

Reimbursement Recommendation

Elafibranor (Iqirvo)

Indication: For the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA

Sponsor: Ipsen Biopharmaceuticals Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Iqirvo?

Canada's Drug Agency (CDA-AMC) recommends that Iqirvo be reimbursed by public drug plans for the treatment of primary biliary cholangitis (PBC) in adults with an inadequate response to ursodeoxycholic acid (UDCA), or as monotherapy in adults who are unable to tolerate UDCA, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Iqirvo should only be covered to treat adult patients who have a diagnosis of PBC; who have either not responded adequately to UDCA treatment after taking it for at least a year, with a stable dose maintained for a minimum of 3 months, or who are unable to tolerate UDCA treatment; and who have a total bilirubin level of no higher than 2 times the upper limit of normal (ULN) as well. In addition, patients should have no history or current evidence of other liver diseases. Initial coverage for Iqirvo should not exceed 12 months.

What Are the Conditions for Reimbursement?

Iqirvo should only be reimbursed if prescribed by or in consultation with a specialist, such as a gastroenterologist, a hepatologist, or other physicians with expertise in managing PBC, and if the cost of Iqirvo is reduced. For renewal after the initial authorization, Iqirvo should follow the same renewal criteria as obeticholic acid, in accordance with the reimbursement criteria of each public drug plan for treating PBC. For ongoing renewals, physicians must confirm that the patient's initial response to Iqirvo achieved during the first 12 months has been maintained. Renewal of coverage should be assessed on an annual basis.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that at 1 year of treatment, Iqirvo (in combination with UDCA in patients with an inadequate response to UDCA, or as monotherapy in those unable to tolerate UDCA) resulted in improved response to the treatment (alkaline phosphatase [ALP] $< 1.67 \times \text{ULN}$, normal total bilirubin level, and ALP decrease of $\geq 15\%$ from baseline), when compared with placebo.
- Iqirvo meets some important patient needs by offering an additional treatment option that could result in improved treatment response and normalized ALP levels.

Summary

- Based on the CDA-AMC assessment of the health economic evidence, Iqirvo does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Iqirvo compared with obeticholic acid.
- Based on public list prices, Iqirvo is estimated to cost the public drug plans approximately \$326 million over the next 3 years. The actual budget impact is highly uncertain.

Additional Information

What Is PBC?

PBC is an autoimmune disease that damages the bile ducts in the liver. Over time, if left untreated, PBC can lead to permanent scarring of liver tissue, which is called cirrhosis of the liver, and can cause liver failure and death. In 2015, there were about 318 patients in Canada diagnosed with PBC.

Unmet Needs in PBC

Although many patients with PBC respond to first-line treatment with UDCA, approximately one-third of UDCA-treated patients have an inadequate response to UDCA or are intolerant. There is a need for treatments that can cure the disease, normalize ALP levels, reduce symptoms such as pruritus, and improve patients' quality of life.

How Much Does PBC Cost?

Treatment with Iqirvo is expected to cost approximately \$76,220 per patient per year.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that elafibranor be reimbursed 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, only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

One phase III, double-blind, placebo-controlled trial (ELATIVE, N = 161) demonstrated that treatment with elafibranor resulted in greater improvement in biochemical response in adult patients with PBC in combination with UDCA in those with an inadequate response to UDCA, or as monotherapy in those unable to tolerate UDCA, at 12 months compared with placebo (50.9% versus 3.8%; odds ratio = 37.6; 95% confidence interval [CI], 7.6 to 302.2; $P < 0.0001$). In the ELATIVE trial, biochemical response was a composite end point defined as an ALP less than 1.67 times the ULN, a total bilirubin at or below the ULN, and a decrease in ALP of at least 15% from baseline. The ELATIVE trial also demonstrated that elafibranor resulted in a clinically important increase in the proportion of patients with normalized ALP levels when compared to placebo (14.8% versus 0%; odds ratio = infinity; 95% CI, 2.79 to infinity; $P = 0.0019$). The effect of elafibranor on clinical outcomes such as progression to end-stage liver disease or transplant-free survival is unknown. In addition, there was no statistically significant difference between the treatment groups regarding symptoms of pruritus or fatigue.

There is no direct comparative evidence between elafibranor and other treatments for patients with PBC in a second-line setting. Indirect evidence from a network meta-analysis (NMA) submitted by the sponsor comparing elafibranor to obeticholic acid was [REDACTED] in biochemical response, ALP normalization, change in ALP levels, improvement in pruritus symptoms, or risk of study discontinuation due to pruritus. In addition, substantial uncertainty in treatment effect estimates exists due to limitations like small sample sizes and differences in study design.

Patients identified a need for effective and safe treatment options that can improve disease management, slow or halt disease progression, alleviate symptoms, and improve health-related quality of life (HRQoL). CDEC noted that, while there is no evidence that elafibranor would slow or halt disease progression, alleviate symptoms, or improve HRQoL, elafibranor represents an alternative to currently available treatments, and it helps patients achieve biochemical response and normalize ALP levels.

Using the sponsor-submitted price for elafibranor and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for elafibranor plus UDCA was \$247,220 per quality-adjusted life-year (QALY) gained compared with obeticholic acid. At this incremental cost-effectiveness ratio, elafibranor is not cost-effective at a willingness to pay (WTP) threshold of \$50,000 per QALY gained for adult patients with PBC with an inadequate response to UDCA. A price reduction is required for elafibranor to be considered cost-effective at a \$50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with elafibranor should be reimbursed when initiated in adults who have all of the following: 1.1. A PBC diagnosis as demonstrated by at least 2 of 3 diagnostic factors: 1.1.1. $ALP \geq 1.67 \times ULN$ for ≥ 6 months 1.1.2. Positive AMA titre or presence of PBC-specific ANAs 1.1.3. Liver biopsy consistent with PBC 1.2. An inadequate response to UDCA after a UDCA trial of ≥ 12 months prior and a stable dose for ≥ 3 months, or unable to tolerate UDCA treatment. An inadequate response is defined as $ALP \geq 1.67 \times ULN$ 1.3. Total bilirubin $\leq 2 \times ULN$	Evidence from the ELATIVE trial demonstrated that treatment with elafibranor resulted in clinical benefit in patients with these characteristics. The majority of patients included in the ELATIVE trial (approximately 95%) were receiving UDCA at baseline. Therefore, there is limited evidence about the safety and efficacy of elafibranor for patients who are intolerant to UDCA.	CDEC noted that lack of response to UDCA should be assessed after at least 12 months of treatment. CDEC noted that intolerance to UDCA can be based on clinical judgment. Elafibranor could be initiated similarly to obeticholic acid as per the reimbursement criteria for each public drug plan. In the ELATIVE trial, patients who were unable to tolerate UDCA treatment must not have received UDCA for at least 3 months before screening.
2. Patients must not have history or presence of other concomitant liver diseases.	There is no evidence to support a benefit of elafibranor treatment in patients with a history or presence of other concomitant liver diseases because they were excluded from the ELATIVE trial.	—
3. The maximum duration of initial authorization is 12 months.	The ELATIVE trial assessed the primary and secondary end points at week 52.	—
Renewal		
4. For renewal after initial authorization, elafibranor should be renewed in a similar manner to obeticholic acid as per the reimbursement criteria for each public drug plan for the treatment of PBC.	There is no evidence that elafibranor should be held to a different standard than obeticholic acid when considering renewal.	The clinical experts noted to CDEC that in a scenario that patients' ALP level did not drop below $1.67 \times ULN$ but still achieved 15% to 20% reduction from baseline, clinicians would consider that these patients significantly benefited from elafibranor and would continue this treatment, even though meeting both criteria ($ALP < 1.67 \times ULN$ and ALP decrease $\geq 15\%$) is preferable. The clinical experts suggested that treatment should be continued if the reduction in ALP levels from baseline was at least 15%, and that if the reduction in ALP level from baseline is

Reimbursement condition	Reason	Implementation guidance
		no greater than 15% to 20%, patients should switch to another treatment.
5. For subsequent renewal, the physician must provide proof that the initial response achieved after the first 12 months of therapy with elafibranor has been maintained. Subsequent renewals should be assessed annually.	Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment.	—
Prescribing		
6. Elafibranor must be prescribed by, or in consultation with, a specialist such as a gastroenterologist, a hepatologist, or other clinicians with expertise in managing PBC.	This is meant to ensure that elafibranor is prescribed to patients it is appropriate for and that AEs are managed in an optimized and timely manner.	Elafibranor could be prescribed similarly to obeticholic acid as per the reimbursement criteria for each public drug plan.
Pricing		
7. The cost of elafibranor should be negotiated so that it does not exceed the drug program cost of treatment with obeticholic acid.	The indirect treatment comparison of elafibranor to obeticholic acid was highly uncertain in estimating rates of achieving cholestasis and reducing itch. Additionally, there was uncertainty in the economic model in terms of its ability to estimate relative survival due to liver disease, changes in health state utility, and the long-term efficacy of treatment. As such, there is insufficient evidence to justify a cost premium for elafibranor over obeticholic acid.	—
Feasibility of adoption		
8. The economic feasibility of the adoption of elafibranor must be addressed.	At the submitted price, the incremental budget impact of elafibranor plus UDCA is expected to be greater than \$40 million in years 1, 2, and 3. At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate(s).	—

AE = adverse event; ALP = alkaline phosphatase; AMA = antimitochondrial antibody; ANA = antinuclear antibody; CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; PBC = primary biliary cholangitis; UDCA = ursodeoxycholic acid; ULN = upper limit of normal.

Discussion Points

- **Unmet needs in PBC:** CDEC considered the needs identified by patients, which included improving disease management, improving symptom control, and HRQoL. CDEC discussed that while in the ELATIVE trial, treatment with elafibranor may have resulted in a higher proportion of patients who

achieved a biochemical response, no differences were observed in the improvement in symptoms of pruritus [REDACTED], nor any change in low-density lipoprotein (LDL) levels from baseline, when comparing elafibranor with placebo.

- **GRADE assessment:** CDEC discussed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of selected outcomes from the ELATIVE trial and noted that the certainty of the outcomes of biochemical response, ALP normalization, and change from baseline in ALP levels were considered “moderate,” while the certainty of patient-reported HRQoL and safety outcomes were rated “low.” Additionally, CDEC highlighted that the correlation between these biomarkers and long-term clinical outcomes remains unknown. Also, there was limited evidence on the effect of elafibranor in patients who were intolerant to UDCA.
- **Biochemical response as a surrogate end point for long-term clinical outcomes:** CDEC noted that in the ELATIVE trial, clinically meaningful outcomes for patients with PBC, such as survival or disease progression to fibrosis or cirrhosis, were not adequately evaluated or the results were not available at the time of this review. Instead, changes in ALP, total bilirubin, and liver enzymes were used as surrogate markers in clinical trials to predict the benefit of treatment in the absence of data on these hard outcomes. The primary outcome in the ELATIVE trial was to measure the biochemical response to treatment at week 52 (defined as a composite biochemical end point; that is, $ALP < 1.67 \times ULN$ and $total\ bilirubin \leq ULN$ and $ALP\ decrease \geq 15\%$). Although this biochemical response is not validated, it has been used in other trials for patients with PBC. In addition, the clinical relevance of normalizing ALP in terms of longer survival, slower disease progression, and improved HRQoL still needs to be demonstrated for elafibranor.
- **Adverse effects:** CDEC noted that evidence from the ELATIVE trial suggested that elafibranor may result in fewer serious adverse events but more adverse events of special interest (e.g., creatine phosphokinase (CPK) elevation, total bilirubin elevation, muscle pain or myalgia) when compared with placebo. There is uncertainty in long-term safety due to the lack of a comparator group and missing data in the long-term extension (LTE) period of the ELATIVE trial.
- **Indirect evidence:** CDEC discussed the sponsor-submitted NMA, which included 2 randomized controlled trials (RCTs) comparing elafibranor with obeticholic acid in patients with PBC in a second-line setting. CDEC noted that the indirect evidence from this NMA was [REDACTED] whether treatment of elafibranor differs from obeticholic acid in terms of biochemical response, ALP normalization, and change in ALP levels from baseline, improvement in symptoms of pruritus, or the risk of study discontinuation due to pruritus. Elafibranor may be related to fewer occurrences of pruritus (as an adverse event, of any severity) compared to obeticholic acid 10 mg. However, there was substantial uncertainty in the treatment effect estimates from the NMA due to the limitations of the available indirect evidence.
- **Place in therapy:** CDEC discussed the place in therapy of elafibranor for the treatment of PBC and noted that elafibranor can be used as a second-line treatment for patients who do not respond to, have inadequate symptom control from, or cannot tolerate the first-line treatment (UDCA) for PBC. It

was also noted that, currently, obeticholic acid is a relevant comparator for elafibranor as a second-line therapy in patients with PBC.

- **Use in combination with obeticholic acid:** CDEC noted that there is no available data on the efficacy or safety of combining obeticholic acid with elafibranor, and hence, elafibranor should not be reimbursed when used in combination with obeticholic acid.
- **Budget impact:** The estimated budget impact is highly sensitive to assumptions about eligibility for public coverage, market share for obeticholic acid, and the rate of elafibranor uptake. CDEC noted a large divergence between the assumptions made by the sponsor and those made by CDA-AMC in consultation with clinical experts. These divergences translated to a 7-fold increase in the estimated 3-year budget impact. Decisions about the adoption of elafibranor should be guided by best estimates of current rates of obeticholic acid use, particularly given the context of the place in therapy of obeticholic acid, as described previously. The uncertainty in the estimate of the budget impact is compounded by the methodological concerns present in the sponsor's submitted model. An alternative analysis conducted using a validated tool built by CDA-AMC estimated an even greater budget impact, although this alternative estimate does not reflect treatment-specific mortality rates.

Background

PBC is a rare, progressive, chronic autoimmune disease of the liver characterized by the slow, immune-mediated destruction of small intrahepatic bile ducts. Over time, if left untreated, PBC can progress to cirrhosis of the liver and cause liver failure and death. Patients commonly present with pruritus and fatigue. At the end-stage, liver disease, progressive jaundice, malnutrition, portal hypertension, and liver failure occur, which can lead to premature death in the absence of a liver transplant. PBC occurs predominantly in females (more than 90%), and most patients are diagnosed between the ages of 30 and 65 years. A diagnosis of PBC is made based on an elevated level of ALP, presence of antimitochondrial antibody (AMA), and histologic evidence of nonsuppurative cholangitis and destruction of interlobular bile ducts. The estimated age- and sex-adjusted incidence rate for PBC was 30.3 cases per 1,000,000 per year. In 2015, the prevalence of PBC was estimated to be 318 cases per 1,000,000 in Canada.

Treatments for PBC aim to slow disease progression, maintain the integrity of the liver and prevent complications associated with PBC and end-stage liver disease, and provide symptom control. UDCA is the first-line therapy for all patients with PBC. However, it does not improve symptoms of fatigue or pruritus. In Canada, up to 32% of UDCA-treated patients have an inadequate response to UDCA or are intolerant (< 5%). Obeticholic acid can be used for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in those unable to tolerate UDCA. However, obeticholic acid commonly worsens existing symptoms, such as pruritus and fatigue, and it is contraindicated in patients with decompensated cirrhosis or patients with compensated cirrhosis who have evidence of portal hypertension. Other options as second-line therapy for PBC are peroxisome proliferator-activated receptor agonists, such as fibrates.

Elafibranor is approved by Health Canada 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. A Notice of Compliance with Conditions for elafibranor was issued on April 25, 2025. The sponsor's reimbursement request is aligned with the approved Health Canada indication. Elafibranor is a dual peroxisome proliferator-activated receptor alpha-delta agonist that modulates complementary pathways involved in PBC pathogenesis. It is available as 80 mg tablets, and the recommended dosage is 80 mg taken orally once daily.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 ongoing, phase III, randomized, double-blind, placebo-controlled trial, ELATIVE (N = 161) in patients with PBC who had an inadequate response or intolerance to UDCA; 1 LTE study; and 1 indirect treatment comparison
- patients' perspectives gathered by 2 patient groups: the Canadian Liver Foundation and the Canadian PBC Society
- input from public drug plans that participate in the reimbursement review process
- 2 clinical specialists with expertise in diagnosing and treating patients with PBC
- input from 1 clinician group: Canadian Network for Autoimmune Liver disease (CaNAL)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Input was submitted by 2 patient groups for this review, the Canadian Liver Foundation and the Canadian PBC Society, which reached out to patients, caregivers, and health care professionals across 5 provinces through online surveys and in-person meetings.

The patient groups noted how response to treatment is variable and can decline over time. In addition, not all patients' disease responds adequately to first-line therapy for PBC (i.e., UDCA), and despite treatment, they may continue to experience insufficient disease control, ongoing symptoms, or adverse effects. The groups stated how disease symptoms (e.g., severe fatigue, pruritus, brain fog, and joint pain) and the additional burden of multiple chronic comorbidities greatly impair HRQoL, daily activities, ability to work, and ability to maintain relationships for both patients and caregivers. Input from the groups described how patients can have other autoimmune diseases and symptoms that delay diagnosis, thus allowing PBC to progress untreated and putting patients at greater risk of advanced disease and the need for liver transplant. Complications of advanced PBC include variceal bleeding, portal hypertension, hepatocellular carcinoma, and jaundice.

Patients are looking for safe and effective therapies that improve disease management, slow or halt disease progression, and improve HRQoL. Moreover, respondents indicated that disease control (e.g., normalization of ALP levels), effective symptom management, and reducing the day-to-day burden of living with PBC are important outcomes. They are also looking for a treatment that is easy to use and has minimal adverse effects. The groups added that difficulty accessing obeticholic acid and the adverse effects of the drug are issues with the current second-line treatment.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts identified the following unmet needs associated with currently available treatments for patients with PBC:

- There is a lack of curative therapy for PBC.
- Approximately one-third of patients with PBC do not respond to first-line treatment with UDCA, and UDCA does not improve PBC symptoms such as pruritus.
- Currently, obeticholic acid is the only Health Canada–approved second-line treatment for patients who do not adequately respond to UDCA. Although biochemical responses (response to treatment assessed by a change in the levels of biochemical markers that are specific for PBC, such as normalization of ALP, reduction in ALP level from baseline, or reduction in total bilirubin from baseline) were observed in these patients, obeticholic acid often worsens the PBC symptoms of pruritus and fatigue, and obeticholic acid cannot be used in patients with cirrhosis and those with portal hypertension.
- Treatment of PBC symptoms and their alleviation (pruritus and fatigue) remains an important unmet need.

The clinical experts indicated that elafibranor can be used as a second-line treatment for patients who do not respond to, have inadequate symptom control from, or cannot tolerate the first-line treatment (UDCA) for PBC. The clinical experts noted that the features of patients most likely to respond to treatment with elafibranor are not fully understood; however, based on the clinical trial data, patients with lower hepatic biochemistry at baseline would have a better treatment response. For patients with higher ALP levels, presence of advanced liver fibrosis or cirrhosis, presence of ductopenia on biopsy (if performed), and severe pruritus at baseline, their biochemical response to elafibranor is likely to be lower.

According to the clinical experts, important outcomes for patients with PBC are biochemical responses, symptom control for pruritus and fatigue, and a decrease in liver stiffness measurements. Usually, patients' biochemical responses are measured at 6 and 12 months after initiating treatment. According to the clinical experts, clinical trials with a longer duration (i.e., at least 2 years) would be required to observe a meaningful change in liver stiffness measurements.

According to the clinical experts consulted for this review, elafibranor will be discontinued if patients do not respond to the treatment or if they experience intolerable adverse effects from the treatment.

The clinical experts noted that, in general, health care services for patients with PBC can be provided within primary care ambulatory clinics, with specialist oversight and input being provided on an as-needed basis and/or depending on the availability of a specialist. For patients who do not respond to previous treatments, have persistent refractory symptoms, or have progressive disease, specialist input is required.

Clinician Group Input

Input was submitted by 1 clinician group for this review, CaNAL, consisting of 7 physicians from 4 provinces with expertise in hepatology and gastroenterology who contributed to the input.

In general, the clinician group input was consistent with the input provided by the clinical experts consulted for this review. According to the clinicians, current treatments indicated for PBC do not sufficiently achieve biochemical control of the disease for all patients, do not address disease symptoms (may even worsen pruritus), have adverse effects, and cannot be used in patients with cirrhosis and portal hypertension. Use of off-label treatments (e.g., bezafibrate and fenofibrate) is associated with adverse effects and potential liver toxicity. Moreover, there are no treatments specifically approved for PBC symptom control. Patients who present with late-stage disease or who progress on standard of care therapy to end-stage disease are also in need of new treatments. The clinician group stated that elafibranor would be used as a second-line treatment and could be used alongside UDCA (similar to the Health Canada indication).

The clinician group confirmed that the clinical trial outcomes (including biochemical response measured with liver tests) align with those used in practice. While clinicians look for treatments most likely to normalize ALP and bilirubin levels and improve symptoms, they also recognize the importance of therapies that support improved liver tests (e.g., although an ALP of less than 1.67 times the ULN would be clinically meaningful, a reduction of at least 20% in ALP levels for patients with high-risk disease would also be considered clinically valuable). Symptom response (e.g., pruritus) should also be evaluated qualitatively with the patient.

CaNAL suggested that treatment discontinuation should be considered if serum liver tests deteriorate, if significant myalgias occur, CPK levels rise, or creatinine levels rise. Other reasons for discontinuation include concerns about drug interactions, pregnancy, or the development of impaired liver function.

PBC is mainly managed in an outpatient setting by specialists in gastroenterology, and some patients are seen by hepatologists (who are originally gastroenterologists by training).

Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Obeticholic acid is indicated for the treatment of PBC in combination with UDCA in adults with an inadequate response	The clinical experts indicated that in a clinical trial, patients usually receive 1 year of treatment with UDCA before

Implementation issues	Response
to UDCA, or as monotherapy in adults unable to tolerate UDCA. Obeticholic acid is in a similar place in therapy as elafibranor in that both can be considered when the patients do not respond well to UDCA or cannot tolerate UDCA. What duration is reasonable for a treatment with UDCA to determine if the patients have had an adequate response to the treatment or not?	elafibranor can be offered. In clinical practice, for the patients who are considered to have progressive disease, a higher risk of treatment failure, and ALP levels that are less likely to be normalized when on UDCA (such as those who are younger, have higher ALP at baseline, and have more severe pruritus and established fibrosis), the clinician would prefer to start a second-line therapy sooner. The clinical experts indicated that it is reasonable to evaluate patients' response to UDCA at 6 months of treatment, which has also been suggested by clinical evidence. CDEC noted that a lack of response to UDCA should be assessed after at least 12 months of treatment, and that a determination of intolerance to UDCA can be based on clinical judgment.
Considerations for initiation of therapy	
Disease diagnosis, scoring, or staging for eligibility: • In the ELATIVE trial, a diagnosis of PBC was based on the presence of at least 2 of 3 of the following diagnostic criteria: an elevated serum ALP level ($> 1.5 \times \text{ULN}$), serum AMA, and liver biopsy consistent with PBC. • In your experience, are AMA blood tests available at all sites, or could these diagnostic requirements pose an equity issue? • In the event that the AMA test is negative and a liver biopsy is not possible, are there other ways to confirm a diagnosis of PBC? • Do the diagnostic criteria reflect common diagnostics conducted in clinical practice, or are other criteria more commonly used?	The clinical experts noted that the AMA blood tests are available in all tertiary care centres in each province. The experts did not think these diagnostic requirements pose an equity issue. Even for patients living in remote areas, the samples can be sent to a central lab. In the event that an AMA test is negative and a liver biopsy is not possible, a diagnosis of PBC cannot be confirmed, and the patient should be evaluated by a specialist, and a discussion is needed. The clinical experts confirmed that these are standard criteria and reflect common diagnostics conducted in clinical practice. The experts also indicated that even if a patient has a negative AMA or ANA test, the patient may still have positive special antibodies related to PBC, such as anti-SP100 and anti-GP210 autoantibodies. Therefore, a diagnosis of PBC should be established based on test results for AMAs, ANAs, and the 2 PBC-specific antibodies. CDEC agreed with the clinical experts.
Other patient characteristics for eligibility (e.g., age restrictions, comorbidities): • In the ELATIVE trial, patients with a bilirubin $> 2 \times \text{ULN}$ were excluded "to ensure adequate representation of moderately advanced disease or patients at risk of progression to clinical outcomes." Patients with clinically significant hepatic decompensation or other hepatic conditions (e.g., primary sclerosing cholangitis, alcoholic liver disease, autoimmune hepatitis) were also excluded. • Is there a concern for indication creep? If so, is there any evidence that elafibranor would be effective for other indications outside of PBC?	The clinical experts noted that clinicians are not concerned about indication creep. In clinical practice, clinicians would not give a patient this treatment unless a diagnosis of PBC was confirmed. CDEC agreed with the clinical experts.
Prior therapies required for eligibility: • Both obeticholic acid and elafibranor are placed as second-line therapies after first-line treatment with UDCA. • What dose and duration of UDCA would be appropriate before	The clinical experts indicated that, as a first-line therapy for patients with PBC, the dosage of UDCA is 13 mg/kg to 15 mg/kg, taken orally once daily. In general, the recommended duration of the UDCA therapy is 1 year before providing

Implementation issues	Response
providing coverage for elafibranor? Is there a concern that 1 patient will be prescribed both drugs (obeticholic acid and elafibranor) at the same time?	coverage for elafibranor. If the patients cannot tolerate this dosage (which occurs in 3% to 5% of the PBC population), elafibranor would be offered as first-line therapy. CDEC noted that there is no evidence that elafibranor is the preferred second-line therapy over obeticholic acid. The duration of UDCA to adequately determine inadequate response appears to be 12 months, which is similar to the duration used in the ELATIVE trial, but the choice of a second-line option is not clear from the evidence provided. The clinical experts assumed that the only scenario in which a patient may need 2 approved drugs (e.g., adding obeticholic acid to existing elafibranor) would be if the patient's ALP level fails to be $< 1.67 \times \text{ULN}$. However, if there is evidence showing that the patient is having seriously progressive disease (uncontrolled ALP and elevated total bilirubin which is indicative of cirrhosis), obeticholic acid should not be added, or if obeticholic acid was used as second-line therapy, it should be discontinued due to safety concerns and contraindications of this drug. In this case, a third-line therapy may be considered, and the criteria for the use of third-line therapies in this patient population need to be established. Because obeticholic acid has a different mechanism of action compared to elafibranor or fibrates, it may be an option as a third-line therapy for controlling advanced and/or progressive disease. CDEC noted that there is no available efficacy or safety data for the combination of obeticholic acid and elafibranor.
Eligibility for re-treatment: There is no cure for PBC. Therefore, patients are likely to remain on therapy, if effective, for the duration of their lives or until there is a significant change in their treatment requirements.	Comment from the drug programs to inform CDEC deliberations.
Consistency with initiation criteria associated with other drugs reviewed by CDA-AMC in the same therapeutic space: - In the CDEC recommendation for obeticholic acid, it is recommended that obeticholic acid be reimbursed 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, if the following conditions are met: - that patients are under the care of a specialist with experience in the diagnosis and management of PBC - that the price of elafibranor is reduced by at least 60%. - The drug plans suggested that if elafibranor is recommended to be reimbursed, the implementation criteria in the recommendation should align with those in the obeticholic acid recommendation, and additionally, there should be a requirement of 12-month trial of UDCA, which is similar to the trial conditions in ELATIVE.	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
Considerations for continuation or renewal of therapy	
If elafibranor is recommended to be reimbursed, the continuation or renewal criteria in this recommendation should align with existing criteria for obeticholic acid and be similar to the trial conditions. However, considering that most of the outcomes in the trial are surrogate markers, it may be appropriate to seek a greater reduction in the level of PBC biomarkers (for example, ALP).	Comment from the drug programs to inform CDEC deliberations.
Is a lower ALP level after the medical treatment a sign of better prognosis for patients with PBC?	CDEC agreed with the clinical experts that a lower ALP level after the treatment is a sign of better prognosis, only if the bilirubin level stays low. When the level of bilirubin starts elevating, a lower ALP level can suggest that bile ducts are being lost and the disease is progressing.
If a patient failed to achieve the outcomes outlined in the ELATIVE trial (e.g., $ALP < 1.67 \times ULN$, total bilirubin $\leq ULN$, and ALP decrease $\geq 15\%$), are there circumstances where it would be appropriate for the patient to retry this therapy or continue therapy? If so, what are those circumstances and how much time should have passed? Specifically: • What is an appropriate duration of a trial to achieve the aforementioned outcomes? • Under what circumstances can patients continue to be treated with elafibranor if the aforementioned outcomes are not met? For patients not meeting the aforementioned outcome criteria, would they be able to restart the medication in the future?	CDEC agreed with the clinical experts that it would be appropriate for the patient to be re-treated with elafibranor, even though elafibranor may not be fully effective. The evidence suggests that it may still have a protective effect for patients whose disease is progressing. The clinical experts discussed the value of outcome measures used for assessing treatment effect. In a scenario in which a patients' ALP level did not drop below $1.67 \times ULN$ but still achieved 15% to 20% reduction from baseline, most clinicians would feel that the patient significantly benefited from elafibranor and would continue this treatment, even though meeting both criteria ($ALP < 1.67 \times ULN$ and ALP decrease $\geq 15\%$) is preferable. The clinical experts suggested that treatment should be continued if the reduction in ALP levels from baseline was at least 15%, and that if the reduction in ALP level from baseline is no greater than 15% to 20%, patients should switch to another treatment. CDEC recommended that, for renewal after initial authorization, elafibranor should be renewed in a similar manner to obeticholic acid as per the reimbursement criteria for each public drug plan for the treatment of PBC. In terms of duration of treatment, the clinical experts stated that, in clinical trials, treatment effect was usually measured at 1 year. Over time, the reduction in ALP levels mostly occurs within 1 to 3 months of treatment and, thereafter, a plateau is observed. However, most patients wish to continue the treatment for at least 1 year. CDEC recommended that the initial authorization be for 12 months, and that subsequent renewals should be assessed annually. The clinical experts indicated that, if the patients do not meet the criteria (e.g., $ALP < 1.67 \times ULN$, total bilirubin $\leq ULN$, and ALP decrease $\geq 15\%$) after treatment, clinicians would restart the treatment if there was an opportunity, given that there is a continuous protective effect for "partial responders" from elafibranor in this progressive disease. Furthermore, the limited options used as second-line therapies for patients with advanced and/or progressive PBC is another factor to consider

Implementation issues	Response
	when selecting the appropriate treatment. For example, in clinical practice, for older patients who need second-line therapy and who are not candidates for liver transplant, it is difficult to find another treatment that is suitable for them. CDEC noted that, in the absence of a correlation between biochemical response and more meaningful clinical outcomes, it would not be appropriate for patients to continue drug therapy if they have not shown evidence of a biochemical response.
Considerations for discontinuation of therapy	
PBC is a progressive disease for which there is no cure. As PBC progresses, is there a possibility that the primary outcomes of the ELATIVE trial (ALP < 1.67 × ULN or at least 15% decrease from baseline, total bilirubin < ULN) are no longer maintained, yet the patient still experiences benefit? Besides the biochemistry responses, what other measures might be used in clinical practice to determine ongoing benefit from the treatment?	The clinical experts agreed that, in progressive PBC, it is possible for patients to experience benefit even when the primary outcomes of the ELATIVE trial are no longer maintained. The clinical experts stated that, besides the biochemistry responses, other measures that would be used in clinical practice to determine ongoing benefit from the treatment include PBC-related symptoms (e.g., itch) and fibrosis (FibroScan is available mainly at tertiary care centres). CDEC indicated that, in the ELATIVE trial, treatment with elafibranor failed to show a positive impact on symptoms. In the absence of a correlation between biochemical response and more meaningful clinical outcomes, it would not be appropriate to continue drug therapy in patients who have not shown evidence of a biochemical response.
Considerations for prescribing of therapy	
In a phase II trial with 3 treatment arms (NCT03124108), patients were randomly assigned to elafibranor 80 mg, elafibranor 120 mg, or placebo. Do you foresee dose creep for elafibranor in practice, beyond the recommended 80 mg oral daily?	CDEC agreed with the clinical experts that, in clinical practice, a dose creep for elafibranor is not expected because there will not be an added benefit from the doses beyond the recommended dosage of 80 mg oral elafibranor per day.
Obeticholic acid requires the patient to be under the care of a gastroenterologist. Would it be appropriate for other specialists who are not gastroenterologists to diagnose and guide therapy for PBC? If not, what aspect of care (e.g., diagnosis, treatment guidance) can/should only be done by gastroenterologists?	The clinical experts noted that, in general, health care services for patients with PBC can be provided within primary care ambulatory clinics, with specialist oversight and input being provided on an as-needed basis and/or depending on the availability of a specialist. For patients who do not respond to previous treatments (in the second-line setting or beyond) with persistent refractory symptoms or with progressive disease, specialist input is required. CDEC agreed with the clinical experts.

ALP = alkaline phosphatase; AMA = antimitochondrial antibody; ANA = antinuclear antibody; CDEC = Canadian Drug Expert Committee; PBC = primary biliary cholangitis; UDCA = ursodeoxycholic acid; ULN = upper limit of normal.

Clinical Evidence

Systematic Review

Description of Studies

The evidence included in this review consisted of 1 ongoing, phase III, double-blind, placebo-controlled RCT, ELATIVE (N = 161). The purpose of this study was to evaluate the efficacy and safety of elafibranor (80 mg) 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. Patients had a diagnosis of PBC according to these criteria (at least 2 of 3 should have been met): ALP elevated for at least 6 months before randomization, positive AMA titre or presence of PBC-specific antinuclear antibody, and liver biopsy consistent with PBC. Eligible patients should also have received at least 12 months of prior UDCA therapy and have been on a stable dose for at least 3 months at study entry or be unable to tolerate UDCA. At baseline, the patients were required to have an ALP level higher than 1.67 times the ULN, and a total bilirubin level of no more than 2 times the ULN. Patients were excluded if they had a history or presence of other concomitant liver disease, liver transplant, cirrhosis, or portal hypertension. The primary efficacy end point of this study was biochemical cholestasis response, with secondary end points including ALP normalization, change from baseline in ALP levels, improvements in PBC symptoms (e.g., pruritus and fatigue), and change from baseline in LDL level. Safety outcomes were presented in this report as well. At baseline, the patient characteristics were generally balanced between the 2 groups. Of the 161 patients in the study, most were female (female = 95.7%; male = 4.3%) and white (white = 91.3%; others [including American Indian or Alaska Native, Asian, or Black or African American] = 7.5%; not reported = 1.2%). The median age (range) was 58.0 (38 to 75) years in the elafibranor group and 56.0 (36 to 76) years in the placebo group. Overall, the median time (range) since PBC diagnosis was 6.5 (1 to 33) years in the elafibranor group and 6.0 (1 to 28) years in the placebo group. PBC Worst Itch Numeric Rating Scale (WI-NRS) score was 4 or higher in approximately 41% of patients in both groups. The mean level of ALP at baseline was 321 U/L in the elafibranor group and 323.1 U/L in the placebo group. The mean level of total bilirubin was 9.7 μ mol/L in the elafibranor group and 9.4 μ mol/L in the placebo group. Liver stiffness was slightly worse in the placebo group (9.85 kPa in the elafibranor group and 10.73 kPa in the placebo group); 8.7% of patients treated with elafibranor and 14.0% of patients treated with placebo had a measurement of greater than 16.9 kPa on the liver stiffness index.

Efficacy Results

Primary and secondary analyses on the efficacy outcomes were conducted in the intention-to-treat (ITT) analysis set.

Biochemical Response to Treatment

Biochemical response was the primary efficacy end point in the ELATIVE trial. It was defined as an ALP lower than 1.67 times the ULN, total bilirubin of 1 $\times$ ULN or lower, and an ALP decrease of 15% or more. At week 52, the primary end point was met: 55 patients (50.9%) in the elafibranor group had a biochemical cholestasis response, compared with 2 (3.8%) in the placebo group. The between-group difference was 47.2% (95% CI, 32.0 to 56.9). The odds ratio (OR) of the comparison for a cholestasis response with elafibranor versus placebo was 37.6 (95% CI, 7.6 to 302.2; P < 0.0001). Based on the results for each

component of this composite end point, the biggest difference between treatment groups was observed in the change in ALP, where at week 52, the proportion of patients with ALP $< 1.67 \times \text{ULN}$, ALP decrease $\geq 15\%$ from baseline, and total bilirubin $\leq \text{ULN}$ were 52% versus 9%, 75% versus 17%, and 85% versus 83% for the elafibranor and placebo treatment groups, respectively. The findings were robust to sensitivity analyses with different handling of intercurrent events and alternative assumptions about missing data. Results were consistent in direction of effect across patient subgroups (predefined subgroups based on age, gender, race, UDCA treatment at baseline, prior obeticholic acid treatment, ALP level at baseline, total bilirubin level at baseline, albumin level at baseline, geographic region, PBC WI-NRS score at baseline, liver stiffness at baseline, and advanced disease stage at baseline).

ALP Normalization

ALP normalization was defined as an ALP lower than or equal to the ULN. ALP normalization at week 52 was achieved by 16 patients (14.8%) in the elafibranor group and no patients (0%) in the placebo group. The between-group difference was 14.8% (95% CI, 6.1 to 22.7). The OR was infinity (95% CI, 2.786 to infinity; $P = 0.0019$). The results were similar using the per-protocol analysis set.

Change From Baseline in ALP Level

At week 52, the least square (LS) mean change from baseline in ALP was -117.0 U/L (95% CI, -134.4 to -99.6) in the elafibranor 80 mg group and -5.3 U/L (95% CI, -30.4 to 19.7) in the placebo group. The LS mean difference between groups was -111.7 U/L (95% CI, -142.0 to -81.3 ; $P < 0.001$). The mean percent change from baseline at week 52 was -38.9% (standard deviation [SD] = 24.8) in the elafibranor group compared to 1.7% (SD = 18.5) in the placebo group, with a treatment estimate between groups in favour of elafibranor of -40.6% (95% CI, -47.8 to -33.4 ; $P < 0.0001$).

Symptoms

The PBC WI-NRS is used to measure the worst itch over the past 24 hours on a scale ranging from 0 (no itch) to 10 (worst itch imaginable). The sponsor suggested a [REDACTED] (possible absolute range [REDACTED]) as the clinically meaningful thresholds for this pruritus parameter. In the pruritus ITT analysis set (including patients from the ITT analysis set with baseline PBC WI-NRS score ≥ 4), the LS mean change from baseline through week 52 in PBC WI-NRS score was -1.930 (95% CI, -2.602 to -1.258) in the elafibranor group and -1.146 (95% CI, -2.143 to -0.150) in the placebo group. The LS mean difference between elafibranor and placebo was -0.784 (95% CI, -1.986 to 0.418 ; $P = 0.1970$). Similar results were observed using the pruritus per-protocol analysis set and the ITT analysis set.

The LS mean change from baseline through week 24 in PBC WI-NRS score in the pruritus ITT analysis set was -1.598 (95% CI, -2.246 to -0.951) in the elafibranor group and -1.255 (95% CI, -2.201 to -0.309) in the placebo group. The LS mean difference between elafibranor and placebo was -0.343 (95% CI, -1.489 to 0.803 ; $P = 0.5522$). Similar results were observed using the pruritus per-protocol analysis set and the ITT analysis set.

The PROMIS Fatigue Short Form 7a consists of 7 items measuring the experience of fatigue and its interference with daily activities over the past week, with higher scores indicating greater fatigue. The

LS mean change from baseline to 52 weeks in PROMIS scores were [REDACTED] [REDACTED] for the elafibranor group and [REDACTED] for the placebo group. The LS mean difference from placebo was [REDACTED]).

Change From Baseline in LDL Level

At week 52, the LS mean change from baseline in the level of LDL-cholesterol was -0.41 mmol/L (95% CI, -0.56 to -0.27) in the elafibranor group and -0.24 mmol/L (95% CI, -0.45 to -0.04) in the placebo group. The LS mean difference between elafibranor and placebo was -0.17 mmol/L (95% CI, -0.42 to 0.08).

Harms Results

In the ELATIVE trial, safety analyses were conducted for all patients who were administered at least 1 dose of the study drug. The vast majority of the patients experienced an adverse event, 96.3% in the elafibranor group and 90.6% in the placebo group. The most commonly reported treatment-emergent adverse events were gastrointestinal tract-related, including vomiting, diarrhea, nausea, or constipation.

The proportion of patients who experienced serious adverse events was 10.2% (11 patients) in the elafibranor group and 13.2% (7 patients) in the placebo group. Isolated cases of serious adverse events were reported in the 2 treatment groups; none occurred in more than 3 patients.

The incidence of treatment-emergent adverse events that led to treatment discontinuation was 10.2% in the elafibranor group and 9.4% in the placebo group.

Two deaths due to serious adverse events were reported in the elafibranor group: multiple organ dysfunction syndrome in 1 patient, and biliary sepsis and acute kidney injury in the other patient. None of these events were considered related to the study drug by the investigator.

The incidence of adverse events of special interest was 29.6% (32 patients) in the elafibranor group and 26.4% (14 patients) in the placebo group. Patients treated with elafibranor reported slightly more cases of elevated CPK (3.7% versus 0%), increased bilirubin (2.8% versus 1.9%), rhabdomyolysis (0.9% versus 0%), and myalgia (2.8% versus 0), but fewer increased transaminases (0% versus 1.9%) compared to those treated with placebo.

For adverse events of special interest, 4 patients in the elafibranor group and no participants in the placebo group reported CPK elevations of severe intensity or leading to permanent study drug discontinuation, 1 patient in the placebo group and none in the elafibranor group reported transaminase elevations from baseline of severe intensity or leading to permanent study drug discontinuation, 1 patient in the elafibranor group and no participants in the placebo group reported muscle injury.

The clinical experts consulted for this review noted that most adverse events are manageable and that there were no unusual safety signals identified.

Critical Appraisal

In the ELATIVE trial, in general, patients' baseline characteristics were balanced between the elafibranor group and placebo group (e.g., the demographic characteristics, time since initial diagnosis of PBC, level of

ALP and total bilirubin at baseline, and severity of pruritus at study entry), and consistent with patients seen in clinical practice in Canada. There were some imbalances between the 2 treatment groups, such as liver stiffness. It was unclear if this discrepancy would have an impact on the interpretation of results.

Some of the outcome measures in this study, including the primary and key secondary outcomes, were linked to biomarkers, such as a composite biochemical response, in which change in ALP plays an important role, or change from baseline in ALP. In the ELATIVE trial, clinically meaningful outcomes for patients with PBC were not adequately evaluated or the results were not available at the time of this review, such as survival or disease progression to fibrosis or cirrhosis. Certain PBC-related biomarkers (e.g., change in ALP, total bilirubin, liver enzymes) were used as surrogates in clinical trials to predict the benefit of treatment in the absence of data on these hard outcomes. There is evidence implying that a reduction in ALP level and total bilirubin level was associated with longer overall survival and transplant-free survival among patients with PBC. The primary outcome in the ELATIVE trial, a biochemical response to treatment at week 52 (defined as a composite biochemical end point — that is, $\text{ALP} < 1.67 \times \text{ULN}$ and $\text{total bilirubin} \leq \text{ULN}$ and $\text{ALP decrease} \geq 15\%$), although not validated, has been adopted in several clinical trials involving patients with PBC. The clinical experts consulted for this review also agreed that this is a reasonable and acceptable surrogate for clinically relevant outcomes. However, the actual clinical relevance of ALP normalization of the composite cholestasis end point to benefit of prolonged survival or delayed disease progression needs to be quantitatively demonstrated for elafibranor.

Patients' HRQoL was reflected by symptom control in the ELATIVE trial. Typical PBC symptoms, like pruritus and fatigue, were assessed using various disease-specific instruments such as PBC WI-NRS and PROMIS Fatigue Short Form 7a. These are validated scales used in measuring symptom improvement in patients with PBC. A minimally important difference for PROMIS Fatigue Short Form 7a (≥ 3 points change) has been identified, whereas no minimally important difference for the WI-NRS summary score has been established. The pruritus analysis set (patients with a baseline WI-NRS score ≥ 4 , which reflects moderate to severe pruritus) was analyzed for improvement of pruritus, which was approximately 40% of the overall population in the ELATIVE trial. Therefore, results for these end points have some level of uncertainty due to the small sample size, which means that prognostic balance may not have been met and analyses were likely underpowered, which reduces the level of certainty for these end points.

In this trial, multiplicity adjustment was performed in the analysis of the primary end point (composite biochemical cholestasis response) and the key secondary end points (ALP normalization rates and change from baseline in pruritus scores). There was no control for multiplicity for other efficacy or safety outcomes in the ELATIVE trial; thus, all other secondary end points were considered supportive. Type I error was not of concern, given that these additional end points did not reach a conventional level of statistical significance.

Predefined sensitivity analyses were conducted to evaluate the robustness of the results of the primary analysis as well as the analyses of key secondary end points. Overall, the results of sensitivity analyses were generally aligned with the primary analysis of biochemical response, which supported the robustness of the results. Prespecified subgroup analyses generally supported consistency of the overall direction of effect

of elafibranor across subgroups; some subgroups were composed of small numbers of patients, resulting in wide CIs.

Based on feedback from the clinical experts consulted for this review, the eligibility criteria and baseline characteristics of patients randomized in the ELATIVE trial generally reflected patients with PBC in the second-line treatment setting in Canada that would be offered elafibranor therapy, although the study population in ELATIVE had relatively higher ALP levels at baseline but milder symptoms of itchiness.

The clinical experts considered the inclusion criteria of the ELATIVE trial standard for clinical trials of PBC. For exclusion criteria, the experts suggested that patients with elevated liver enzymes (exceeding the thresholds specified in the exclusion criteria) may still be eligible to receive treatment with elafibranor in clinical practice. Other exclusion criteria in this study are reasonable in clinical practice and should be followed.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The threshold for a clinically important effect for biochemical cholestasis response in the study population was not obtained. Therefore, the target of the certainty of evidence assessment was the presence or absence of any (non-null) effect for response rates. The thresholds for a clinically important effect for the normalization in ALP level from baseline, change from baseline in ALP level and LDL level, and change from baseline in the occurrence of harm events in the study population were not obtained either. Therefore, the target of the certainty of evidence assessment was the presence or absence of any (non-null) effect for these end points. The threshold for a clinically important effect for the PBC WI-NRS summary score was set according to the presence or absence of an important effect based on a clinically meaningful threshold (CMT) identified by the sponsor. The threshold for a clinically important effect for the PROMIS Fatigue Short Form 7a score was set according to the presence or absence of an important effect based on the minimally important difference estimates identified in the literature.

Table 3 presents the GRADE summary of findings for elafibranor versus placebo.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- biochemical cholestasis response
- ALP normalization
- change from baseline in ALP levels
- change from baseline in pruritus scores
- change from baseline in fatigue scores
- change from baseline in LDL
- any serious adverse events
- adverse events of special interest.

Table 3: Summary of Findings for Elafibranor Versus Placebo for Patients With PBC

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Elafibranor	Difference		
Cholestasis response (ITT analysis set)							
Biochemical response to treatment at week 52, defined as ALP < 1.67 × ULN and total bilirubin ≤ ULN and ALP decrease of ≥ 15%. Follow-up: 52 weeks	161 (1 RCT)	OR: 37.56 (7.64 to 302.25)	38 per 1,000	509 per 1,000 (416 to 602 per 1,000)	472 more per 1,000 (320 to 569 more per 1,000)	Moderate ^a	Elafibranor likely results in a clinically important increase in the proportion of patients with a biochemical cholestasis response at week 52 when compared with placebo.
ALP normalization Follow-up: 52 weeks	161 (1 RCT)	OR: Infinity (2.79 to infinity)	0	148 per 1,000	148 more per 1,000 (61 to 227 more per 1,000)	Moderate ^a	Elafibranor likely results in a clinically important increase in the proportion of patients with a normalized ALP level at week 52 when compared with placebo.
Change from baseline in ALP Follow-up: 52 weeks	161 (1 RCT)	NA	−5.3 U/L (−30.4 to 19.7)	−117.0 U/L (−134.4 to −99.6)	−111.7 U/L (−142.0 to −81.3)	Moderate ^a	Elafibranor likely results in a clinically important greater reduction in ALP level from baseline to week 52 when compared with placebo.
Symptoms							
PBC WI-NRS for symptom of pruritus (pruritus ITT analysis set; scores range from 0 to 10, higher scores indicate more severe itch)							

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Elafibranor	Difference		
LS mean change from baseline at week 52, points Follow-up: 52 weeks	66 (1 RCT)	NA	-1.15 (-2.14 to -0.15)	-1.93 (-2.60 to -1.26)	-0.78 (-1.99 to 0.42)	Low ^b	Elafibranor may result in little to no clinically important difference in pruritus when compared with placebo at week 52.
LS mean change from baseline at week 24, points Follow-up: 24 weeks	66 (1 RCT)	NA	-1.26 (-2.20 to -0.31)	-1.60 (-2.25 to -0.95)	-0.34 (-1.49 to 0.80)	Low ^b	Elafibranor may result in little to no clinically important difference in pruritus at week 52 when compared with placebo.
PROMIS Fatigue Short Form 7a T-score for symptom of fatigue (ITT analysis set; higher scores indicate increased fatigue)							
LS mean change from baseline at week 52, points Follow-up: 52 weeks	161 (1 RCT)	NA				Low ^c	Elafibranor may result in  a clinically important difference in fatigue at week 52 when compared with placebo.
Lipid profile (ITT analysis set)							
LS mean change from baseline in LDL-C at week 52 Follow-up: 52 weeks	161 (1 RCT)	NA	-0.24 mmol/L (-0.45 to -0.04)	-0.41 mmol/L (-0.56 to -0.27)	-0.17 mmol/L (-0.42 to 0.08)	Low ^d	Elafibranor may result in little to no difference at week 52 in the level of LDL when compared with placebo. The clinical importance of the change is uncertain.
Harms (safety analysis set)							
Proportion of patients with any SAEs Follow-up: 52 weeks	161 (1 RCT)	NR	132 per 1,000	102 per 1,000 (NR)	30 less per 1,000 (155 less to 67 more per 1,000)	Low ^e	Elafibranor may result in fewer SAEs at week 52 when

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Elafibranor	Difference		
							compared with placebo.
Proportion of patients with AEOSIs ^f Follow-up: 52 weeks	161 (1 RCT)	NR	264 per 1,000	296 per 1,000 (NR)	32 more per 1,000 (121 less to 168 more per 1,000)	Low ^g	Elafibranor may result in more AEOSIs at week 52 when compared with placebo.

AEOSI = adverse event of special interest; ALP = alkaline phosphatase; CI = confidence interval; ITT = intention-to-treat; LDL = low-density lipoprotein; LS = least square; NA = not applicable; NR = not reported; PBC = primary biliary cholangitis; RCT = randomized controlled trial; SAE = serious adverse event; ULN = upper limit of normal; WI-NRS = Worst Itch Numeric Rating Scale.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

^aRated down 1 level for serious imprecision. There was no known threshold for a clinically important effect for the rate of ALP normalization, but it was considered that the effect estimate and entire confidence interval were consistent with an important benefit. The sample size and/or number of events contributing to the analysis is small, suggesting some concern for potential prognostic imbalance and overestimation of the true effect.

^bRated down 2 levels for very serious imprecision. It was judged that the point estimate and both bounds of the 95% CI suggest little to no important difference based on a threshold of clinical importance of 1.8 to 3.7 points suggested by the sponsor. The sample size is very small, increasing concern for prognostic potential imbalance and increasing the risk that the effect may be unstable.

^cRated down 1 level for serious imprecision. It was judged that the point estimate and both bounds of the 95% CI suggest [REDACTED] important difference, considering a literature-based minimal important difference of 3 points for PROMIS Fatigue Short Form 7a. The sample size is small, which could result in prognostic imbalance and increase the risk that the effect may be unstable.

^dRated down 1 level for serious imprecision. It was judged that the 95% CIs are wide and the lower bound of the 95% CI includes the potential for little to no important difference in harm. A threshold of clinical importance could not be estimated, so the null was used. In addition, certainty of evidence was rated down 1 level due to the risk of bias — approximately 15% of the patients did not have data at week 52, increasing the uncertainty of the study results.

^eRated down 2 levels for very serious imprecision. No threshold of clinical importance could be established; therefore, the null was used. The point estimate suggests benefit, but the 95% CI includes the possibility of little to no difference and harm.

^fAEOSIs identified by the sponsor included the following: CPK elevations of severe intensity of leading to permanent study drug discontinuation; muscle injury symptoms of severe intensity corresponding to muscle pain or myalgia, muscle spasms or tremor, or muscle weakness; transaminases elevations from baseline of severe intensity or leading to permanent study drug discontinuation; autoimmune hepatitis; liver injury events of severe intensity corresponding to hepatic injury, hepatic impairment or hepatic failure; gastrointestinal symptoms of severe intensity corresponding to abdominal pain, constipation, diarrhea, nausea, decreased appetite, vomiting, acute cholecystitis, or acute pancreatitis; fatigue and asthenia of severe intensity; serum creatinine elevations of severe intensity or leading to permanent study drug discontinuation; renal injury events of moderate or severe intensity corresponding to renal injury, renal failure, renal impairment, or renal colic; neurologic abnormalities of moderate to severe intensity corresponding to tremor, ataxia, or fasciculations; Parkinson disease or parkinsonism; peripheral edema of moderate to severe intensity; weight gain of more than 5% from baseline; major adverse cardiovascular events corresponding to nonfatal myocardial infarction or unstable angina, nonfatal stroke, unstable angina, hospitalization for heart failure, or coronary revascularization (bypass or percutaneous coronary intervention); treatment-emergent pregnancy and outcomes of pregnancy.

^gRated down 2 levels for very serious imprecision. No threshold of clinical importance could be established; therefore, the null was used. The point estimate suggests harm, but the 95% CI includes the possibility of little to no difference and benefit.

Source: Clinical Study Report for ELATIVE, and additional information provided by the sponsor.

LTE Studies

Description of Studies

The sponsor identified 1 ongoing, LTE study (ELATIVE OLE), which follows the double-blind phase of the ELATIVE trial to further investigate the long-term efficacy and safety of elafibranor in patients with PBC and inadequate response or intolerance to UDCA. The LTE study is still ongoing, and the results presented in this report are from the June 2024 data cut-off. The number of patients contributing to the analyses declined over time. Of the 108 patients who participated in the double-blind period, 61 (56.5%) contributed data at week 104, and 13 (12.0%) contributed data at week 156. There were fewer patients available for analysis in the pruritus elafibranor set.

Efficacy Results

All available results are for patients who received elafibranor in both the double-blind and LTE studies (and no results were available for the patients who crossed over from placebo to elafibranor). The proportion of patients experiencing a cholestasis response was 55.7% (34 of 61 patients) at week 104 and 84.6% (11 of 13 patients) at week 156 for patients who continued on elafibranor in the LTE study. The proportion of patients with ALP normalization was 13.1% (8 of 61 patients) at week 104 and 38.5% (5 of 13 patients) at week 156. The mean change from baseline in ALP values was -125.9 U/L (SD = 97.7 U/L) at week 104 and -169.2 U/L (SD = 86.3 U/L) at week 156. The mean change from baseline in pruritus score on the WI-NRS was -3.11 (SD = 2.28) at week 104 and -4.43 (SD = 3.29) at week 156. Results for the PROMIS Fatigue Short Form 7a in the LTE period were not reported in the Clinical Study Report. There were no results available for LDL-cholesterol from the LTE period.

Harms Results

Of all the patients who received elafibranor, [REDACTED] of patients reported at least 1 treatment-emergent adverse event among patients who originally received elafibranor and placebo during the double-blind period (inclusive of data up to 104 weeks), respectively. The most common treatment-emergent adverse events among patients who continued on elafibranor were [REDACTED]
[REDACTED]
[REDACTED] were the most commonly reported treatment-emergent adverse events among those who crossed over from placebo to elafibranor. The most common treatment-emergent adverse events reported in the LTE data were consistent with those reported in the double-blind period. Overall, [REDACTED] and [REDACTED] of patients who originally received elafibranor and placebo during the double-blind period, respectively, reported at least 1 serious adverse event, while [REDACTED] and [REDACTED] of patients, respectively, stopped treatment due to treatment-emergent adverse events. In total, 2 (1.9%) patients who received elafibranor died.

Critical Appraisal

The data available for the LTE study appeared to be for patients who received elafibranor at any time during either the double-blind or LTE periods and did not exclude patients who did not enrol specifically in the ELATIVE OLE trial (e.g., discontinued from the ELATIVE trial). There is no relevant comparator group in the LTE phase, which precludes causal conclusions about the relative efficacy and harms of elafibranor at longer

follow-up (beyond the 52-week double-blind period). Longer-term efficacy and safety data of elafibranor are available for up to 156 weeks; however, as this is an ongoing study, there is a larger proportion of missing data for later time points. As a result of the missing data and lack of statistical testing, it is not possible to make valid comparisons across time points. The open-label design increases the potential for bias for subjective outcomes, such as the pruritus measures and reporting of adverse events. The impact of concomitant treatments cannot be established as these were not reported. Because completion of the ELATIVE trial was required for enrolment, patients who discontinued the pivotal study were excluded, resulting in a patient population that may be more responsive and more tolerant to the study treatment, thereby introducing selection bias.

Indirect Comparisons

Description of Studies

One NMA was submitted by the sponsor to compare the treatment benefits and harms of elafibranor (as second-line therapy) with other active therapies for the treatment of PBC. A feasibility assessment was conducted to determine the feasibility of conducting indirect comparisons in the study population for the outcome of interest and to assess the heterogeneities across the included studies. The comparative efficacy of elafibranor versus obeticholic acid on cholestasis response, ALP normalization, improvement in pruritus, and harms was evaluated based on evidence from 2 RCTs: ELATIVE and POISE.

Efficacy Results

For this submission, obeticholic acid was identified as the most relevant comparator for elafibranor in the study population. Comparative evidence of elafibranor versus obeticholic acid was only available through a sponsor-submitted indirect treatment comparison. Based on the results of NMA, the indirect evidence [REDACTED] elafibranor differs from obeticholic acid in terms of biochemical cholestasis response, ALP normalization, and improvement in pruritus (although the mean between-group difference in the PBC-40 itch score from baseline to week 52 did not include the null) in patients with PBC and with inadequate response or intolerance to first-line UDCA therapy.

Harms Results

The indirect evidence [REDACTED] elafibranor differs from obeticholic acid in terms of the risk of treatment discontinuation due to pruritus within 12 months of treatment. For the outcome of “odds of occurrence of pruritus as an adverse event of any severity within 12 months,” the 95% credible interval of the OR for the comparison of elafibranor versus obeticholic acid 10 mg did not include the null and favoured elafibranor.

Critical Appraisal

In this sponsor-submitted indirect treatment comparison, it was not clear if study selection, data extraction, or risk of bias assessment in the included studies were conducted by 2 reviewers independently.

Two RCTs were included in the NMA. They were similar in study design, lengths of follow-up, definitions of outcome measures (e.g., cholestasis response, ALP normalization, and symptom control), patients' age, proportion of female participants, ALP levels at baseline, prior UDCA therapy, and liver stiffness

measurements at baseline. Heterogeneities identified in the analysis populations included total bilirubin levels at baseline (ELATIVE: 9.4 to 9.7 $\mu\text{mol/L}$; POISE: 10.3 to 11.8 $\mu\text{mol/L}$), and proportion of patients who reported pruritus at baseline (ELATIVE: 41 to 42% reported moderate to severe pruritus; POISE: 53 to 64% reported pruritus). There is also temporal discordance in data collection period between studies: in the POISE trial, patients were recruited between 2012 and 2013, while in the ELATIVE trial, patients were recruited and assigned to treatment groups between 2020 and 2022. The changes in treatment patterns and supportive care over time are potential sources of heterogeneity between studies and would undermine the validity of the NMA, which relies on the transitivity assumption being upheld.

In this NMA, the following patient characteristics at baseline were identified as potential effect modifiers or prognostic factors according to the clinicians consulted by the sponsor: age, cirrhosis, ALP levels at baseline, antinuclear antibody–positive status, and total bilirubin levels. It was unclear how these effect modifiers were identified. Antinuclear antibody status was not reported in either study. The clinical experts consulted for this CDA-AMC review suggested that male patients, patients with more severe pruritus, and the Indigenous patient population need to be included as well because these patients may have suboptimal responses to the treatment and poorer prognoses.

The level of uncertainty in evidence increased due to the limited number of included trials in the NMA and a lack of closed loops in the networks, such that the consistency assumption could not be tested. Confidence in the estimates for relative efficacy of elafibranor versus obeticholic acid was limited due to imprecision indicated by the wide credible intervals for some of the efficacy outcomes and [REDACTED] treatment may be favoured. Results of sensitivity analyses using LS means from the ELATIVE trial for pruritus efficacy outcomes were consistent with those of the base case analyses supporting the robustness of the analyses.

In this indirect treatment comparison, some efficacy end points of interest to patients and clinicians, such as liver fibrosis or disease progression measurements, were not investigated. Therefore, the relative treatment effect of elafibranor versus obeticholic acid on these important patient outcomes remains unknown. Furthermore, obeticholic acid was the only comparator for elafibranor in this NMA; thus, it is not possible to explore the comparative efficacy and safety of this drug versus other treatments available in the second-line setting, such as fibrates.

Studies Addressing Gaps in the Evidence From the Systematic Review

There were no studies that met the criteria for addressing gaps in the systematic review evidence.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target populations	Adults with an inadequate response to UDCA, or adults unable to tolerate UDCA
Treatment	Elafibranor with or without UDCA
Dose regimen	80 mg daily
Submitted price	\$208.68 per tablet
Submitted treatment cost	\$19,055 per 3-month cycle
Comparators	• UDCA • OCA
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (43 years)
Key data sources	The ELATIVE trial was used to inform the efficacy and safety data for elafibranor and UDCA, while a network meta-analysis was used to inform the relative efficacy of elafibranor and OCA.
Submitted results	• The sequential ICER for elafibranor vs. OCA was \$185,646 per QALY gained (incremental costs = \$331,657; incremental QALYs = 1.79).
Key limitations	• The estimated relative efficacy of elafibranor compared to OCA for achieving cholestasis and reducing itch was derived from an indirect treatment comparison that was associated with a high degree of uncertainty. Consequently, the comparative effectiveness of elafibranor and OCA is highly uncertain. • The sponsor's estimate of excess mortality for patients in the high-risk PBC biochemistry health state lacks face validity. While clinical experts confirmed that high-risk PBC is associated with an increased risk of subsequent liver disease, they did not agree that the estimated risk of death among those in the high-risk state was realistic. • The sponsor's assumptions about the health utility associated with different levels of PBC risk lacked face validity and were insufficiently supported by evidence. The sponsor pooled data from multiple studies, which is methodologically inappropriate. The sponsor also assumed a linear relationship between risk category and health state utility that was not supported by evidence and that clinical experts did not find to be realistic. Both of these assumptions favoured elafibranor. • The long-term durability of the response and itch severity beyond the trial period remains uncertain. The sponsor's submitted model assumed that the treatment effect would persist over a patient's lifetime, which favoured the cost-effectiveness of elafibranor. The available long-term data from 78 weeks of follow-up were not sufficiently robust to support such an assumption. • The sponsor's approach to probabilistic analysis did not allow for the proper estimation of decision uncertainty. There was a notable discrepancy between the deterministic and probabilistic estimates of the ICER, which appeared to be driven by the properties of a Dirichlet distribution. Additionally, the sponsor used arbitrary values rather than empirical estimates to express parameter uncertainty and artificially constrained the range of probabilistic values with Excel functions.

Component	Description
CDA-AMC reanalysis results	- To address the identified limitations, CDA-AMC made the following revisions to the sponsor's model: applying corrections to the probabilistic analysis, replacing the per-cycle excess mortality rate for the high-risk PBC biomarker health state, and assuming identical health utility values for the moderate- and mild-risk PBC health states. - In the CDA-AMC base case: - Compared with OCA, elafibranor was associated with an ICER of \$247,220 per QALY gained (incremental costs = \$331,637; incremental QALYs = 1.34). Due to the limitations in the ITC and other methodological limitations in the economic evaluation, the ICER is highly uncertain, and there was insufficient evidence to support a price premium for elafibranor over OCA. - Compared to UDCA, the ICER of elafibranor was \$131,680 per QALY gained (incremental costs = \$543,908, incremental QALYs = 4.13). A price reduction of at least 61% would be needed for elafibranor to be cost-effective at a WTP threshold of \$50,000 per QALY gained.

CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life-year; OCA = obeticholic acid; PBC = primary biliary cholangitis; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid; vs. = versus.

Budget Impact

CDA-AMC identified several limitations with the sponsor's analysis:

- The sponsor's submitted budget impact analysis model was unnecessarily complex and difficult to validate.
- The prevalence of PBC may have been underestimated, and the incidence was not explicitly modelled.
- The modelled mortality risks were uncertain.
- The treatment cost of elafibranor and obeticholic acid included the cost of treatment for "off treatment" patients. Given that market shares represent the patients "on treatment," the respective treatment costs should not reflect costs incurred by patients "off treatment."
- The sponsor's approach to restrict the total population to those aged 25 years and older was inappropriate. The coverage rate was underestimated.
- The use of compliance rate to adjust actual drug costs underestimated treatment costs.
- The market share of obeticholic acid lacked face validity and was overestimated.
- The market uptake of elafibranor was uncertain and may have been underestimated.

Due to the overly complex structure of the sponsor's model, CDA-AMC was unable to make appropriate corrections for the submitted model to meet face validity. CDA-AMC undertook reanalyses to address some of the limitations of the sponsor's submitted base case. These reanalyses included increasing the proportion of the population who were adults eligible for coverage, assuming 100% compliance, excluding treatment costs incurred by patients who were "off treatment" and adjusting market share assumptions to reflect clinical expert feedback.

Based on the CDA-AMC base case, the 3-year budget impact is expected to be \$326,565,458 (Year 1: \$98,689,468; Year 2: \$110,731,840; Year 3: \$117,144,150) should the public drug plans reimburse elafibranor for the treatment of PBC in adults with an inadequate response to UDCA, or as monotherapy in

adults unable to tolerate UDCA. This estimate is subject to uncertainty due to the methodological limitations of the sponsor's submitted budget impact analysis model.

The estimated budget impact is sensitive to changes in the market share assumptions for elafibranor and obeticholic acid.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunskey, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: April 24, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None



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