CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

OBETICHOLIC ACID (OCALIVA — INTERCEPT PHARMACEUTICALS CANADA)
Indication: Primary biliary cholangitis

RECOMMENDATION:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that obeticholic acid be reimbursed for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA, if the following conditions are met:

Conditions:

- Patients should be under the care of a specialist with experience in the diagnosis and management of PBC.
- Reduction in price of at least 60%.

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Reasons for the Recommendation:

1. In one randomized, double-blind, placebo-controlled trial (Study 747-301, POISE; N = 216), a greater proportion of patients treated with obeticholic acid (starting at 5 mg per day and increasing to 10 mg per day for patients with an inadequate response) achieved improved biochemical outcomes (as measured by alkaline phosphatase [ALP] < 1.67 times the upper limit of normal [ULN] and bilirubin ≤ ULN and a drop in ALP of at least 15%) at 12 months compared with placebo (46% versus 10%; odds ratio 9.1 [95% confidence interval, 3.6 to 23.2]; $P < 0.0001$). Several natural history studies involving patients with PBC have indicated that higher levels of these biochemical markers were associated with worse prognoses and that improvement in these markers correlates with better treatment outcomes.
2. The cost-effectiveness of obeticholic acid remains highly uncertain given the limited clinical evidence that is available, the limitations of the manufacturer's model, and the uncertainty in the long-term clinical course of PBC. A price reduction would increase the probability that obeticholic acid is cost-effective for all patients who meet the Health Canada–approved indication. When obeticholic acid is used in combination with UDCA, a price reduction of at least 60% is required to achieve an incremental cost-utility ratio (ICUR) of $50,000 per quality-adjusted life-year (QALY).

Of Note:

1. CDEC noted that UDCA is considered the first-line treatment for PBC and that obeticholic acid would be used as an add-on treatment for those patients who experience an inadequate response to UDCA. The majority of patients included in the POISE trial (93%) were receiving UDCA at baseline. Therefore, there is limited evidence about the safety and efficacy of obeticholic acid for patients who are intolerant to UDCA.
2. CDEC noted that intolerance to UDCA (usually due to gastrointestinal side effects) is likely to occur in only a small percentage of patients with PBC (approximately 10%). Intolerance should be confirmed by the treating specialist after a sufficient trial of UDCA.
3. CDEC noted that approximately 50% of patients receiving obeticholic acid in the POISE trial did not achieve the composite end point of ALP < 1.67 × ULN and total bilirubin ≤ ULN and ALP decrease ≥ 15% from baseline to 12 months. Discontinuation criteria should be developed in consultation with clinical experts for patients with an inadequate response to treatment with obeticholic acid.

Discussion Points:

- CDEC discussed the need for alternative therapies for treating PBC given that only one treatment, UDCA, is currently available and that approximately 40% to 50% of patients have an inadequate response to UDCA and approximately 10% of patients are intolerant. PBC is a serious disease that can lead to life-threatening complications and can significantly affect patients' quality of life. The incidence of PBC is likely less than 30 cases per million.
- The POISE trial had a relatively short duration, which makes it difficult to ascertain whether the improved biochemical outcomes experienced by patients will translate into clinically meaningful improvements in quality of life or survival. More data are expected in 2023 from two trials studying the clinical effects of obeticholic acid, including death and transplant, in patients with early to advanced PBC and moderate to severe hepatic impairment. In addition to these studies, the manufacturer is strongly encouraged to fund an international prospective PBC disease registry of all patients.
- The cost-effectiveness results for patients treated with obeticholic acid who are intolerant to UDCA are highly uncertain due to the small number of these patients included in the POISE trial (< 10 patients per treatment arm) and the manufacturer's assumption that obeticholic acid would have the same efficacy in UDCA-tolerant and UDCA-intolerant patients. The scarcity of data limits the ability of the CADTH Common Drug Review (CDR) to further assess the cost-effectiveness of obeticholic acid.

Background:

Obeticholic acid has a notice of compliance with conditions, pending results of ongoing clinical studies, from Health Canada. It is indicated for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. Obeticholic acid is a farnesoid x receptor agonist. It is available as 5 mg and 10 mg oral tablets, and the Health Canada–approved recommended starting dosage is 5 mg once daily with up-titration to 10 mg after six months if there is inadequate biochemical response. Starting patients with 10 mg of obeticholic acid is not recommended due to an increased risk of pruritus.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of randomized controlled trials and pivotal studies of obeticholic acid, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals with PBC.

Patient Input Information

Two patient groups (the Canadian Primary Biliary Cholangitis Society [CPBCS] and the Canadian Liver Foundation [CLF]) responded to the CDR call for patient input. Information in their submissions was obtained through online surveys; additionally, CPBCS gathered information from in-person conversations during PBC self-management workshops.

- Patients identified two major and common problems resulting from PBC that diminish their quality of life: fatigue and itch. Fatigue, patients say, has a negative impact on various activities of daily living as well as on their social lives, their relationships, and their ability to work. Itch is described as far beyond that associated with a typical rash or insect bite, and it is often worse at night, interfering with sleep. Products intended to reduce itch have limited impact, and constant scratching can predispose patients to serious cutaneous infections. Some patients reported various cognitive problems, including "brain fog," depression, and increased anxiety, all of which they attributed to PBC. In addition, patients expressed concern about the more serious long-term consequences of PBC, including cirrhosis, hepatocellular carcinoma, and the eventual need for a liver transplant.
- There is only one therapy currently available for PBC: UDCA. Side effects include itch and fatigue, which are also two of the key symptoms of PBC, as well as weight gain, dizziness, flu-like symptoms, dyspepsia, acid reflux, and constipation.

- Patients are eager to have another option to manage PBC and are hopeful that obeticholic acid can have a positive impact on disease progression and improve their quality of life by reducing the impact of symptoms such as fatigue. Many are aware that taking obeticholic acid can, at least temporarily, increase itch.
- CLF says it heard from two patients who had used obeticholic acid and who said it was very helpful.

Clinical Trials

The CDR systematic review included one manufacturer-sponsored multi-centre double-blind randomized controlled trial (POISE; N = 216) with adult patients with PBC who either had failed to achieve targets on UDCA or had not tolerated UDCA. Patients were randomized in a 1:1:1 manner to 12 months of therapy with either obeticholic acid 10 mg daily, placebo, or obeticholic acid starting at 5 mg and increasing to 10 mg daily after six months for those with an inadequate response. Of the two obeticholic acid treatment arms, it is the obeticholic titration arm that reflects the Health Canada–approved recommended dosage for obeticholic acid, as starting patients on 10 mg of obeticholic acid is not recommended due to an increased risk of pruritus. The study was designed to test the superiority of each of the obeticholic acid interventions to placebo; the primary end point was to assess the superiority of the obeticholic acid 10 mg intervention to placebo, and the key secondary efficacy end point was to test the superiority of the obeticholic acid titration arm to placebo. The key secondary efficacy end point was tested only if the primary end point was statistically significant. Withdrawals occurred in 10% of patients in the obeticholic acid titration treatment arm and 4% of patients in the placebo arm.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Biochemical markers: composite of patients achieving ALP < 1.67 × ULN and total bilirubin ≤ ULN and ALP decrease ≥ 15% from baseline at 12 months.
- Health-related quality of life: assessed using the PBC-40 instrument, which includes six domains: fatigue, emotional and social, cognitive function, general symptoms, and itch.
- Hepatic fibrosis: enhanced liver fibrosis (ELF) scoring system and Fibroscan Transient Elastography, which measures hepatic stiffness.

POISE was not powered nor was it of sufficient duration to assess key clinical outcomes of importance to patients such as mortality and morbidity, cirrhosis, or need for liver transplant. Health-related quality of life, including symptoms such as itch and fatigue, as well as mortality and other clinical outcomes were of primary importance to patients based on their input to CDR.

Efficacy

As noted above, the primary outcome in the POISE trial compared the obeticholic acid 10 mg arm to placebo for the composite of patients achieving ALP < 1.67 × ULN and total bilirubin ≤ ULN and ALP decrease ≥ 15% from baseline at 12 months, while the key secondary outcome compared the obeticholic acid titration arm to placebo for the same composite. Since obeticholic acid 10 mg is not indicated as a starting dose in Canada, this arm was not considered relevant for this review. Obeticholic acid demonstrated superiority over placebo for both the primary and key secondary outcomes, with 46% of patients in the obeticholic acid titration arm versus 10% of placebo patients achieving the key secondary composite end point after 12 months of therapy (odds ratio 9.1 [95% confidence interval, 3.6 to 23.2]; $P < 0.0001$). Among other secondary outcomes, after 12 months of treatment, patients in the obeticholic acid titration arm also experienced reduced ALP (least squares mean difference −28.2% reduction [standard error 3.4]; $P < 0.0001$) and bilirubin (least squares mean difference −18.3% reduction [standard error 6.3]; $P = 0.0039$) versus placebo. Although no specific minimal clinically important difference was found for these biomarkers, any reduction from baseline is considered to be clinically relevant. There was no statistically significant difference between the obeticholic acid titration arm and the placebo arm in mean change from baseline for any of the individual components of the disease-specific health-related quality-of-life instrument (PBC-40) after 12 months. There was one death, in a patient receiving obeticholic acid, and no events related to

morbidity, cirrhosis, or transplant. There was no improvement in fibrosis scores versus placebo; however, this result and the lack of clinical events may be due to the short duration of the study.

Harms (Safety and Tolerability)

- In the POISE trial, there were more serious adverse events with obeticholic acid compared with placebo (16% versus 4% of patients). There was no pattern of specific serious adverse events that occurred more frequently than others.
- Overall, the proportion of patients experiencing adverse events were similar with obeticholic acid compared with placebo (93% versus 90% of patients, respectively)
- Pruritus is the major tolerability issue associated with obeticholic acid therapy. The proportion of patients experiencing pruritus was 56% of patients in the obeticholic acid titration arm and 38% in the placebo arm.

Cost and Cost-Effectiveness

Obeticholic acid is available as 5 mg and 10 mg oral tablets at a unit price of $98.63 for both strengths. The recommended starting dosage of obeticholic acid is 5 mg daily in adult patients who have not achieved an adequate biochemical response to an appropriate dosage of UDCA for at least one year or who are intolerant of UDCA. If an adequate reduction in ALP and/or total bilirubin has not been achieved after six months of obeticholic acid 5 mg daily, and the patient is tolerating obeticholic acid, the dosage should be increased to 10 mg once daily. The maximum recommended dosage of obeticholic acid is 10 mg once daily. The annual cost of obeticholic acid is $36,000.

The manufacturer submitted a cost-utility analysis assessing obeticholic acid for the treatment of PBC in two populations: the UDCA-intolerant population (comparing obeticholic acid to no treatment) and the population of patients with an inadequate response to UDCA (UDCA-tolerant; comparing obeticholic acid + UDCA to UDCA alone). The base-case analysis was conducted from the perspective of the Canadian health care system over a lifetime time horizon (50 years). The model captures the two components of the natural history of the disease: the PBC-specific liver disease component, representing the progression of PBC based on ALP and bilirubin biomarkers, and the liver disease clinical outcome component, which is entered once patients progress to decompensated cirrhosis or hepatocellular carcinoma. Results from the POISE study were used to inform health state transitions for each three-month cycle for the first year (for obeticholic acid alone, obeticholic acid + UDCA, and UDCA alone). After year 1, PBC-specific health state transitions were calculated based on data from the Global and UK PBC Study cohorts. Utility data specific to cholangitis patients were used for PBC-specific health states, and Canadian data were used for liver disease clinical-outcome states.

CDR identified the following key limitations with the manufacturer's economic submission:

- The use of a 50-year model time horizon was not substantiated by trial evidence or supported by clinical opinion and is associated with a high level of uncertainty.
- The utility values attributed to the model health states lack face validity. These values were selected from several studies assessing quality of life mainly in patients with chronic hepatitis, with a significant variation of quality-of-life results between studies on the same population.
- The assumption that first-year efficacy data for patients treated with obeticholic acid alone (i.e., UDCA-intolerant patients) will be the same as efficacy data for patients treated with obeticholic acid + UDCA (i.e., UDCA-tolerant patients) due to the low proportion of patients intolerant to UDCA in the POISE trial is highly questionable.
- The transition probabilities beyond one year, based on long-term safety extension studies, were assessed by the clinical reviewers to present several limitations.

In the revised base case, CDR varied the health state utility values and reduced the time horizon to 20 years to account for the above limitations; however, these results should be interpreted with caution as the uncertainty regarding the comparative efficacy and safety data could not be addressed, particularly for UDCA-intolerant patients, given the very limited evidence. The CDR base case for the UDCA-tolerant population resulted in ICURs ranging from $153,155 to $218,310 per QALY gained for obeticholic acid + UDCA compared with UDCA alone; for the UDCA-intolerant population, the ICURs ranged from $118,341 to $138,666 per QALY gained for obeticholic acid compared with no treatment. For the UDCA-tolerant population, a price reduction for obeticholic acid of at least 60% is required for an ICUR of $50,000 per QALY and of at least 50% for the UDCA-intolerant patients.

Due to the limitations of the submitted analysis, the reliability of the cost-effectiveness results is uncertain, especially for the UDCA-intolerant population. Should future evidence become available, the assessment of the cost-effectiveness of obeticholic acid in PBC would benefit from being revisited.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

May 17, 2017, Meeting

Regrets:

None

June 21, 2017, Meeting

Regrets:

Two CDEC members could not attend the meeting.

Conflicts of Interest:

One CDEC member did not participate due to considerations of conflict of interest.