Obeticholic Acid for the Treatment of Primary Biliary Cholangitis: Effectiveness, Value, and Value-Based Price Benchmarks

Draft Background and Scope

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Background:

Primary biliary cholangitis (PBC), which has until recently been called primary biliary cirrhosis, is a rare, chronic, progressive autoimmune liver disease that affects mainly middle-aged women. The prevalence varies between different countries and regions; in the US, up to 130,000 individuals may have PBC. Diagnosis is increasingly occurring in asymptomatic patients, triggered through an investigation of increased levels of alkaline phosphatase on routine blood tests. Fatigue and pruritus are the most common symptoms of PBC, and both can be debilitating in some patients. Progression of disease to liver cirrhosis and need for liver transplant occurs over 10 to 20 years, depending on the disease stage and presence of symptoms at diagnosis. Among patients who are diagnosed once symptomatic, median survival has been estimated to range from six to ten years without liver transplant. In contrast, in a cohort of patients who were asymptomatic at diagnosis, none developed cirrhosis during a median follow-up of 17.8 years.

Ursodeoxycholic Acid (UDCA) is the only drug approved by the FDA for the treatment of PBC. Patients with early stage disease treated with UDCA have an overall survival similar to the general population. For patients with moderate to severe disease, UDCA treatment significantly improves average time to requirement for liver transplantation. However, treatment with UDCA does not improve fatigue and pruritus, and between 20% and 40% of patients with PBC do not achieve adequate improvement in biochemical measures of liver function. Adding off-label treatment with either bezafibrate and/or budenoside is increasingly being tested in clinical practice and investigated in phase III trials. However, bezafibrate is not sold in the United States and budenoside should not be used in patients with later stage disease with impaired liver function.

Obeticholic acid (OCA) is a novel bile acid analogue that has shown positive effects on biochemical markers of liver function in phase II trials (NCT00550862) and is currently under consideration by the FDA for treatment of PBC after failure of UDCA. A one-year double-blind phase III trial, known by the acronym POISE, started in January 2012 to measure the impact of obeticholic acid on the level of alkaline phosphatase (NCT02308111). This trial is being continued as an open label safety extension until January 2018. Another phase III trial started in December 2014 and will measure the impact on clinical outcomes including events related to cirrhosis, liver transplantation and death (NCT02308111). The data collection for this trial, called COBALT (NCT02308111), is scheduled to last until December 2022.
Report Aim:
This project will evaluate the health and economic outcomes of obeticholic acid as a second-line treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

Scope of the Assessments:
The proposed scope for these assessments is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be culled from phase II or III randomized controlled trials and comparative cohort studies as well as high-quality systematic reviews and meta-analyses where available. We will supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://www.icer-review.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/).

Analytic Framework:
Figure 1: Analytic Framework: Obeticholic Acid for the Treatment of Primary Biliary Cholangitis

Populations
The population of focus for the review will include adults with PBC ages 18 years and older who have had an inadequate response to UDCA or who are unable to tolerate UDCA.

Interventions
The intervention of interest will be OCA added to UDCA or as a monotherapy for patients unable to tolerate UDCA. OCA is administered as oral tablets in doses of 5-10 mg once daily.

Comparators
Comparators will be continued use of UDCA in patients able to tolerate such therapy and usual care for patients intolerant to UDCA.
Outcomes
This review will examine key clinical outcomes related to PBC and its treatment, including surrogate outcomes in available clinical trials. Outcomes of interest will include:

- Biochemical response (e.g., alkaline phosphatase, bilirubin)
- Other markers of liver function (e.g., ALT, AST, GGT)
- Measures of liver fibrosis
- Bleeding from portal hypertension
- Cirrhosis
- Liver transplantation
- Survival
- Health-related quality of life
- Adverse events (e.g., pruritus, fatigue, effects on cholesterol)

Timing
Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings
All relevant settings will be considered, including inpatient, clinic, and outpatient settings.

Economic Evaluation & Simulation Models Focusing on Comparative Value:
As a complement to the evidence review and to estimate long-term impact, we will develop a simulation model to assess the lifetime cost-effectiveness of OCA relative to standard treatment with UDCA. Model structure will be based in large part on previously published data regarding the natural history of PBC. The population modeled will be adult patients most likely to be treated with OCA (i.e., who have had an inadequate response to UDCA or who are unable to tolerate UDCA). Key model inputs and estimates will differ to reflect varying levels of disease severity and risk of progression to cirrhosis. Risks of side effects and quality of life for patients in different disease states will also be incorporated into the model. OCA efficacy will be estimated based on analysis of pivotal trial results.

Key model outputs will include rates of clinical response and disease progression as well as time spent in each health state, treatment-related adverse events, disease-related survival, and the impact of these measures on health-related quality of life. Costs will include those of current and subsequent treatment, management of adverse events, and ongoing PBC-related care. The time horizon will be lifetime. Results will be expressed primarily in terms of the incremental cost per quality-adjusted life year (QALY) gained relative to the standard treatment strategy.

We will also assess the potential budgetary impact of each regimen over a 5-year time horizon, utilizing information on treatment costs and cost offsets from extended response and/or time off treatment. Potential budgetary impact analyses will assume a product “uptake” rate over the 5-year period based on ICER criteria. Finally, we will develop a “value-based price benchmark” for OCA, reflecting prices aligned with long-term cost-effectiveness thresholds and below a threshold for potential budgetary impact that would exceed growth targets for national health care costs.

References: