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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

OBETICHOLIC ACID (Ocaliva)

(Intercept Pharma Canada, Inc.)

Indication: For the treatment of primary biliary cholangitis

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Abbreviations

ALP	alkaline phosphatase
CDR	CADTH Common Drug Review
HBV	hepatitis B virus
ICUR	incremental cost-utility ratio
OCA	obeticholic acid
PBC	primary biliary cholangitis
QALY	quality-adjusted life-year
UDCA	ursodeoxycholic acid
ULN	upper limit of normal

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Obeticholic acid (OCA)
Study Question	The objective of this economic evaluation was to assess the cost-effectiveness of OCA for the treatment of PBC, most specifically the cost-effectiveness of OCA + UDCA compared with UDCA monotherapy in UDCA-tolerant patients, and of OCA monotherapy compared with no treatment in UDCA-intolerant patients.
Type of Economic Evaluation	Cost-utility analysis
Target Population	• Adult PBC patients with an inadequate response to UDCA (UDCA-tolerant) • Adult PBC patients who are unable to tolerate UDCA (UDCA-intolerant)
Treatment	OCA (5 mg or 10 mg) orally once daily
Outcome	QALY
Comparators	• UDCA-tolerant: oral UDCA at 13 mg/kg/day to 15 mg/kg/day in 2 to 4 divided doses • UDCA-intolerant: placebo (no treatment)
Perspective	Canadian public health care payer
Time Horizon	Lifetime (50 years)
Results for Base Case	• UDCA-tolerant patients: $82,921 per QALY for OCA plus UDCA vs. UDCA alone • UDCA-intolerant patients: $61,365 for OCA alone vs. no treatment
Key Limitations	CDR identified the following limitations: • Uncertainty with the model time horizon: The submitted model used a lifetime time horizon up to 50 years with the average age for the population at 56 years. The 50-year time horizon is clinically questionable, as supported by the clinical expert consulted by CDR. Data were available for modelling up to 15 years. It was considered that a time horizon of 20 years was more appropriate and would reduce the uncertainty of the model results. • Utility values for model's health states: The choice and application of the utility values in the model from different publications raised uncertainty. CDR conducted 3 scenario analyses using alternative studies reporting Canadian data in chronic hepatitis patients. • Exclusion of disutility associated with adverse events: The manufacturer's submitted model excluded disutility due to adverse events. This contradicts feedback from clinical opinion that pruritus impacts patient quality of life. CDR could not test this limitation with certainty because of the model structure and limited data. • Durability of response beyond the randomized trial duration: The manufacturer's model included long-term data from studies with several noted limitations. This increases the uncertainty of the results of the economic analysis. Better alternative data are not available. • Risk of progression beyond year 2: The manufacturer assumed that individuals in the OCA group faced the same risk of progression from low/moderate-risk PBC to high-risk PBC from year 2 onward based on long-term UDCA data. Based on clinical expert opinion, this assumption is insufficiently supported, which increases the uncertainty of the results of the economic analysis.
CDR Estimate(s)	• As described above, the health state utility values and the impact of the model time horizon were assessed in the CDR base case. CDR also adjusted the discount rate to 5% for costs and benefits, the submission having been reviewed under the third edition of the CADTH guidelines for economic evaluations. • CDR base case for OCA + UDCA when compared with UDCA alone in the UDCA-tolerant patient population resulted in an ICUR range between $153,155 and $218,310 per QALY gained, and $118,341 to $138,666 per QALY gained in UDCA-intolerant patient population compared with no treatment. • Using the CDR base-case analysis, a price reduction for OCA between 60% and 70% was required for OCA + UDCA to be cost-effective in UDCA-tolerant patients, and between 50% and 55% was required for OCA to be cost-effective in UDCA-intolerant patients with PBC. • The cost-effectiveness conclusion for OCA patients who were intolerant to UDCA is unclear.

[redacted]	The model assumed an efficacy similar to that for patients treated with OCA + UDCA; this was due to the low proportion of patients intolerant to UDCA in the POISE trial (7% of patients). There is uncertainty over extending these efficacy data to the patients treated with OCA.

CDR = CADTH Common Drug Review; ICUR = Incremental cost-utility ratio; OCA = obeticholic acid; PBC = primary biliary cholangitis; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid; vs. = versus.

Drug	Obeticholic acid 5 mg or 10 mg
Indication	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.
Listing Request	As per indication
Dosage Form(s)	Tablets
NOC/c Date	May 24th, 2017
Manufacturer	Intercept Pharmaceuticals Canada, Inc.

Executive Summary

Background

Obeticholic acid (OCA) is a selective farnesoid X receptor agonist, available as 5 mg and 10 mg oral tablets at a unit price of $98.63 (for both 5 mg and 10 mg). The review of OCA is 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 (proposed indication). The recommended starting dosage of OCA is 5 mg once 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 to UDCA. If an adequate reduction in alkaline phosphatase (ALP) or total bilirubin has not been achieved after six months of OCA 5 mg once daily, and the patient is tolerating OCA, the dosage should be increased to 10 mg once daily. The maximum recommended dosage of OCA is 10 mg once daily.[1]

The manufacturer submitted a cost-utility analysis assessing OCA in two populations: the UDCA-intolerant population (comparing OCA with no treatment), and the population of patients with an inadequate response to UDCA (UDCA-tolerant; comparing OCA plus UDCA with UDCA alone). The base-case analysis was conducted from the perspective of the Canadian health care system over a lifetime horizon (50 years) with future costs and benefits discounted at 1.5 %.[1] The model consisted of 10 health states with transitions taking place every three months, capturing patient progression over time. The model captured 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 (three health states), and the liver disease clinical outcome component (seven health states), which is entered once patients progress to decompensated cirrhosis or hepatocellular carcinoma.[1] For the OCA groups and UDCA group, results from the pivotal phase III POISE study were used to inform health state transitions for each three-month cycle for the first year. 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. Resource use and costs were collected from clinical trials, published literature, expert opinion, and standard Canadian sources.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several key limitations with the model submitted by the manufacturer. First, the use of a 50-year model time horizon was not substantiated by trial evidence or supported by clinical opinion. Considering the patient with PBC starting age of around 56 years for the model based on the POISE trial, and taking into account the chronic progressive

nature of PBC and the length of available long-term safety trials for OCA (maximum of five years), a shorter time horizon of 20 years was deemed more appropriate and reduced the uncertainty of the model results, which increase over the long term.

Second, the choice of utility values used by the manufacturer for model health states is questionable. The utility inputs used to model the impact of OCA on the quality of life of patients with PBC were mainly from studies that assessed patients with chronic hepatitis, adding in uncertainty to the model results. Based on a literature review performed by CDR, a wide variance in the utility values in patients with chronic hepatitis was identified, raising the uncertainty with the included utility inputs by the manufacturer. CDR tested different sets of utility values.

Another limitation was the manufacturer's assumption that first-year efficacy data for patients treated with OCA alone (i.e., UDCA-intolerant patients) would be the same as data for patients treated with OCA plus UDCA (i.e., UDCA-tolerant patients) due to the low proportion of patients intolerant to UDCA in the POISE trial (n = 5; 7% of patients). Although the expert's opinion was that this limitation should be treated with caution, there was inconclusive evidence to predict the effect of this limitation on the results.

Finally, for the transition probabilities beyond one year, the manufacturer included long-term safety extension studies that the clinical reviewers assessed as presenting several limitations, thereby raising uncertainty concerning the model results.

In the revised base case, CDR varied the health state utility values and reduced the time horizon to 20 years. CDR also adjusted the discount rate for costs and benefits from 1.5% to 5%, the submission having been reviewed under the third edition of the CADTH guidelines for economic evaluations. In the CDR base case for the UDCA-tolerant population, the incremental cost-utility ratio (ICUR) ranged from $153,155 to $218,310 per quality-adjusted life-year (QALY) gained for OCA compared with UDCA; and for the UDCA-intolerant population, the ICUR ranged from $118,341 to $138,666 per QALY gained for OCA compared with no treatment.

Conclusions

The efficacy and safety of OCA compared with either UDCA alone or no treatment in UDCA-tolerant or UDCA-intolerant patients, respectively, was based on studies with noted limitations that raise uncertainty over the comparative efficacy and safety of OCA in both populations, especially in the long term. The results from the economic analysis are particularly uncertain for the population of patients who are UDCA-intolerant, for whom insufficient data were available from the POISE study and hence for whom treatment data for UDCA-tolerant patients were used.

Other limitations identified by CDR with the manufacturer's submission included inputs the model was most sensitive to: time horizon and source of utility data. The CDR base case conducted reanalyses addressing these limitations to assess the level of uncertainty concerning the manufacturer's base-case results.

Using the CDR base-case analysis, a price reduction for OCA of between 60% and 70% was required for OCA plus UDCA to achieve $50,000 per QALY and between 30% and 50% to achieve $100,000 per QALY in UDCA-tolerant patients. In UDCA-intolerant patients with PBC, a price reduction for OCA of between 50% and 55% was required for OCA to achieve $50,000 per QALY and between 15% and 25% to achieve $100,000 per QALY.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis based on a Markov state-transition model to determine the cost-effectiveness of obeticholic acid (OCA) in two populations: the ursodeoxycholic acid (UDCA)-intolerant population (comparing OCA monotherapy with no treatment) and a population of patients with an inadequate response to UDCA (UDCA-tolerant; comparing OCA plus UDCA with UDCA alone). The model consisted of 10 health states, with transitions taking place every three months, capturing patient progression over time (Figure 1). The model health states covered the two components of the natural history of the disease: the primary biliary cholangitis (PBC)–specific liver disease component, representing the progression of PBC based on alkaline phosphatase (ALP) and bilirubin biomarkers (three health states), and the liver disease clinical outcome component (seven health states), which is entered once patients progress to decompensated cirrhosis or hepatocellular carcinoma.[1]

The liver disease component of the model included the following health states: low-risk PBC health state (ALP 1.67 times the upper limit of normal [ULN] or lower and bilirubin normal), moderate-risk PBC health state (ALP more than 1.67 times ULN, bilirubin normal), and high-risk PBC health state (bilirubin abnormal and rising and/or compensated cirrhosis), while the clinical end point component of the model included the health states decompensated cirrhosis, hepatocellular carcinoma, pre–liver transplant, liver transplant, post–liver transplant, excess mortality, and PBC re-emergence.[1]

For the OCA groups (OCA monotherapy and OCA plus UDCA) and UDCA monotherapy group, results from the pivotal phase III POISE clinical trial were used to inform health state transitions for each three-month cycle for the first year. After year 1, PBC-specific health state transitions were calculated based on data from the Global and UK PBC study cohorts.[1] For the OCA groups, it was assumed that patients in the low-risk and moderate-risk PBC health states would follow similar trends in progression as patients identified as responders in the Global PBC cohort. Therefore, the decompensation rate observed in UDCA responders from the Global cohort was used to estimate progression over time for the OCA groups. For the UDCA group, transition probabilities were calibrated to the liver transplant–free survival data published from the Global and UK PBC groups after applying risk scores from the POISE patient-level data. For the no-treatment group, the PBC-specific health state transitions were based on literature. Transition probabilities between liver disease clinical outcome health states were based on the literature.[1]

Utility data specific to cholangitis patients from published literature were used for PBC-specific health states,[2-4] and Canadian data were used for liver disease clinical outcome states.[2]

Resource use and costs were collected from clinical trials, published literature, and expert opinion. A Canadian study in chronic hepatitis B virus (HBV) reported costs for early HBV states and end-stage liver disease states.[5] The costs for the liver disease clinical outcome states were assumed to be similar between patients with PBC and HBV, minus the medication costs for HBV.[1] The frequency of liver tests and bone mineral density measurements were based on the American Association for the Study of Liver Diseases PBC practice guidelines and validated by a clinical advisor. The frequencies of remaining resources (e.g., physician visits) were estimated by a clinical advisor.[1] The unit costs for the individual resources identified were obtained from the Ontario Physician Fee Schedule, and for laboratory tests from the Ontario Schedule of Benefits.[6,7]

Separate base-case analyses were performed for patients with an inadequate response to UDCA (UDCA-tolerant) and for UDCA-intolerant patients. The base-case analyses considered the perspective of the Canadian health care system over a lifetime horizon (50 years), with future costs and benefits discounted at 1.5 %.[1]

Manufacturer's Base Case

The manufacturer's results are summarized in Table 2. The results of the analyses in both populations (UDCA-tolerant and UDCA-intolerant) found the OCA groups were associated with additional costs of more than $500,000 compared with the comparators. A detailed assessment of the results (Appendix 4) indicated that the incremental total costs for both analyses were composed primarily of treatment cost differences. In terms of outcomes, OCA reduced the estimated cases of high-risk PBC and of liver disease–specific clinical outcomes in both patients who are tolerant to UDCA and those who are intolerant to UDCA; this led to increased quality-adjusted

life-years (QALYs) with OCA, when added to UDCA treatment or alone, in comparison with either UDCA alone or no treatment, respectively.

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	Incremental Cost Per QALY
UDCA-Tolerant Population					
UDCA	$115,452	9.95			
OCA + UDCA	$705,334	17.06	$589,882	7.11	$82,921
UDCA-Intolerant Population					
No treatment	$116,310	7.72			
OCA alone	$681,721	16.94	$565,411	9.21	$61,365

OCA = obeticholic acid; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid.
Source: Manufacturer's pharmacoeconomic submission.[1]

Summary of Manufacturer's Sensitivity Analyses

The model results were most sensitive to the time horizon used, with shorter time horizons resulting in larger incremental cost-utility ratios (ICURs). In the sensitivity analyses for the UDCA-tolerant patient population, the ICUR ranged from $74,000 to $426,900 per QALY, with the results displaying sensitivity to the time horizon, calibration of PBC transition probabilities, discounting, and source of utility data. Reducing the time horizon to five years resulted in an ICUR of $426,900 per QALY. Use of the liver transplant–free survival data from the Global PBC cohort for calibration of the moderate-risk PBC transition probability resulted in an ICUR of $74,025 per QALY. In the sensitivity analyses in the UDCA-intolerant population, the ICUR ranged from $57,600 to $226,000 per QALY. The results were similar for the UCDA-tolerant population, showing that the parameters for time horizon, utility data, and discounting had the largest impact on the ICUR. Reduction of the time horizon to five years resulted in an ICUR of $226,000 per QALY. Excluding discounting from the model resulted in an ICUR of $57,642 per QALY.

The probabilistic sensitivity analyses for both the patients with an inadequate response to UDCA (UDCA-tolerant) and the UDCA-intolerant patients yielded all simulations in the upper right quadrant of the cost-effectiveness plane (more costly and more effective). The probabilistic sensitivity analyses for OCA in the UDCA-tolerant population shows that, at a threshold of about $50,000, the probability of OCA being cost-effective is 0.0%, while at a threshold of $100,000, OCA has a 95.4% probability of being cost-effective. However, in the UDCA-intolerant population, and at a threshold of around $50,000, the probability of OCA being cost-effective is 35.5%, while at a threshold of $100,000; OCA has a 99.9% probability of being cost-effective.

Limitations of Manufacturer's Submission

- *Time horizon:* The submitted model used a lifetime time horizon of 50 years. The average age for the population included in the model was 55.8 years old. Based on the chronic and progressive nature of PBC, and according to the clinical expert consulted for this review, the assumption of a 50-year model duration was considered clinically questionable and exceeded the available long-term evidence of a 15-year period (Global PBC Study Group).[1] The CADTH Common Drug Review (CDR) used a shorter time horizon of 20 years based on clinical expert opinion that accounted for the average patient age in the model (56 years), prognosis of PBC, and length of available safety trials (maximum of five years). Also, this reduction of the model time horizon reduces the uncertainty of the model results, which increase over the long term.
- *Utility values for model health states:* The manufacturer did not identify any Canadian studies specific to PBC, and therefore relied on a multinational study (including Canadian data) that assessed utility values in chronic hepatitis patients, including utilities for end-stage liver disease and liver transplant (Table 11). The manufacturer also used a US study reporting utility values specific to cholestatic liver disease (Table 11). The choice and application of the utility values to the different model health states from these two publications raises questions and uncertainty. The multinational study with Canadian data by Levy et al. (2008)[2] assessed the impact of chronic hepatitis B on quality of life using the standard gamble method. CDR identified other Canadian studies that assessed quality of life with both hepatitis B and hepatitis C with results that point to a variance in the utility values

for the same health states despite using the same method (standard gamble). CDR conducted three scenario analyses using alternative studies with Canadian data in chronic hepatitis patients (using the manufacturer's assumptions) (Table 24).

- *Exclusion of disutility associated with adverse events:* The manufacturer's submitted model excluded any disutility due to adverse events by assuming the disutility experienced to be small and to occur only over a short duration. Feedback from the clinical expert for this review indicated that the disutility from experiencing pruritus, a well-documented adverse event associated with OCA, was considered persistent and known to impact the patient's quality of life. The incidence of pruritus in the economic model was higher in the OCA plus UDCA group than in the UDCA plus placebo group (50% versus 37%). However, because of the structure and design of the submitted model and limited data, CDR was unable to conduct a sensitivity analysis to include this aspect.
- *Durability of response beyond trial duration:* The manufacturer's model included long-term safety data from the POISE trial as well as from two phase II studies, 747-201 and 747-202, thereby providing data for up to five years.[1] The CADTH clinical review noted several limitations with the three studies. Since two are uncontrolled studies, it remains unclear whether the changes observed in the safety profile were due to the natural course of the disease or were attributable to long-term treatment with OCA. In addition, all efficacy end points were considered exploratory, and no corrections were applied to adjust for multiplicity. Finally, during the long-term safety extension, patients were able to add, delete, or adjust the dose of concomitant UDCA; this makes it difficult to ascertain the absolute safety and efficacy of OCA alone. Moreover, patients were eligible to receive higher doses of OCA (more than 25 mg daily) during the long-term safety extensions versus what was allowed during the randomized placebo-controlled phase (≤ 10 mg daily), making it difficult to draw concrete comparisons between effects and harms observed between the two phases. CDR could not test with enough certainty this limitation of the model's transition probabilities.
- *Efficacy data for OCA patients who are UDCA intolerant is limited*: Because of the low proportion of patients intolerant to UDCA (7% of patients in POISE), the sample size for patients that were treated with OCA alone was extremely small (n = 5), and first-year efficacy data were assumed to be the same as for patients treated with OCA plus UDCA (i.e., UDCA-tolerant patients). Patients with an inadequate response to UDCA (UDCA-tolerant) qualified for OCA because of this inadequate response to UDCA. The manufacturer assumed that the efficacy seen in patients treated with OCA plus UDCA would be due to OCA, and not the UDCA, therefore extending the efficacy data to the patients treated with OCA alone, which is questionable. Although the expert's opinion was that this limitation should be treated with caution, there was inconclusive evidence to predict the effect of this limitation on the manufacturer's results. CDR could not test this limitation with enough certainty due to lack of data at this time.
- *Risk of progression beyond year 2*: In the base case, the manufacturer assumed that individuals in the OCA group faced the same risk of progression from low/moderate-risk PBC to high-risk PBC from year 2 onward. A risk of 9% progression over 15 years was assumed based on the UDCA data from the Global PBC Study Group for both treatment groups (OCA and OCA plus UDCA), as the POISE trial provided data only for the first year. Based on clinical expert opinion, there is a lack of strong evidence to support this assumption being applicable to the OCA group. The manufacturer conducted a sensitivity analysis in which the risk of progression was set to zero in both treatment groups, leading to minimal effects on the ICUR results.

Of note, the manufacturer's base-case analyses applied a discount rate of 1.5% to both costs and benefits based on the draft updated CADTH guidelines for economic evaluation of health technologies.[8] Based on the CADTH guidelines at the time of submission; a 5% discount rate was recommended. A sensitivity analysis was conducted by the manufacturer using the currently approved 5% discount rate. For the CDR base-case and scenario analyses, the 5% discount was applied.

CADTH Common Drug Review Reanalyses

As described above, the CDR base case varied the model time horizon and health state utility values (three scenarios) and adjusted the discount rate to reflect guidelines at the time of submission. One-way and multi-way sensitivity analyses were performed varying these model components (Appendix 4). The model was particularly sensitive to variations in health state utility values and in the time horizon.

The CDR base case for OCA plus UDCA when compared with UDCA alone in UDCA-tolerant patients resulted in an ICUR range of $153,155 to $218,310 per QALY gained. The ICUR results vary when using utility values from the studies by Woo et al. (2012) and Chong et al. (2003) as well as the publication by Levy et al. (2008) that was used by the manufacturer.[2,9,10] In patients who are UDCA-intolerant, the CDR base case for OCA compared with no treatment resulted in an ICUR range of $118,341 to $138,666 per QALY gained.

Table 3: Summary of CDR Multi-Way Analyses Using Alternative Health State Utility Values

	ICUR ($ per QALY)			
Treatment	**Manufacturer Base Case**	**CDR Base Case (Levy et al.)[2]**	**CDR Alternate Base Case (Woo et al.)[9]**	**CDR Alternate Base Case (Chong et al.)[10]**
UDCA-Tolerant				
OCA + UDCA vs. UDCA alone	$82,921	$218,310	$153,155	$210,973
UDCA-Intolerant				
OCA alone vs. no treatment	$61,365	$138,666	$118,341	$133,077

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; OCA = obeticholic acid; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid; vs. = versus.
Source: Manufacturer's pharmacoeconomic submission.[1]

CDR undertook a price-reduction analysis using both the manufacturer's and the CDR's base-case analyses. Using the manufacturer's base-case analysis, a price reduction for OCA of about 35% was required for OCA plus UDCA to achieve $50,000 per QALY compared with UDCA alone in UDCA-tolerant patients with PBC, and a price reduction of about 15% was required for OCA compared with no treatment in UDCA-intolerant patients with PBC. For the CDR price-reduction analyses, the scenario using inputs from the publication of Levy et al. (2008), Woo et al. (2012), and Chong et al. (2003) were selected to produce an ICUR range for the CDR base case. Using the CDR base-case analysis, a price reduction for OCA of between 60% and 70% was required for OCA plus UDCA to achieve $50,000 per QALY and between 30 and 50% to achieve $100,000 per QALY in UDCA-tolerant patients; between 50% and 55% was required for OCA to achieve $50,000 per QALY and between 15% and 25% to achieve $100,000 per QALY in UDCA-intolerant patients with PBC.

Table 4: CDR Reanalysis Price Reduction Scenarios in UDCA-Tolerant Patients

	ICURs of Submitted Drug Versus Comparator			
Price	**Base-Case Analysis Submitted By Manufacturer**	**Reanalysis by CDR (Levy et al. 2008)[2]**	**Reanalysis by CDR (Woo et al. 2012)[9]**	**Reanalysis by CDR (Chong et al. 2003)[10]**
Submitted	$82,921	$218,310	$153,155	$210,973
10% reduction	$73,866	$194,415	$136,104	$187,881
25% reduction	$60,283	$158,573	$110,526	$153,243
30% reduction	$55,756	$146,625	**$102,000**	$141,698
35% reduction	$51,228	$134,678	$93,475	$130,152
40% reduction	$46,701	$122,731	$84,949	$118,606
48% reduction	$39,457	$103,615	$71,308	**$100,133**
50% reduction	$37,646	**$98,836**	$67,897	$95,514
60% reduction	$28,591	$74,941	**$50,846**	$72,422
70% reduction	$19,536	**$51,046**	$33,794	**$49,331**

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; UDCA = ursodeoxycholic acid.

Table 5: CDR Reanalysis Price Reduction Scenarios in UDCA-Intolerant Patients

	ICURs of Submitted Drug Versus Comparator			
Price	**Base-Case Analysis Submitted By Manufacturer**	**Reanalysis by CDR (Levy et al. 2008)[2]**	**Reanalysis by CDR (Woo et al. 2012)[9]**	**Reanalysis by CDR (Chong et al. 2003)[10]**
Submitted	$61,365	$138,666	$118,341	$133,077
10% reduction	$54,374	$122,638	$104,663	$117,695
15% reduction	$50,878	$114,625	**$97,824**	$110,005
20% reduction	$47,383	$106,611	$90,985	$102,314
22% reduction	$45,984	$103,405	$88,249	**$99,238**
24% reduction	$44,586	**$100,200**	$85,514	$96,161
25% reduction	$43,887	$98,597	$84,146	$94,623
50% reduction	$26,409	$58,529	**$49,950**	$56,170
55% reduction	$22,914	**$50,515**	$43,111	**$48,479**
60% reduction	$19,418	$42,502	$36,272	$40,789

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; UDCA = ursodeoxycholic acid.

The manufacturer's final product monograph stated that continuation of OCA treatment in patients with no improvement in biochemical markers of PBC after one year on the maximum effective dose (10 mg) should be assessed based on the clinical course of PBC and potential risks and benefits of continued use of OCA.[11] Testing such a stopping rule in the submitted model would be highly uncertain due to the variability of clinical opinion and the uncertainty surrounding any possible long-term effects for OCA in such a population.

Patient Input

Input was received from the Canadian Primary Biliary Cholangitis Society and the Canadian Liver Foundation. According to the input, patients expect OCA to slow and control disease progression, leading to better quality of life and closer-to-normal life expectancy, decreasing liver failure, and leading to fewer liver transplants and deaths. Patients also expect OCA to address symptoms such as fatigue, although some patients are concerned about increased side effects, accessibility, and cost. The manufacturer's economic submission considered the treatment effects of OCA on disease progression as well as on quality of life in both patients who are UDCA-tolerant and those who are UDCA-intolerant.

Conclusions

The efficacy and safety of OCA compared with either UDCA alone or no treatment in UDCA-tolerant (with an inadequate response to UDCA) or UDCA-intolerant patients, respectively, was based on studies with noted limitations that raise uncertainty over the comparative efficacy and safety of OCA in both populations, especially in the long term. The results from the economic analysis are particularly uncertain for the population of UDCA-intolerant patients, for whom insufficient data were available from the POISE study and hence for whom treatment data for UDCA-tolerant patients were used.

Other limitations identified by CDR with the manufacturer's submission included inputs the model was most sensitive to: time horizon and source of utility data. The CDR base case conducted reanalyses to address most of the limitations, where possible, to assess the level of uncertainty over the manufacturer's base-case results.

Using the CDR base-case analysis, a price reduction for OCA of between 60% and 70% was required for OCA plus UDCA to achieve $50,000 per QALY and between 30% and 50% to achieve $100,000 per QALY in UDCA-tolerant patients. In UDCA-intolerant patients with PBC, a price reduction for OCA of between 50% and 55% was required for OCA to achieve $50,000 per QALY and between 15% and 25% to achieve $100,000 per QALY.

Appendix 1: Cost Comparison

The comparators presented in Table 6 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Existing Product Listing Agreements are not reflected in the table, and the table may therefore not represent the actual costs to public drug plans.

Table 6: CDR Cost Comparison Table for the Management of Primary Biliary Cholangitis

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Obeticholic acid	**5 mg 10 mg**	**tab**	**98.6301[a]**	**5 mg once daily, increasing to 10 mg once daily after 6 months based on efficacy and tolerability**	**98.63**	**36,000**
Ursodeoxycholic acid (Ursodiol generics)	250 mg 500 mg	tab	0.7636 1.4483	13 mg/kg/day to 15 mg/kg/day in 2 to 4 divided doses	2.90 to 3.05[b]	1,057 to 1,115

CDR = CADTH Common Drug Review; tab = tablet.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed January 2017) unless otherwise indicated and do not include markups and dispensing fees.[12]

[a] Manufacturer's submitted price.[1]

[b] Assumes a 70 kg patient; 13 to 15 mg/kg is 910 mg to 1,050 mg daily, rounded to 1,000 mg daily. Lower cost is 500 mg twice daily; higher cost is 250 mg four times daily.

Appendix 2: Summary of Key Outcomes

Table 7: When considering only costs, outcomes, and quality of life, how attractive is OCA plus UDCA relative to UDCA alone (CDR reanalyses)?

OCA + UDCA vs. UDCA Alone	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	$153,155 to $218,310 per QALY					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; OCA = obeticholic acid; UDCA = ursodeoxycholic acid; vs. = versus.
Source: Manufacturer's pharmacoeconomic submission.[1]

Table 8: When considering only costs, outcomes, and quality of life, how attractive is OCA relative to no treatment in UDCA-intolerant patients (CDR reanalyses)?

OCA vs. No Treatment	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	$118,341 to $138,666 per QALY					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; OCA = obeticholic acid; UDCA = ursodeoxycholic acid; vs. = versus.
Source: Manufacturer's pharmacoeconomic submission.[1]

Appendix 3: Additional Information

Table 9: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	None		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

Table 10: Authors' Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer
☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

CDR = CADTH Common Drug Review.

Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer developed a Markov state-transition model describing the progression of the disease over a lifetime (50-year) time horizon. The model is composed of 10 health states with transition every three months (Figure 1). The model health states displayed two components of the natural history of the disease: the primary biliary cholangitis (PBC)–specific disease component, showing the progression of PBC based on alkaline phosphatase (ALP) and bilirubin biomarkers; and the liver disease component once patients start progressing to decompensated cirrhosis (DCC) or hepatocellular carcinoma (HCC) or are added to the liver transplantation waiting list.[1]

A cohort of 1,000 patients was entered in the model to simulate the costs and outcomes associated with each of the treatment strategies compared. At the end of each three-month cycle, patients faced a probability of moving to a subsequent health state.[1] Patients in both the ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) groups could move between the three PBC-specific health states based on the biochemistry data available from the POISE trial.[13] The model included three PBC health states contingent on their level of ALP and bilirubin at baseline, as follows:

1. Low-risk PBC: ALP level at 1.67 times upper limit of normal (ULN) or lower and normal bilirubin (total bilirubin 1.0 times ULN or lower)
2. Moderate-risk PBC: ALP more than 1.67 times ULN and normal bilirubin
3. High-risk PBC: abnormal bilirubin (total bilirubin more than 1.0 times ULN or compensated cirrhosis)

Patients in the high-risk PBC health state could progress to DCC or HCC, with their associated costs and health-related quality of life. It was assumed that patients in the high-risk PBC health state would be in a worse condition than patients with compensated cirrhosis alone because elevated bilirubin is correlated with liver failure. Once in the DCC health state, patients could either remain in that state, progress to HCC, or progress to a pre–liver transplant waiting list. HCC patients could either remain in that state, progress to a pre–liver transplant waiting list, or die. Following liver transplantation, patients faced a probability of dying or of moving to the post-transplantation phase. The possibility that PBC could recur is included in the model, and after re-emergence of PBC patients were at risk of needing a second liver transplantation.

In the model, once patients reached DCC or HCC, they were assumed to continue UDCA but to reduce OCA use to once weekly. Once patients reached the pre–liver transplant waiting list they were assumed to stop both UDCA and OCA treatment. The manufacturer assumed that standard practice was to maintain treatment with UDCA until the patient began to prepare for liver transplant, based on clinical expert opinion.[1] Because the OCA product monograph suggests that patients with moderate to severe hepatic impairment could be initiated with OCA 5 mg once weekly, the manufacturer assumed most clinicians would continue OCA at this dosage until the pre–liver transplant stage. The manufacturer's model included the additional OCA costs but with no additional clinical benefit.

Age-specific and gender-specific general population mortality rates were applied to each health state in the model. The risk of death was considered to be highest in the last and most severe states (i.e., DCC, HCC, pre–liver transplantation, liver transplant, and post–liver transplantation). The excess mortality associated with these health states is depicted by the bold arrows in Figure 1. Excess mortality represents the disease-specific mortality associated with DCC, liver transplant, or HCC.[1]

In the POISE trial, treatment-emergent adverse events (TEAEs) were defined as any adverse event that newly appeared, increased in frequency, or worsened in severity following initiation of the investigational product. Related TEAEs included all events reported that had a possible, probable, or definite relationship with the investigational product. Since pruritus and fatigue are two of the most common symptoms observed in PBC patients, their occurrence was expected. The model included the most frequently reported related TEAEs to account for the possible increase in any TEAE related to all active treatments (i.e., OCA or UDCA). In all group, the most commonly reported related TEAE was pruritus. The incidence and number of patients with related TEAEs of pruritus was 27 patients (37%) in the placebo group, 35 patients (50%) in the OCA titration group, and 48 patients (66%) in the OCA 10 mg group. Fatigue and nausea were the only other related TEAEs that occurred at an incidence of 5% or more. Since the number of OCA monotherapy patients (UDCA-intolerant) was limited (n = 5 [6.8%] in the placebo group, n = 5 [7.1%] in the OCA titration group, and

n = 6 [8.2%] in the OCA 10 mg group), the incidence of TEAEs was assumed to be the same as for patients treated with OCA plus UDCA (UDCA-tolerant). For UDCA-intolerant patients receiving no treatment, no TEAEs were considered.

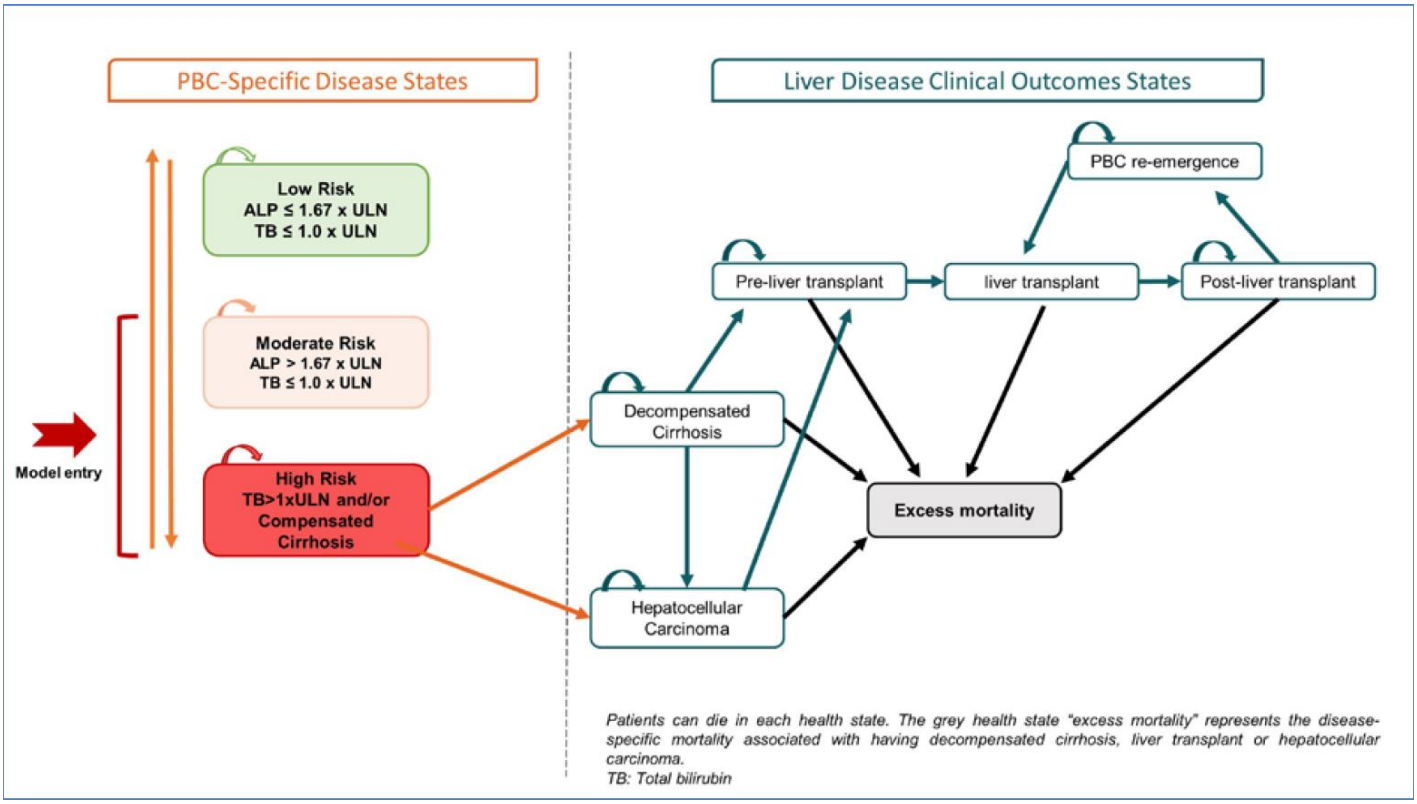
The health states within the model were assigned utility values reflecting the health-related quality of life that patients experienced while in that state. As patients progressed from low-risk PBC to high-risk PBC and subsequent end-stage liver disease states, utility values decreased. The manufacturer conducted a literature search to identify Canadian utility values for PBC and end-stage liver disease states. The search did not identify any Canadian studies specific to PBC; therefore, alternative sources were identified that assessed utility values in chronic hepatitis patients, including utilities for end-stage liver disease and liver transplant. Two Canadian studies, Levy et al. (2008)[2] and Hsu et al. (2012),[3] that provide utility values for advanced liver disease patients with chronic hepatitis C were identified. Two US studies, Younossi et al. (2001)[4] and Bondini et al. (2007),[14] which assessed utility values specific to cholestatic liver disease (PBC and primary sclerosing cholangitis) and PBC, respectively, were also identified.

Table 11: Summary of Manufacturer Base Case Health State Utility Values

Health State	Utility Value	Source
Low-risk PBC	0.84	From Younossi et al. (2001) based on utility value for cholestatic patients at the outpatient practices of the Cleveland Clinic.[4] The manufacturer assumed that patients in these health states experience the same utility, as PBC is largely asymptomatic in its early stages.[1]
Moderate-risk PBC	0.84	
High-risk PBC	0.65	From Levy et al. (2008) based on utility values in patients with chronic hepatitis B from respondents in 6 countries: US, Canada, UK, Spain, Mainland China, and Hong Kong.[2] The manufacturer assumed the utility values for the high-risk PBC health state to be comparable to compensated cirrhosis.
Decompensated cirrhosis	0.44	
Hepatocellular carcinoma	0.46	
Pre–liver transplant: utility at wait listing	0.44	Assumed to be comparable to decompensated cirrhosis
Pre–liver transplant: 3 months after wait listing	0.44	
Pre–liver transplant: 6 months after wait listing	0.44	
Re-emergence of PBC	0.65	Assumed to be comparable to high-risk PBC
3 months following liver transplant	0.51	Assumed to be the average between decompensated cirrhosis and the first-year post–liver transplant
6 months following liver transplant	0.58	From Levy et al. (2008) based on utility values in patients with chronic hepatitis B from respondents in 6 countries: US, Canada, UK, Spain, Mainland China, and Hong Kong[2]
12 months following liver transplant	0.58	
24 months following liver transplant	0.84	Assumed to be the same as low-risk PBC

PBC = primary biliary cholangitis.

Figure 1: Model Structure Overview



ALP = alkaline phosphatase; PBC = primary biliary cholangitis; TB = total bilirubin; ULN = upper limit of normal.

Source: Manufacturer's pharmacoeconomic submission.[1]

Table 12: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	The effectiveness of OCA in patients with PBC who have an inadequate response to UDCA or are unable to tolerate UDCA is based on the phase III POISE trial, which was an international, randomized, double-blind, placebo-controlled, parallel-group, 12-month study that evaluated the efficacy and safety of OCA. Patients were randomized to receive placebo, OCA 5 mg, or OCA 10 mg for the first 6 months. At month 6, patients in the OCA 5 mg titration group who did not achieve the primary end point and who tolerated the drug titrated from OCA 5 mg to 10 mg for the final 6 months of the study.[13] Two, 3-month, multi-centre, double-blind, placebo-controlled phase II studies (747-201 and 747-202) were conducted in addition to the POISE trial.[15,16] A total of 299 patients randomized in the double-blind portion of these studies (200 patients to OCA and 99 patients to placebo) enrolled and were treated with OCA in the long-term safety extension study.[13]	The CDR clinical review noted the short duration of the phase II trials as well as the small sample size. The clinical reviewers also noted that they were uncontrolled studies; therefore, it remained unclear whether the changes observed in the safety profile were due to the natural course of the disease or were attributable to long-term treatment with OCA.
Utilities	For the base case, the cholestatic liver disease–specific utility value from Younossi et al. (2001)[4] was used for the low-risk	The selection of the publication by Levy et al. (2008)[2] was not clear, as there are several

Data Input	Description of Data Source	Comment
	PBC and moderate-risk PBC health states. The utility values for the high-risk PBC health state (considered comparable to compensated cirrhosis) and the end-stage liver disease health states were obtained from Levy et al. (2008).[2] The utility values from Hsu et al. (2012),[3] as well as alternative values for the low-risk PBC and moderate-risk PBC health states from Bondini et al. (2007)[14] with Levy et al. values used for the high-risk PBC state and onward, were used in sensitivity analyses.[1]	publications that assess the impact of chronic hepatitis conditions on patients' quality of life.
Resource Use		
AEs	Only costs associated with 3 notable AEs were included in the model (fatigue, pruritus, and nausea).	The manufacturer assumed that adverse events would be short and have no disutility associated with them. Feedback from the clinical expert noted that pruritus tends to be a persistent adverse event throughout treatment and does impact the patient's quality of life.
Mortality	The 3-month probabilities of death by age and gender were obtained from Statistics Canada life tables (2009–2011).[17] The weighted average probability for each age was calculated assuming a 9:91 ratio of men to women in order to be consistent with the population in the POISE trial.[1]	Acceptable
Costs		
Drug	Drug costs for OCA 5 mg and 10 mg tablets were provided by the manufacturer.[1] Costs of UDCA were obtained from the Ontario Drug Benefit Formulary/ Comparative Drug Index.[12] No dispensing fees or markups were applied in the model.	Acceptable
Event	The frequencies of resources (e.g., physician visits) were estimated by a clinical advisor. The unit costs for the individual resources identified were obtained from the Ontario Physician Fee Schedule[6] and for laboratory costs from the Ontario Schedule of Benefits .[7]	Acceptable
AEs	The costs for treatment of AEs were estimated through consultation with a clinical advisor consulted by the manufacturer. Three AEs were included in the model: fatigue ($0), pruritus ($480.60), and nausea ($5.79).[1]	The costs associated with AEs were applied once in the model, during the first cycle.
Health state	The costs for the liver disease clinical outcome states were assumed to be similar between patients with PBC and chronic HBV, minus the medication costs that are HBV-related. The Canadian study by Gagnon et al. (2004)[5] of HBV provided costs for early HBV states and end-stage liver disease states.	Acceptable

AE = adverse event; CDR = CADTH Common Drug Review; HBV = hepatitis B virus; OCA = obeticholic acid; PBC = primary biliary cholangitis; UDCA = ursodeoxycholic acid.

Table 13: Manufacturer's Key Assumptions

Assumption	Comment
In the first year, OCA-treated and UDCA-treated patients can progress freely among the 3 PBC-specific disease states based on transition probabilities derived from the POISE OCA and UDCA regimen groups. For year 2 onward, long-term PBC progression for OCA patients was assumed to follow a similar decompensation rate as UDCA responders, based on the Global PBC study.[1] UDCA patients progress between PBC health states based on transition probabilities calibrated to reflect the LTFS estimated based on the POISE patient-level data using both the Global and UK risk scores.[18]	Appropriate
Patients suffering from DCC have serious symptoms and complications from cirrhosis such as ascites, hepatic encephalopathy, or portal hypertension; these were combined in the model into a single health state based on the assumption that a patient can have several complications simultaneously in clinical practice.[1]	Appropriate
All patients in the DCC health state are assumed to be candidates for liver transplantation.[1]	Appropriate
All patients in the HCC health state are assumed to be candidates for liver transplantation.[1]	Appropriate
Background mortality is assumed to be the same as in the general population.	Appropriate
In the absence of PBC-specific inputs, chronic hepatitis C data were used as proxy for the transition probabilities in the liver disease clinical outcomes component of the model.	Appropriate as per feedback from clinical expert
Once patients reach DCC or HCC, it is assumed that the dosage for OCA will be decreased to once a week, until patients reach the pre–liver transplant health state, when they will cease OCA completely.	Appropriate as per feedback from clinical expert
In the model, once patients reach DCC or HCC they are assumed to continue UDCA but reduce OCA use to once weekly, until patients reach the pre–liver transplant waiting list, when they are assumed to stop both UDCA and OCA treatment.	Appropriate as per feedback from clinical expert
Based on clinician opinion, it is assumed that once patients are in the immediate pre-transplant stage, OCA would be discontinued.[1]	Appropriate as per feedback from clinical expert
The model conservatively assumes OCA treatment costs in the decompensated state, but with no additional clinical benefit due to the limited clinical data available for OCA treatment in patients with decompensated disease.	Appropriate as per feedback from clinical expert
It was assumed that patients in the high-risk PBC health state would be in a worse condition than patients with compensated cirrhosis alone because elevated bilirubin is correlated with liver failure.	Appropriate as per feedback from clinical expert
Discontinuation was assumed to occur at the beginning of treatment and was applied only in the first cycle.	Appropriate as per feedback from clinical expert
The model does not account for any disutility due to AEs. The disutility experienced was assumed to be small and would occur over a short duration.	Inappropriate. As per feedback from clinical expert, pruritus is documented to be a persistent adverse event that impacts the patient's quality of life.

AE = adverse event; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LTFS = liver transplant–free survival; OCA = obeticholic acid; PBC = primary biliary cholangitis; UDCA = ursodeoxycholic acid.

Manufacturer's Results

For **UDCA-tolerant** patients on OCA, when added to UDCA, the result indicated a reduction in the estimated number of cases of high-risk PBC, DCC, and HCC, as well as a reduction in liver transplants and liver-related deaths, thereby increasing the total life-years gained with OCA when added to UDCA. OCA is also associated with an increase in quality-adjusted life-years (QALYs) gained compared with UDCA-alone therapy.

Table 14: Outcome Results of Manufacturer's Base-Case Analysis by Treatment Group in UDCA-Tolerant Population

Outcome	UDCA	OCA + UDCA	Difference
Total cases of high-risk PBC	858	282	575
Total cases of DCC[a]	779	227	−551
Total cases of HCC[a]	110	21	−89
Total liver transplants[a]	135	38	−97
Total liver deaths[a]	720	203	−517
Life-years[b]	14.42	21.03	6.61
QALY[b]	9.95	17.06	7.11

DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; OCA = obeticholic acid; PBC = primary biliary cholangitis; UDCA = ursodeoxycholic acid.
[a] Per 1,000 patients (undiscounted) as per manufacturer submission.[1]
[b] Discounted
Source: Manufacturer's pharmacoeconomic submission.[1]

The drug treatment costs and the costs associated with adverse events increased with the use of OCA. However, the manufacturer's model demonstrates that drug costs and adverse event costs appear to be slightly offset by a reduction in the disease management cost.

Table 15: Discounted Cost Results of Manufacturer's Base-Case Analysis by Treatment Group in UDCA-Tolerant Population

Outcome	UDCA	OCA + UDCA	Difference
Treatment costs	$14,622	$668,601	$653,978
Adverse event costs	$52	$76	$24
Disease management costs	$100,777	$36,657	–$64,121
Total costs	$115,452	$705,334	$589,882

OCA = obeticholic acid; UDCA = ursodeoxycholic acid.
Source: Manufacturer's pharmacoeconomic submission.[1]

Table 16: Cost-Effectiveness Results of Manufacturer's Base-Case Analysis by Treatment Group in UDCA-Tolerant Population

Treatment	Total Cost	Total QALY	Incremental Cost	Incremental QALY	ICUR
UDCA	$115,452	9.95			
OCA + UDCA	$705,334	17.06	$589,882	7.11	$82,921

ICUR = incremental cost-utility ratio; OCA = obeticholic acid; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid.
Source: Manufacturer's pharmacoeconomic submission.[1]

For **UDCA-intolerant** patients on OCA, the result also indicated a reduction in the estimated cases of high-risk PBC, DCC, and HCC, as well as a reduction in liver transplants and liver deaths, thereby increasing the life-years gained with OCA when added to UDCA. OCA is also associated with an increase in QALY gained compared with no treatment.

Table 17: Outcome Results of Manufacturer's Base-Case Analysis by Treatment Group in UDCA-Intolerant Population

Outcome	No Treatment	OCA	Difference
Total cases of high-risk PBC	755	285	−470
Total cases of DCC[a]	855	231	−624
Total cases of HCC[a]	127	21	−106
Total liver transplants[a]	152	39	−114
Total liver deaths[a]	811	207	−604
Life-years[b]	12.17	20.90	8.73
QALY[b]	7.72	16.94	9.21

DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; OCA = obeticholic acid; PBC = primary biliary cholangitis; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid.
[a] Per 1,000 patients (undiscounted) as per manufacturer submission.[1]
[b] Discounted.
Source: Manufacturer's pharmacoeconomic submission.[1]

The drug treatment costs and the costs associated with adverse events also increased with the use of OCA in the UDCA-intolerant population. The model also demonstrated that drug costs and adverse event costs appear to be slightly offset by a reduction in the disease management cost.

Table 18: Cost Results of Manufacturer's Base-Case Analysis by Treatment Group in UDCA-Intolerant Population

Outcome	No Treatment	OCA	Difference
Treatment costs	$0	$644,158	$644,158
Adverse event costs	$0	$76	$76
Disease management costs	$116,310	$37,487	–$78,823
Total costs	$116,310	$681,721	$565,411

OCA = obeticholic acid; UDCA = ursodeoxycholic acid.
Source: Manufacturer's pharmacoeconomic submission.[1]

Table 19: Cost-Effectiveness Results of Manufacturer's Base-Case Analysis by Treatment Group in UDCA-Intolerant Population

Treatment	Total Cost	Total QALY	Incremental Cost	Incremental QALY	ICUR
UDCA	$116,310	7.72			
OCA + UDCA	$681,721	16.94	$565,411	9.21	$61,365

ICUR = incremental cost-utility ratio; OCA = obeticholic acid; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid.
Source: Manufacturer's pharmacoeconomic submission.[1]

Manufacturer's Sensitivity Analyses

The manufacturer conducted several deterministic sensitivity analyses varying model parameters as well as scenario analyses that assessed the impact of physicians not adhering to the treatment guidelines by initiating OCA at 10 mg instead of the recommended dose titration (5 mg to 10 mg).

The results of the sensitivity analyses for the population of patients with an inadequate response to UDCA (UDCA-tolerant) demonstrated incremental cost-utility ratio (ICUR) values ranging from $74,000 to $426,900 per QALY, indicating that the time horizon, calibration of PBC transition probabilities, discounting, and source of utility data had the largest impacts on the ICUR. The most dramatic increase in the incremental cost-effectiveness ratio occurred when the time horizon was reduced to five years; the ICUR increased by 415% to $426,900 per QALY. Use of a time horizon of 20 years, the liver transplant–free survival data from the UK PBC cohort for calibration of the moderate-risk PBC transition probability, discounting of 5%, and alternative utility values (Hsu et al. 2012) led to increases of 38.4%, 23.7%, 22.5%, and 19.0% in the ICUR, respectively, compared with the base-case value. The largest decrease in the ICUR, −10.7%, occurred with use of the liver transplant–free survival data from the Global PBC cohort for calibration of the moderate-risk PBC transition probability. When no discounting was included in the model, it resulted in a decrease of 8.1% in the ICUR compared with the base case.

For the UDCA-intolerant population, the sensitivity analyses resulted in an ICUR range from $57,600 to $226,000 per QALY. The results were similar to those for the UDCA-tolerant population, showing that the parameters for time horizon, utility, and discounting had the largest impacts on the ICUR. The most dramatic increase in the ICUR occurred when time horizon was reduced to five years: the ICUR increased by 268% to $226,000 per QALY. Use of a 20-year time horizon, alternative utility values (Hsu et al. 2012), and discounting by 5% led to increases of 23.6%, 18.0%, and 16.8% in the ICUR, respectively, compared with the base case. The largest decrease in the ICUR, −6%, was demonstrated when no discounting was included in the model.

The results of the scenario analyses using OCA 10 mg showed ICURs of about 10% lower than in the base case for both patient populations.

Table 20: Summary of Manufacturer's Scenario Analysis (OCA 10 mg + UDCA): Incremental Cost-Effectiveness of OCA 10 mg + UDCA Versus UDCA in UDCA-Tolerant Population

Treatment	Total Cost	Total QALY	Incremental Cost	Incremental QALY	ICUR
UDCA	$115,452	9.95			
OCA 10 mg + UDCA	$622,144	16.72	$506,692	6.77	$74,819

ICUR = incremental cost-utility ratio; OCA = obeticholic acid; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid.
Source: Manufacturer's pharmacoeconomic submission.[1]

Table 21: Summary of Manufacturer's Scenario Analysis (OCA 10 mg): Incremental Cost-Effectiveness of OCA 10 mg Versus No Treatment in UDCA-Intolerant Population

Treatment	Total Cost	Total QALY	Incremental Cost	Incremental QALY	ICUR
No treatment	$116,310	7.72			
OCA 10 mg	$602,426	16.56	$486,115	8.84	$54,984

ICUR = incremental cost-utility ratio; OCA = obeticholic acid; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid.
Source: Manufacturer's pharmacoeconomic submission.[1]

Manufacturer's Probabilistic Sensitivity Analysis

The manufacturer conducted a probabilistic sensitivity analysis based on a Monte Carlo simulation in which the model was run for 1,000 simulations. In each simulation, parameter values were randomly selected based on statistical distributions simultaneously for all varied parameters. In the case of OCA in the UDCA-tolerant patient population, the results show that at a threshold of $50,000, the probability of OCA being cost-effective is 0.0%. At a threshold of $100,000, OCA has a 95.4% probability of being cost-effective. In the case of OCA in the UDCA-intolerant patient population, the results show that at a threshold of about $50,000, the probability of OCA being cost-effective is 35.5%. At a threshold of $100,000, OCA has a 99.9% probability of being cost-effective.

CADTH Common Drug Review Reanalyses

Time horizon: The manufacturer's base-case analysis used a 50-year time horizon based on PBC being a chronic and progressive disease in order to capture later consequences, benefits, and costs. However, there is lack of long-term data to support the assumption that the effects of OCA would be sustained without waning over time. The CADTH Common Drug Review (CDR) used a shorter time horizon of 20 years based on clinical expert opinion that accounted for the average patient age in the model (56 years), prognosis of PBC, and length of available safety trials (maximum of five years). Also, this reduction of the model time horizon reduces the uncertainty of the model results, which increase over the long term. The results are shown in Table 22.

Table 22: Summary of CDR Sensitivity Analyses Using a Time Horizon of 20 Years

Treatment	Total Cost	Total QALY	Incremental Cost	Incremental QALY	ICUR
UDCA-Tolerant Population					
UDCA	$86,802	8.767			
OCA + UDCA	$508,297	12.440	$421,495	3.673	$114,755
UDCA-Intolerant Population					
No treatment	$92,816	7.081			
OCA alone	$491,524	12.340	$398,708	5.259	$75,817

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; OCA = obeticholic acid; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid.
Source: Manufacturer's pharmacoeconomic submission.[1]

Discount rate: At the time of submission, the discount rate according to the CADTH guidelines on economic evaluation (third edition) was set at 5% for both costs and benefits. The manufacturer's economic model applied a discount rate of 1.5% based on the draft CADTH guidelines (fourth edition). CDR conducted analyses using a 5% discount rate.

Table 23: Summary of CDR Sensitivity Analyses Using a Discount Rate of 5%

Treatment	Total Cost	Total QALY	Incremental Cost	Incremental QALY	ICUR
UDCA-Tolerant Population					
UDCA	$75,056	7.542			
OCA + UDCA	$467,535	11.404	$392,479	3.863	$101,608
UDCA-Intolerant Population					
No treatment	$77,377	6.098			
OCA alone	$451,915	11.322	$374,538	5.224	$71,694

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; OCA = obeticholic acid; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid.
Source: Manufacturer's pharmacoeconomic submission.[1]

Utility values for model health states: The manufacturer did not identify any Canadian studies specific to PBC and therefore relied on a multinational study (including Canadian data) that assessed utility values in chronic hepatitis patients, also including utilities for end-stage liver disease and liver transplant. The manufacturer also used a US study reporting utility values specific to cholestatic liver disease. The choice and application of the utility values to the different model health states from these two publications raise questions and uncertainty. The multinational study with Canadian data by Levy et al. (2008)[2] assessed the impact of chronic hepatitis B on quality of life using the standard gamble method. CDR identified other Canadian studies that assessed quality of life from both

hepatitis B and hepatitis C, with results that point to a variance in the utility values for same health states despite using the same method (standard gamble). CDR conducted three scenario analyses using alternative studies with Canadian data in chronic hepatitis patients (using the manufacturer's assumptions) (Table 24).

Table 24: Results of CDR Reanalyses Varying Utility Inputs in Model Health States

Health State	Manufacturer's Base Case	Levy et al. (2008)[2]	Woo et al. (2012)[9]	Chong et al. (2003)[10]
Low-risk PBC	0.84[a]	0.66	0.89	0.76
Moderate-risk PBC	0.84[a]	0.66	0.89	0.76
High-risk PBC	0.65[b]	0.65	0.87	0.74
DCC	0.44	0.44	0.82	0.66
HCC	0.46	0.46	0.84	0.65
Pre–liver transplant: utility at wait listing	0.44[c]	0.44	0.82	0.66
Pre–liver transplant: 3 months after wait listing	0.44[c]	0.44	0.82	0.66
Pre–liver transplant: 6 months after wait listing	0.44[c]	0.44	0.82	0.66
Re-emergence of PBC	0.65[d]	0.65	0.87	0.74
3 months following liver transplant	0.51[e]	0.58	0.86	0.69
6 months following liver transplant	0.58	0.58	0.86	0.69
12 months following liver transplant	0.58	0.58	0.86	0.69
24 months following liver transplant	0.84[f]	0.66	0.89	0.76
ICUR ($ per QALY)				
UDCA-tolerant patients	$82,921	$120,977	$83,934	$110,813
UDCA-intolerant patients	$61,365	$88,594	$70,394	$80,818

CDR = CADTH Common Drug Review; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; ICUR = incremental cost-utility ratio; PBC = primary biliary cholangitis; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid.
[a] Utility for cholestatic patients from Younossi et al. (2001).[4]
[b] Assumed to be compensated cirrhosis.
[c] Assumed to be comparable to DCC.
[d] Assumed to be comparable to high-risk PBC.
[e] Assumed to be the average between DCC and the first-year post–liver transplant.
[f] Assumed to be the same as low-risk PBC.

Multi-way CDR reanalyses: CDR conducted multi-way scenario reanalyses that varied the health state values and were based on a 20-year time horizon at a discount rate of 5% on both costs and benefits. The multi-way analyses varied the health state utility inputs according to the values reported in the publications by Levy et al. (2008),[2], Woo et al. (2012),[9] and Chong et al. (2003).[10]

Table 25: Summary of CDR Multi-Way Analyses Using Health State Utility Values From Levy et al. (2008)

Treatment	Total Cost	Total QALY	Incremental Cost	Incremental QALY	ICUR
UDCA-Tolerant Population					
UDCA	$62,926	6.157			
OCA + UDCA	$387,410	5.382	$324,484	1.486	$218,310
UDCA-Intolerant Population					
No treatment	$67,292	5.824			
OCA alone	$374,570	7.598	$307,278	2.216	$138,666

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; OCA = obeticholic acid; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid.
Source: Manufacturer's pharmacoeconomic submission.[1]

Table 26: Summary of CDR Multi-Way Analyses Using Health State Utility Values From Woo et al. (2012)

Treatment	Total Cost	Total QALY	Incremental Cost	Incremental QALY	ICUR
UDCA-Tolerant Population					
UDCA	$68,411	8.322			
OCA + UDCA	$387,410	10.405	$318,999	2.083	$153,155
UDCA-Intolerant Population					
No treatment	$67,292	7.754			
OCA alone	$374,570	10,351	$307,278	2.597	$118,341

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; OCA = obeticholic acid; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid.
Source: Manufacturer's pharmacoeconomic submission.[1]

Table 27: Summary of CDR Multi-Way Analyses Using Health State Utility Values From Chong et al. (2003)

Treatment	Total Cost	Total QALY	Incremental Cost	Incremental QALY	ICUR
UDCA-Tolerant Population					
UDCA	$62,926	7.324			
OCA + UDCA	$387,410	8.862	$324,484	1.538	$210,973
UDCA-Intolerant Population					
No treatment	$67,292	6.505			
OCA alone	$374,570	8.814	$307,278	2.309	$133,077

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; OCA = obeticholic acid; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid.
Source: Manufacturer's pharmacoeconomic submission.[1]

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