not clear. Additionally, standardized definitions may assist those entities collecting data in ensuring that data are collected in ways to maximize both internal and external validity of the data and increase the likelihood that the information is useful to payers, clinicians, and other stakeholders.

References

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