

Obeticholic Acid for the Treatment of Primary Biliary Cholangitis: Comparative Clinical Effectiveness and Value

Summary of Public Comments Received on Initial Draft Report and ICER Response

The Institute for Clinical and Economic Review (ICER) values the opportunity to receive and respond to public comment on its work products by interested stakeholders. There were five sets of stakeholder comments submitted in response to the initial draft ICER report on obeticholic acid (OCA) for the treatment of primary biliary cholangitis (PBC) that was posted on May 25, 2016. Below is a summary of the comments received as well as responses from the ICER team and its research collaborators, including any major changes made to the report.

Comparative Clinical Effectiveness

- The timing of the review was questioned, as the results of the Phase III trial of OCA in PBC (POISE) have not yet been published. In addition, it was assumed that ICER rejected any conference proceedings or presentations using POISE data on quality grounds. In fact, ICER evaluated all available data from these sources as well as information from FDA submissions, and included those relevant to the scope of its evidence review in accordance with its policy on inclusion of grey literature. More on ICER's grey literature policy can be found at: <http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/>

Comparative Value

- One set of comments identified patients intolerant to UDCA as the subgroup with the greatest unmet need and asked for a specific analysis of OCA monotherapy among these patients. Unfortunately, there are no available effectiveness data specifically in this subgroup, and input from clinical experts indicates that UDCA intolerance is extremely rare.
- One stakeholder stated that the ICER model fails to properly account for the development of hepatocellular carcinoma (HCC), because PBC patients may develop HCC from bile duct destruction without first transitioning to compensated cirrhosis. The ICER team and its research collaborators judge that although this concept is biologically plausible, there are no clinical data to inform the rate of such a transition, so creation of such a pathway would be highly speculative at best.

- One stakeholder stated that the ICER analysis does not reflect the need for liver transplantation for PBC patients in the US, citing a total of 2,912 transplants performed between the years 2000 to 2015 according to the UNOS database, that the model omits a health state for PBC patients on liver transplant waitlists, and that it does not take into account the increased risk of progressing to liver transplant or death from a liver-related cause among patients whose total bilirubin exceeds 1.6x the upper limit of normal (ULN). In response to these comments the model has been updated to include a pathway from early stages of PBC (PBC Stage 1–3 and PBC cirrhosis) to liver transplant in patients who had abnormal bilirubin. In addition, these patients were also at higher risk of liver-related death. In the revised model, the number of liver transplants is in line with that reported by UNOS (as reported in stakeholder’s comment).
- One stakeholder stated that the ICER model assumes patients who respond to UDCA 1 year post-treatment never experience PBC disease progression. In actuality, the candidate population for the model is limited to patients without adequate response to UDCA alone (the labeled indication for OCA). Furthermore, patients in both arms—UDCA and OCA+UDCA, continue to have disease progression even after responding to treatment. However, the rate of progression depends on patients’ ALP and bilirubin values.
- One stakeholder made the comment that the patients in the POISE trial are at higher risk than those in the ICER model. We have modified our model to use additional available data from the POISE trial to define baseline population characteristics. Results are similar to those in the initial draft report.
- One stakeholder considers that ICER should have consulted PBC experts to inform the modeling, in particular “rejection” of information from conference proceedings and other presentations. PBC experts were in fact consulted for modeling assumptions, and information from presentations sent by Intercept and from the FDA advisory committee meeting (April, 7th, 2016) were also used to inform the modeling effort.
- A comment was received that the utility parameters in the cost-effectiveness analysis do not appear to accurately reflect the well-being of PBC patients and undervalue the quality of life of PBC patients suffering from the most severe liver complications. The model uses available utility parameters and sensitivity analyses using a range of utility scores also were performed. The outcomes of the model were not influenced to any significant degree by the range of scores.
- Some stakeholders considered certain costs in the model to be underestimated, such as the costs of ongoing management of PBC prior to decompensated cirrhosis and costs of liver transplantation. We subjected both of these parameters to extensive sensitivity analyses that included the estimates proposed in the comment, and found that model results were not materially influenced by these changes.

- A comment has been received that a willingness-to-pay threshold ranging from \$150,000 to \$300,000 would be more appropriate for an orphan drug. However, a commentary from Neumann and colleagues, while acknowledging the variety of thresholds that have been proposed for certain populations, argues that, for comparisons of interventions across all disease categories and subpopulations, a single threshold of \$100,000 or \$150,000 per QALY is reasonable.¹ This also dovetails with World Health Organization guidance that, based on patient preferences and risk attitudes, relevant cost-effectiveness boundaries for any given country/region fall generally in the range of 1-3 times per capita annual income.² In the US, this equates to approximately \$50,000 - \$150,000. We also note that, in our primary analyses, our estimate of the cost-effectiveness of OCA exceeds even the higher thresholds proposed.
- A comment has been received that the models of cost-effectiveness should consider that PBC is a female predominant disease (versus HCV which is male predominant), and that the extra years of longevity may affect QALY calculations. The results of the model published in the draft report assume that 91% of the PBC cohort is female and are thus in line with the comment.

Comments Concerning the Role of ICER and its Processes

- Several commenters considered that ICER's assessment of OCA is premature and will risk impeding physicians' clinical judgement. We recognize that there are gaps in currently-available evidence and that more data are likely to emerge over time, but patients, clinicians, payers, and other stakeholders also need to make decisions now, based on the best available evidence at the present time.
- We were also criticized for a number of process concerns, including not adequately engaging with patient experts and advocates, inadequate public comment periods, inadequate testimony periods at public meetings, and limited accessibility to the New England CEPAC meeting. ICER firmly believes in the importance of patient participation at all stages of its review process and formally invited patient organizations to provide input at multiple stages in the process. ICER contacted the primary patient advocacy organization for PBC and made multiple offers to speak with representatives to get their input and guidance on our review, but the organization informed us they wished to decline our offer. ICER strives to maintain a transparent and open involvement with patients and the public, and is inspired by best international practices in this area, particularly as developed by the Health Technology Assessment International (HTAi) interest group on patient and public participation.³

REFERENCES

1. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness – the curious resilience of the \$50,000-per-QALY threshold. *N Engl J Med* 2014;371(9):796-7.
2. World Health Organization. WHO-CHOICE (CHOosing Interventions that are Cost-Effective). Accessed at: <http://www.who.int/choice/cost-effectiveness/en/>, May 2, 2016.
3. Health Technology international-Interest Group Patient and Public Involvement. Accessed at <http://www.htai.org/interest-groups/patient-and-citizen-involvement/resources/for-patients-and-patient-groups.html>, June 20, 2016