For Treating The Liver Disease Primary Biliary Cholangitis

Does this new drug meet an important need?

What Is Primary Biliary Cholangitis?

Primary Biliary Cholangitis, previously known as primary biliary cirrhosis, is a rare, chronic, progressive autoimmune liver disease that affects mainly middle-aged women. The disease progresses over many years. It begins with autoimmune damage to small bile ducts in the liver with chronic cholestasis and portal inflammation. Primary biliary cholangitis can progress to fibrosis that may lead to cirrhosis and, ultimately, liver failure. Fatigue and pruritus (itching) are the most common symptoms of primary biliary cholangitis, and both can be debilitating in some patients.

The Burden of Primary Biliary Cholangitis

130,000

People in the US have primary biliary cholangitis. Many people are unaware of their disease.

6-10 years

Median survival for symptomatic patients without a liver transplant.

Primary biliary cholangitis is currently the **6th most common** reason for liver transplantation in the US.

Existing Treatments

Until recently, ursodeoxycholic acid (UDCA) was the only FDA approved treatment for primary biliary cholangitis. Treatment with UDCA has been shown to improve measures of liver function, slow progression to fibrosis, and delay the need for liver transplantation. Patients with early stage disease treated with UDCA have an overall survival similar to the general population.

UDCA is generally well tolerated, and beneficial effects can often be seen within weeks or months, though it may take years in some cases. However, around 40% of patients with primary biliary cholangitis do not experience adequate improvement in biochemical measures of liver function with UDCA alone.

UDCA is available in both generic and brand name formulations.

Obeticholic Acid

Obeticholic acid (OCA) is a novel bile acid analogue that has shown positive effects on biochemical markers of liver function in clinical trials. The FDA recently approved the use of OCA in 5 mg and 10 mg doses for the treatment of primary biliary cholangitis in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

$69,350

List price for OCA per year

How strong is the evidence that it improves patient outcomes?

Obeticholic Acid vs. Ursodeoxycholic Acid

Clinical trials have shown that OCA reduces levels of various markers of liver function, including:

- Alkaline phosphatase (*Higher doses of OCA were associated with greater reductions)*
- Total bilirubin
- Aspartate aminotransferase
- Gamma-glutamyl transferase
- Alanine aminotransferase

There are no trials of OCA that have sought to evaluate its impact on patient-centered outcomes of survival, progression to cirrhosis and liver transplant, or quality of life. Evidence does exist from trials of UDCA to demonstrate that reductions in liver function tests, particularly ALP, are correlated with improved patient outcomes.

Elevated **alkaline phosphatase** (ALP) levels are a frequent indicator of progressing disease in patients with primary biliary cholangitis. Three available randomized control trials of OCA+UDCA reported statistically significant reductions in ALP. Greater reductions were noted in patients receiving higher doses of OCA, as well as for patients receiving OCA as monotherapy. In one Phase III trial (the POISE trial), patients taking a titrated dose of OCA (5-10 mg) achieved a similar ALP reduction to those receiving a 10 mg dose, and both were statistically significantly better than placebo.

In the POISE trial, more patients in the OCA-treated groups achieved the primary measure of clinical benefit, which was defined as having a mean ALP less than 1.67 times the upper limit of normal, with at least a 15% reduction, and normal bilirubin, as compared to the placebo group. A secondary analysis evaluated the proportion of patients achieving the POISE trial primary endpoint at 12 weeks for patients taking the 10mg dose of OCA in the Phase II trials; there were statistically significantly higher proportions of patients achieving the composite outcome compared to placebo in both studies.

All trials of OCA reported statistically significant reductions in **other liver biomarkers** across treatment groups, such as aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alanine aminotransferase (ALT). Total bilirubin was also statistically significantly better than placebo for the OCA groups in the POISE trial. For patients receiving OCA as monotherapy, mean change in total bilirubin was not statistically significant during long-term follow-up.

Harms

Clinical trials found:

- Higher doses of OCA increase pruritus. Titrated doses of OCA mitigated the severity of pruritus. In the POISE trial, pruritus occurred more frequently in the OCA-treated groups relative to placebo, with 38%, 56%, and 68% of patients experiencing pruritis in the placebo, 5-10 mg, and 10 mg groups, respectively.
- Adverse changes in lipid levels, mostly due to reductions in high-density lipoprotein (HDL), were also common in all OCA-treated patients. It is unclear if these changes are of clinical significance.

Other serious adverse events occurred with much less frequency and included hepatic decompensation, gastrointestinal disorders, and hyperbilirubinemia. Questions remain as to whether these events were correlated with OCA or manifested independently as a result of progressing disease.

How strong is the evidence that it improves patient outcomes? *(continued)*

Sources of Uncertainty

- Data on clinically-relevant outcomes, including transplant-free survival and mortality, are not yet available. Reduction in ALP was recently accepted by the FDA as a surrogate endpoint reasonably likely to predict clinical benefit.
- Our certainty in the efficacy of OCA is hampered by the lack of peer-reviewed data of the dose regimens selected for marketing approval. Although interim data of the POISE trial is available in the grey literature, such information has not yet been subject to the adjudication process employed for journal publications.
- Although pooled data demonstrated similar efficacy for OCA as monotherapy, data on the use of OCA without concomitant use of UDCA is primarily limited to results from two trials in conference abstracts and regulatory documents. Given that no head-to-head trial has yet been conducted, the true effect of OCA relative to UDCA is uncertain.
- There is lack of data available for patients in later stages of their disease. Across the three trials of primary biliary cholangitis, only 11% had abnormal bilirubin at baseline. Because those patients with higher bilirubin at baseline tended to experience more serious adverse events, there may also be a safety concern for moderately advanced patients.

ICER's Evidence Rating

- For patients with primary biliary cholangitis in the early stages of disease we believe there is moderate certainty that the addition of OCA to UDCA provides an incremental or better net health benefit compared to continued treatment with UDCA alone. The POISE trial and other available data show significant and sustained reductions in ALP with the addition of OCA, yet the reliance on this surrogate outcome and residual uncertainty about the clinical significance of treated-related reductions in HDL lead us at this time to believe there is only moderate certainty of true net health benefit.
- For patients with moderate or severe disease, we judge the evidence to be insufficient at this time to demonstrate a net health benefit given that only a small minority (11%) of patients included in clinical trials of OCA have had moderate disease, and no patients have had advanced disease.
- For patients intolerant to UDCA who receive OCA as monotherapy we judge the evidence to promising but inconclusive on the net health benefit of OCA treatment. Across two clinical trials, only 17% received OCA as monotherapy; none of these results have been published in the peer-reviewed literature; however, results from the grey literature to date have shown improvement in ALP and most other liver function tests from baseline and compared to placebo.

What is a fair price based on its value to patients and the healthcare system?

Long-Term Cost-Effectiveness at List Price

$473,400/QALY

The incremental cost-effectiveness of OCA plus UDCA was approximately $473,400 per QALY.

Using the cost-effectiveness threshold of $100,000 per QALY, OCA at a $69,350/year price **does not represent good value for the money in the long-term** for patients with primary biliary cholangitis who have inadequate response to UDCA.

Potential Short-Term Budget Impact

$313 million per year

Among the estimated 130,000 individuals in the US with primary biliary cholangitis, we assumed that 40% of the treated population would have inadequate response to UDCA and that another 3% would be unable to tolerate UDCA. Applying these assumptions, approximately **24,350 individuals in the US would be eligible for treatment with OCA.**

Assuming a high uptake (50%), we estimate that "unmanaged" uptake would lead to approximately **12,200 people taking OCA after five years.**

After adjusting for differing periods of drug utilization and associated cost-offsets, the weighted potential budgetary impact is approximately **$128,500 per patient.**

With an average annual budget impact of **$312.9 million,** the total potential budgetary impact over five years is approximately **$1.6 billion.**

The annual budget impact of $312.9 million is 35% of the budget impact threshold of $904 million for a new drug, so **OCA does not pose a substantial threat to health system affordability in the short term.**

Eligible Population	Number Treated	Budget impact per patient	Budget impact per year	Budget impact over 5 years
24,350	12,200	$128,500	$312.9M	$1.6B

ICER's Value-Based Price Benchmark

$18,445–$25,261 per year

- This price range reflects an 64–73% discount from the list price of $69,350.

ICER's value-based price benchmark is comprised of two components: a range associated with the prices needed to achieve long-term cost-effectiveness between $100,000–$150,000 per QALY; and, if necessary, a lower price at which short-term potential budget impact does not threaten overall health system affordability.

Public Deliberation and Evidence Votes

New England Comparative Effectiveness Public Advisory Council Panel Votes

The New England CEPAC deliberated on the evidence presented in ICER's report on obeticholic acid at a public meeting on July 15, 2016. The results of the vote are presented below.

Clinical Effectiveness Voting Results

For patients with primary biliary cholangitis, who fail to achieve an adequate reduction in alkaline phosphatase on ursodeoxycholic acid (UDCA) monotherapy, is the evidence adequate to demonstrate a net health benefit with the addition of obeticholic acid to continuing therapy with UDCA?

Yes: 10 votes	No: 4 votes

Comments: Ten members of the New England CEPAC voted that the evidence was adequate to demonstrate a net health benefit for the combination of obeticholic acid and UDCA versus UDCA alone. Members voting "yes" felt that the surrogate endpoint (reduction in ALP levels) could be reasonably expected to correlate with positive clinical outcomes (e.g., delayed progression of the disease or reduced need for liver transplantation). Of the four members who voted that there was not sufficient evidence to demonstrate a net health benefit, several expressed concern about the use of surrogate endpoints over long-term clinical endpoints, and did not feel that there was sufficient evidence to demonstrate that reduction in ALP improves long-term clinical outcomes.

Care Value Voting Results

Given the available evidence for patients with primary biliary cholangitis, what is the care value of adding obeticholic acid to UDCA alone?

Low: 8 votes	Intermediate: 6 votes	High: 0 votes

Comments: The majority of the discussion around care value centered on the high incremental cost-effectiveness ratio for OCA in primary biliary cholangitis, as well as contextual considerations. Those voting for "intermediate" value highlighted the potential for productivity gains from effective primary biliary cholangitis treatment since many patients are working-age women. They also highlighted the relatively high percentage of patients who do not respond to usual care with UDCA alone. The primary rationale for those voting "low" value was the high incremental cost-effectiveness ratio for OCA, driven by the high list price of OCA. Many council members felt that if the price was lower, they would have voted for higher care value.

Key Policy Implications and Recommendations

Patients

- Take a leadership role in advocating for the inclusion of patient-relevant outcomes in clinical studies.

Manufacturers

- Include a broad spectrum of primary biliary cholangitis patients in future studies of OCA.
- Assess the use of non-invasive tests for obtaining information on disease status.
- Seek solutions to the barriers that prevent manufacturers from becoming more transparent about the basis for their pricing decisions.

Clinical Research Community

- Increase efforts to include patient-relevant outcomes in clinical studies.
- Develop long-term clinical studies to enable greater understanding of the relationship between intermediate endpoints and important clinical outcomes.
- Design and conduct studies to ascertain the validity of biomarkers and other factors in identifying which patients are likely to undergo rapid disease progression.

Clinicians

- Propose standardized criteria for defining inadequate response to treatment with UDCA and OCA.
- Employ strategies to improve medication adherence to UDCA and diminish side effects.
- Consider use of histological data from liver biopsies for important baseline and prognostic information.

Insurers

When developing coverage criteria for OCA:

1. Determine the diagnosis of primary biliary cholangitis in accordance with current clinical guidelines.
2. Use clinical experts' opinions and consensus to define criteria for starting and for stopping OCA treatment, as well as determining intolerance to UDCA.
3. Do not exclude patients with moderate-severe primary biliary cholangitis from coverage for OCA.
4. Avoid outcomes-based contracting for OCA in the absence of clearly defined clinical endpoints.

Conclusion

In Summary

The introduction of OCA with or with concomitant use of UDCA in primary biliary cholangitis patients with inadequate response or intolerance to UDCA appears to provide benefits in terms of improving liver biomarkers that may reasonably predict important clinical outcomes. However, at current wholesale acquisition costs, the estimated cost-effectiveness of OCA+UDCA exceeds the range of $100,000-$150,000 per QALY that is used as a benchmark for reasonable long-term value. The potential budget impact of OCA is not estimated to exceed ICER's short-term (five-year) threshold linked to national health care cost growth targets.

Other Considerations

OCA for NASH

ICER also evaluated OCA for use in nonalcoholic steatohepatitis (NASH), as there is expected to be significant interest in using OCA for this indication. However, since Phase III trials are still underway, ICER deemed the available evidence to be inadequate to make a judgment on its value. Due to the preliminary nature of data, ICER felt it premature to assign a value-based price benchmark for use of OCA in treatment of NASH. Policy recommendations specific to the use of OCA for treatment of NASH are available in the full report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit ICER's website (www.icer-review.org).