



Resmetirom and Obeticholic Acid for Non-Alcoholic Steatohepatitis (NASH): Final Policy Recommendations

May 25, 2023

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the April 28, 2023, Midwest CEPAC public meeting on the use of resmetirom and obeticholic acid for the treatment of Non-Alcoholic Steatohepatitis (NASH). 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 one patient, two clinical experts, two payers, and one representative from a pharmaceutical manufacturer 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

Recommendation 1

All stakeholders have an important role to play in ensuring that new treatment options for patients with NASH are introduced in a way that addresses health equity.

NASH is underdiagnosed and undertreated in the United States, with significant racial and socioeconomic disparities. Hispanic Americans have a higher risk of developing NASH. Current infrastructure for the diagnosis and management of NASH is reliant on specialists and academic centers, creating relative barriers to diagnosis and care for patients from rural areas and those with fewer economic resources. If liver biopsy is required for the diagnosis of NASH, this would create greater barriers to patients who lack equal ability to miss work and have social support at home.

To address these concerns:

Life science companies should take the following actions:

- **Support screening for NASH in underserved communities**

As part of direct to consumer advertising, life sciences companies often support case finding initiatives for the diseases of interest. When designing such campaigns for patients with NASH, they should pay particular attention to incentives and structures intended to reach underserved communities.

- **Set initial prices within the bounds of independent value assessment and with further moderation in relation to the uncertainty of longer-term outcomes and the potential size of the eligible patient population**

Payers should take the following actions:

- **Select non-invasive diagnostic criteria that provide equitable access to early detection and treatment across diverse communities**
- **Integrate coverage of NASH treatments with broader approaches to coverage for programs and treatments for obesity**

As noted above, it is not feasible to perform liver biopsies in order to diagnose patients with NASH. Experts at the meeting suggested that the combination of blood tests, such as the FIB-4, and non-invasive measures of liver fibrosis, such as Fibroscan or MRI elastography, could be combined to streamline diagnose. FIB-4 (using age, liver enzymes and platelet count) has a high sensitivity for advanced fibrosis and thus a high negative predictive value. Patients with a low FIB-4 score do not require additional testing. Patients with higher FIB-4 scores should undergo further testing to noninvasively assess fibrosis. The majority of patients can be triaged with this approach, with the few indeterminate cases requiring liver biopsy.

NAFLD and NASH are inextricably linked with obesity, the metabolic syndrome and diabetes. As noted above, significant weight loss ($\geq 10\%$ of body weight) can reverse NASH and decrease the fibrosis stage for individual patients. The Diabetes Prevention Program demonstrated that similar lifestyle interventions are effective at preventing the development of diabetes in patients at high risk. Thus, coverage for NASH drug treatment should be integrated with coverage for intensive lifestyle interventions and drugs to treat obesity for all indications. It will be challenging, but essential to ensure that these efforts are available to patients from diverse communities.

Delivery systems should take the following actions:

- **Develop structures to coordinate the care delivered by primary care providers and specialists to efficiently identify, treat, and support adherence to therapies for NASH in communities underserved in the past.**

There are not enough hepatologists or gastroenterologists available to meet the needs of the millions of patients with NASH. Initial limits to access to care will likely exacerbate existing disparities. The support structures put in place need to be developed intentionally to support outreach to underserved communities.

Payers

Although there is a tremendous need for disease-modifying treatment for NASH, given the lack of clinical outcome data, the spontaneous improvement of histology in 25% of untreated patients, the lack of long term safety data, and that it takes an average of seven years to progress one fibrosis stage, it will be reasonable for payers to use prior authorization as a component of coverage for NASH therapies. Payers should cover intensive weight management programs that include nutritionists and drug therapy given that resolution of NASH has been observed in up to 84% of patients within one year of bariatric surgery. Lifestyle interventions with a sustained body weight reduction of at least 10% lead to NASH resolution in up to 90% and regression in fibrosis in up to 45% of patients. Prior authorization criteria should be based on clinical evidence and input from clinical experts and patient groups. The process for authorization should also be clear, accessible, efficient, and timely for providers.

Recommendation 1

For NASH, both price-volume and outcomes-based agreements may be considered to manage the uncertainties surrounding the annual costs for these drugs.

Although there are important practical challenges, it may be reasonable for US payers to address the uncertainty and high potential volume of therapies for NASH by working with manufacturers to develop and implement either price-volume or outcomes-based agreements. An important principle in this effort should be to start with a fair price.

Payers should ensure that they have addressed key details when operationalizing any outcomes-based agreement for therapies for NASH. The outcomes used to define treatment failure need to be clear and this presents a significant issue in the development of an outcomes-based agreement.

Price-volume agreements may be more feasible to manage the total cost. Payers would need to negotiate for increasing discounts based on increased utilization beyond defined thresholds.

Competitive formulary considerations

Given the preliminary nature of the evidence, it is not possible to clearly distinguish the relative benefits of resmetirom and obeticholic acid. In the short term, should both drugs be approved by the FDA, clinical experts do not believe there are specific patients for whom one drug or the other would be the only clinically appropriate choice. However, experts do note the lower risk of pruritis

and improved lipids with resmetirom, suggesting that it would likely be the preferred choice in many cases. Payers may therefore wish to cover both drugs but create preferential tiering and access for resmetirom as part of negotiating prices that will help make both drugs more affordable. If payers choose to exclude one of the two drugs to maximize their negotiation for lower prices, clear and rapid medical exceptions must be available. For instance, patients with cardiovascular disease should not be required to take obeticholic acid because of its adverse lipid effects. Similarly, patients suffering from chronic diarrhea should not be required to take resmetirom.

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy:

<https://icer.org/wpcontent/uploads/2020/11/Cornerstones-of-Fair-Drug-Coverage--September-28-2020.pdf>

Drug-Specific Coverage Criteria: resmetirom and obeticholic acid

Coverage Criteria Considerations for both Resmetirom and Obeticholic Acid for patients with NASH

Coverage Criteria

Patient Eligibility Criteria

Diagnosis: NASH may be diagnosed using algorithms described in the recent AACE and AASLD guidelines. Insurers considering a requirement of liver biopsy for the initiation of drug therapy and/or monitoring of response to therapy should be aware that liver biopsy presents significant morbidity and practical burdens for patients. In addition, access to liver biopsy is limited by the number of hepatologists, and clinical experts do not believe that it is reasonable to require liver biopsy prior to beginning therapy. With non-invasive testing (like the combination of FIB-4 and imaging measures of fibrosis described above in the equity section) now demonstrating adequate negative and positive predictive values, and potentially offering improved access for diverse communities, liver biopsy should not be universally required for diagnosis.

Clinical eligibility: Patients eligible for therapy will include all patients with stage F2 or F3 fibrosis. MRI assessment of fat fraction was a clinical trial eligibility criterion for resmetirom, but is not required to help identify patients who will benefit from treatment and therefore should not be a required element for insurance coverage.

Exclusions: Patients with cirrhosis (F4 fibrosis) should be excluded until clinical trials in this population demonstrate the safety and efficacy of these drugs. There is limited or no clinical rationale for the exclusion of patients with poorly controlled diabetes, elevated liver enzymes, or prior bariatric surgery from receipt of these drugs despite their exclusion from the pivotal clinical trials.

Step Therapy

As noted earlier, payers should integrate coverage of drugs for NASH with coverage for obesity management and may want to consider step therapy with lifestyle management efforts prior to providing coverage for NASH-specific drugs. Clinical experts and patient advocates do not support a step therapy approach, particularly for patients with more advanced fibrosis or who have not had adequate weight loss from prior efforts at lifestyle management. However, the advent of GLP-1 treatments for obesity may offer a new opportunity for many patients to achieve significant weight loss. If step therapy is required, then payers should cover intensive weight management programs that include nutritionists and drug therapy. Step therapy requiring prior treatment with pioglitazone and/or vitamin E is not reasonable.

Provider Qualification Restrictions

Payers should require that the prescription of initial therapy with resmetirom or obeticholic acid be done by a hepatologist. It is reasonable to limit prescribing to hepatologists or gastroenterologists until more is known about safety and efficacy in real world use. Both therapies have common side effects (diarrhea, pruritis) that hepatologists are skilled in managing. In addition, the initial monitoring for response to therapy should be managed by hepatologists. Once sufficient experience is gained with the initial management of these therapies, it would be reasonable to establish systems for diagnosis and management of NASH by primary care physicians in consultation with hepatologists including electronic or virtual consultation. There is a tradeoff between access to these new therapies and their optimal delivery through real-world experience and the establishment of systems of support for primary care.

Duration of coverage and renewal criteria

Clinical experts advise that it would be reasonable to require assessment of the effectiveness of therapy once 12 to 18 months after initiating therapy. This may include blood tests such as aminotransferase levels and non-invasive assessments of liver fibrosis. Liver biopsy should not be required. Since stabilization of fibrosis can demonstrate clinical benefit for some patients, resolution of NASH or improvement in fibrosis should be not required for continuation of coverage. It would be helpful for specialty societies to develop guidelines clearly defining how to assess the response to therapy for NASH.

Manufacturers

Recommendation 1

Given the prevalence of NASH and the important residual uncertainty about longer-term benefit for both resmetirom and obeticholic acid, manufacturers should price these drugs well within the boundaries of estimated long-term cost-effectiveness. Given the relatively high estimates for value-based price ranges, manufacturers should consider further restraint by pricing at levels at which these are estimated to be cost-neutral or to produce overall cost savings in the long term for the US healthcare system.

NASH is a public health issue in the United States. Millions of patients will meet the coverage criteria for treatment outlined above. It is likely that years and perhaps decades of therapy with these drugs will be required to prevent the progression of liver disease. The impact on pharmaceutical spending is likely to be like the shock of effective, direct acting antiviral therapy for hepatitis C, but costs will continue annually rather than for one treatment cycle. Avoiding the progression to cirrhosis and its sequelae has the potential for substantial cost saving, which should provide ample revenue to pay for these drugs. Lower pricing would translate into greater affordability and greater access for all patients, potentially reducing some of the existing inequities in the management of NASH. Long term value does not always equal short term affordability.

Recommendation 2

Manufacturers should be balanced in their direct to consumer advertising.

Once the FDA has approved the first therapy for NASH, there will likely be an increase in advertising about NAFLD and NASH as silent diseases and for patients to ask their doctors about screening. Given the number of patients that have NAFLD, this should be done in a measured way to avoid overwhelming the healthcare system. In addition, the messaging should highlight that only patients with significant fibrosis require treatment and that most patients with these conditions do not progress to clinically significant liver disease.

Specialty Societies

Recommendation 1

Specialty societies need to take rapid action to update their clinical guidelines in concert with the introduction of resmetirom and obeticholic acid into clinical practice, with sensitivity to the diversity of patients and health systems.

NASH sits at the intersection of multiple health issues including obesity, diabetes, liver disease, and cardiovascular disease. Conflicting guidelines from interested specialty societies could hinder the

efficient and effective diagnosis and treatment of NASH. Hepatologists, gastroenterologists, endocrinologists, cardiologists, and primary care physicians will all be managing patients at risk for NASH. Ideally, the specialty societies would work together either on joint guidelines or with input and endorsement of one society's guideline to provide a consistent message to health care providers, patients, and the payer community.

Hepatologists have unique expertise in patient selection for and the management of these new therapies for NASH, so either they should lead or play an important consulting role in the development of the guidelines.

As noted above, NASH is underdiagnosed and undertreated in the United States, with significant racial and socioeconomic disparities. In addition, patients are cared for in a wide diversity of health systems and insurance plans from integrated systems like Kaiser and the VA to independent practices caring for patients with state Medicaid plans or no insurance at all. The guidelines should be sensitive to the needs of all patients.

Patient Organizations

Recommendation 1

Patient organizations should continue their work educating patients and providers about NASH.

The patient community is sensitive to the limited awareness about NASH in the general population and limited attention given to the disease among healthcare providers. As the first FDA-approved therapies arrive, it will be even more important for them to educate the public about the disease. In addition, they should be ready to educate their members about the balance of benefits and harms of the new therapies to support informed decision-making.

Recommendation 2

Patient organizations have a powerful voice and should apply it to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system.

Patients have experienced current limits to access to the care that they need for managing NASH. As the first FDA-approved medications become available, they can play a pivotal role in advocating for pricing that supports access for all and avoids exacerbating already existing disparities.

Researchers/Regulators

Recommendation 1

The pivotal clinical trials for resmetirom and obeticholic acid need to be continued until their clinical outcomes are met.

The pivotal randomized trials of both resmetirom and obeticholic acid are intended to continue blinded follow-up for 4.5 to 7 years to assess the impact of the drugs on mortality and the development of cirrhosis and its complications. NASH is a common condition with disastrous health outcomes for many patients. This demands the highest level of clinical evidence for treatment. Our current clinical and economic assessments are based on intermediate biopsy outcomes at 12 to 18 months of follow-up. The results, while encouraging, are insufficient to conclude that these drugs will reduce the risk for liver disease in patients with NASH. We applaud the FDA and the companies for continuing blinded follow-up of the trial participants.

Recommendation 2

Simpler diagnostic pathways to identify patients with NASH and significant fibrosis need to be developed and validated in primary care populations.

Given the number of patients with NAFLD and NASH, it is not feasible for hepatologists to be solely responsible for the identification of patients eligible for treatment. Current strategies involving combinations of blood tests, such as FIB-4, and non-invasive measures of liver fibrosis suffer from limited sensitivity, specificity and / or lack of validation in primary care practices.

Recommendation 3

Non-invasive measures of clinical response need to be developed and validated.

We heard from experts during the meeting that the pivotal randomized trials are assessing non-invasive serologic and imaging measures for response to therapy. There is an urgent need for these results to allow for their validation and rapid incorporation into clinical guidelines.

Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the April 28, 2023 Public meeting of Midwest CEPAC.

Appendix Table 1. ICER Staff and Consultants and COI Disclosures

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*No conflicts of interest to disclose, defined as individual health care stock ownership in any health plan or pharmaceutical, biotechnology, or medical device manufacturers, or any health care consultant income or honoraria from health plans or manufacturers.	
†Research support from Gilead on NAFLD identification in Primary Care	

Appendix Table 2. Midwest CEPAC Panel Member Participants and COI Disclosures

Participating Members of Midwest CEPAC	
Eric Armbrecht, PhD , Associate Professor, St. Louis University Center for Health Outcomes Research, School of Medicine and College for Public Health and Social Justice	Heather Guidone, BCPA , Program Director, Center for Endometriosis Care
Alan Balch, PhD , Chief Executive Officer, Patient Advocate Foundation; The National Patient Advocate Foundation	Jill Johnson, PharmD , Professor, Pharmacy Practice, University of Arkansas for Medical Sciences
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*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of \$10,000 during

the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Appendix Table 3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Danielle Brandman, MD, MAS , Medical Director of Liver Transplantation, Weill Cornell Medicine	Dr. Brandman has received prior research funding from Gilead and Genentech for research in the clinical area of this meeting. Dr. Brandman was previously a Principal investigator on clinical trials involving other drugs for NAFLD.
Stephen Dodge, PharmD, MBA , Senior Vice President, Global Medical Affairs, Madrigal Pharmaceuticals	Dr. Dodge is a full-time employee of Madrigal Pharmaceuticals.
Anthony Grillo, PharmD , Vice President, Express Scripts	Dr. Grillo has equity interests in excess of \$10,000 in Cigna Healthcare. Dr. Grillo is a full-time employee within Cigna/Express Scripts.
Jennifer Martin, PharmD , Deputy Chief Consultant, PBM, Department of Veterans Affairs	No conflicts to disclose.
Kimberly Martinez , Patient Advocate	No conflicts to disclose.
Adnan Said, MD, MS , Professor, Gastroenterology and Hepatology, Director, Metabolic Liver Health Clinic, University of Wisconsin School of Medicine and Public Health	Dr. Said has received consulting support in excess of \$5,000 from Mallinckrodt pharmaceuticals and serves as a Site Principal investigator for the REGENERATE study.