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CADTH Reimbursement Recommendation

Odevixibat (Bylvay)

Indication: The treatment of pruritus in patients aged 6 months or older with progressive familial intrahepatic cholestasis
Sponsor: Medison Pharma Canada Inc.
Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Bylvay?

CADTH recommends that Bylvay should be reimbursed by public drug plans for pruritus (itching) in patients aged 6 months or older with progressive familial intrahepatic cholestasis (PFIC) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Bylvay should only be covered to treat patients aged 6 months or older who have been diagnosed with PFIC type 1 (PFIC1) or PFIC type 2 (PFIC2), have severe itching, and have elevated serum bile acids. The first time Bylvay is prescribed, it should be for a trial period of 3 months to ensure that it improves the patient's itching before it is renewed.

What Are the Conditions for Reimbursement?

Bylvay should only be reimbursed if it is prescribed by specialists in managing PFIC, if patients experience an improvement in their itching after using Bylvay for 3 months, and if the cost of Bylvay is reduced. Bylvay should be stopped if the patient receives a liver transplant.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Bylvay improved itching compared to placebo in patients with PFIC1 and PFIC2.
- PFIC is a rare disease accompanied by severe pruritis. Patients identified a need for effective treatments for PFIC that reduce pruritis, delay the course of the disease, avoid or delay the need for surgery or liver transplant, and improve health-related quality of life. Bylvay can reduce patients' pruritis and may affect their quality of life, although the evidence is uncertain.
- Based on CADTH's assessment of the health economic evidence, Bylvay does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Bylvay is estimated to cost the public drug plans approximately $60 million over the next 3 years. However, the actual budget impact is uncertain.

Additional Information

What Is PFIC?

PFIC is a spectrum of rare inherited liver diseases that disrupt the normal flow of bile acids. Patients experience severe itching and a build up of bile

Summary

acids in the body, which damages the liver. PFIC is estimated to affect between 1 in every 50,000 to 100,000 children born worldwide.

Unmet Needs in PFIC

PFIC causes severe itching that can disrupt patients' activities and negatively affect their health-related quality of life. Before Bylvay, there have been no drugs approved to treat itching in PFIC. Patients often are treated with surgery, such as biliary diversion or a liver transplant, which are both associated with risks.

How Much Does PFIC Cost?

The annual per patient cost of treatment with Bylvay is expected to be between $64,256 and $2,313,233 based on weight and dosage received.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that odevixibat be reimbursed for the treatment of pruritus in patients aged 6 months or older with progressive familial intrahepatic cholestasis (PFIC) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

CDEC recognized the rarity of PFIC and the unmet need of patients with this disease who experience severe pruritis. Results from 1 phase III, double-blind, randomized, placebo-controlled trial (PEDFIC 1; N = 62) demonstrated that, compared to placebo, treatment with odevixibat (40 mcg/kg per day and 120 mcg/kg per day) improves pruritus based on the PRUCISION observer-reported (ObsRO) instrument for patients with PFIC type 1 (PFIC1) and PFIC type 2 (PFIC2). The proportion of patients with a pruritus response based on the ObsRO instrument at week 24 was a primary efficacy end point in the regulatory submission to the US FDA. Compared with placebo (n = 20), the least squares mean difference in the proportion of patients who experienced a response in pruritis with odevixibat at 24 weeks was 28.23% (95% confidence interval [CI], 9.83% to 46.64%) for the 40 mcg/kg per day dose (n = 23) and 21.71% (95% CI, 1.87% to 41.54%) for the 120 mcg/kg per day dose (n = 19).

Patients identified a need for effective treatments for PFIC that reduce pruritis, delay the course of the disease, avoid or delay the need for surgery or liver transplant, and improve health-related quality of life (HRQoL). CDEC concluded that odevixibat may provide an effective treatment for pruritis. Pruritis may affect sleep, eating, growth, and patients' and caregivers' quality of life, although the evidence is uncertain about the effects of odevixibat on these outcomes due to imprecision in results of the PEDFIC 1 trial.

Using the sponsor-submitted price for odevixibat and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for odevixibat plus standard of care was $3,462,139 per quality-adjusted life-year (QALY) gained compared with standard of care alone. At this ICER, odevixibat is not cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY for the treatment of pruritus in patients aged 6 months or older with PFIC. A price reduction is required for odevixibat to be considered cost-effective at a WTP threshold of $50,000 per QALY.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients older than 6 months who meet all of the following criteria: 1.1. diagnosis of PFIC1 or PFIC2 1.2. severe pruritis with an ObsRO scratching score of	The PEDFIC 1 trial demonstrated that odevixibat had a clinical benefit in patients with PFIC1 and PFIC2 subtypes who had elevated sBA measured at ≥ 100 µmol/L, a history of significant pruritis, and an average ObsRO scratching score of ≥ 2 (on a scale of 0 to 4) over a 2-week period	Genetic testing should be conducted to confirm patients' PFIC subtype. Clinical experts consulted by CADTH have reported that usual care for PFIC could consist of other therapies used off-label for symptomatic relief of pruritis,

Reimbursement condition	Reason	Implementation guidance
≥ 2, while receiving usual care with at least 1 therapy used for symptomatic relief of pruritis 1.3. sBA levels ≥ 100 µmol/L.	before receiving study treatment. The majority of study participants had baseline use of UDCA and/or rifampicin.	which may include UDCA, rifampicin, or cholestyramine. In the PEDFIC 1 trial, treatment with UDCA, rifampicin, and/or antihistamines was allowed. Medications with effects on bile acids concentration in the GI tract (e.g., cholestyramine, colesevelam, colestipol) were not allowed in the PEDFIC 1 trial. The PRUCISION ObsRO is to be completed by the patient's caregiver twice daily via eDiary, which includes 5-point pictorial responses to assess pruritus. On this scale, a score of 2 corresponds to medium scratching, 3 corresponds to a lot of scratching, and 4 corresponds to worst possible scratching.
2. The maximum duration of initial authorization is 3 months of treatment with a dose of 40 mcg/kg per day.	The recommended daily dose is 40 mcg/kg which may be increased after 3 months of treatment if clinical response is not achieved.	—
Renewal		
3. For renewal after initial authorization, the physician must document response in pruritis, defined as an ObsRO scratching score of ≤ 1 or at least a 1-point decrease from baseline. Odevixibat should be renewed at the 40 mcg/kg per day dose only if patients experience a documented response in pruritis after 3 months of treatment. If no response is observed after 3 months following the initial authorization, renewal of odevixibat should be for a 3-month trial of up to 120 mcg/kg per day dose (maximum of 7,200 mcg per day) and meet the criteria outlined previously in the ObsRO scratching score for ongoing renewal at the lowest effective dose which achieves a response.	Clinical experts reported that pruritis is the most important outcome for assessing response. The recommended daily dose is 40 mcg/kg. However, improvement in pruritus may occur gradually in some patients after initiating therapy. If an adequate clinical response has not been achieved after 3 months of continuous therapy, the dose may be increased. In the PEDFIC 1 trial, the PRUCISION ObsRO instrument was used to measure pruritis response. A positive pruritus assessment was defined as a ObsRO scratching score of 1 or less, or at least a 1-point decrease from baseline.	A 1-point decrease from baseline to week 24 in the PRUCISION ObsRO instrument's scratching score was determined to be a clinically meaningful improvement in pruritus by the investigators of the PEDFIC 1 trial.
4. Subsequent renewals should be assessed every 6 months based on continued maintenance of pruritis response.	Semiannual assessments will help ensure the treatment is used for those benefiting from the therapy.	—

Reimbursement condition	Reason	Implementation guidance
Discontinuation		
5. Odevixibat should be discontinued upon liver transplant.	The PEDFIC 1 trial excluded patients with a prior liver transplant or a liver transplant that was planned within 6 months; therefore, the efficacy of odevixibat in this group of patients is unknown. Based on clinical expert opinion, patients who receive a liver transplant should be discontinued from treatment with odevixibat.	—
Prescribing		
6. Odevixibat must be prescribed by an expert in managing PFIC.	This is to ensure odevixibat is prescribed for the most appropriate patients and that adverse effects are managed appropriately.	—
Pricing		
7. A reduction in price.	The ICER for odevixibat plus standard of care is $3,462,139 when compared with standard of care alone. A price reduction of 98.6% would be required for odevixibat plus standard of care to achieve an ICER of $50,000 per QALY gained compared to standard of care alone. This is based on the CADTH base case, which allows for dose titration to 120 mcg/kg per day. In the CADTH scenario analysis in which dose escalation was removed, a price reduction of 97.9% would be required.	Dose escalation of odevixibat from 40 mcg/kg per day to 120 mcg/kg per day results in a 3-fold increase in drug costs. CDEC noted a lack of a dose-response relationship to justify these increased costs and suggested that the drug costs of odevixibat incurred by the health care system for a single patient should be equal to the costs of a 40 mcg/kg per day dose, regardless of dose escalation.
Feasibility of adoption		
8. The feasibility of adoption of must be addressed.	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 CADTH's estimate(s).	—

CDEC = Canadian Drug Expert Committee; GI = gastrointestinal; ICER = incremental cost-effectiveness ratio; ObsRO = observer-reported outcome; PFIC = progressive familial intrahepatic cholestasis; PFIC1 = progressive familial intrahepatic cholestasis type 1; PFIC2 = progressive familial intrahepatic cholestasis type 2; QALY = quality-adjusted life-year; sBA = serum bile acid; UDCA = ursodeoxycholic acid.

Discussion Points

- **Unmet needs:** Due to the uncertainty associated with the submitted evidence, CDEC deliberated on odevixibat considering the criteria for significant unmet needs described in section 9.3.1 of the *Procedures for CADTH Reimbursement Reviews*. CDEC noted that PFIC is a rare and severe disease associated with morbidity and mortality. Furthermore, families and clinical experts agreed that the current treatment options for severe pruritis associated with PFIC are limited. Considering the rarity

of PFIC and unmet need of this patient population, CDEC concluded that odevixibat has the potential to reduce morbidity associated with PFIC, although the available evidence is associated with uncertainty.

- **PFIC subtypes**: CDEC noted that the PEDFIC 1 trial enrolled patients with PFIC1 and PFIC2, and that a limited number of patients with other subtypes of PFIC were included in the extension phase of the PEDFIC 1 trial and in the PEDFIC 2 trial. Given that the approved indication does not restrict the use of odevixibat to any PFIC subtype, CDEC discussed the generalizability of the evidence in other PFIC subtypes. CDEC indicated that evidence-based practice would limit prescribing of odevixibat to only PFIC subtypes 1 and 2.
- **Serum bile acid (sBA) levels**: CDEC noted that the PEDFIC 1 trial was designed with 2 different primary end points (sBA level and pruritis) to meet regulatory requirements in multiple jurisdictions. The proportion of patients who experienced an sBA response was the primary outcome of the PEDFIC 1 trial for jurisdictions outside of the US, and the only outcome controlled for multiplicity. The PEDFIC 1 trial met this end point, as the adjusted difference in proportions of patients experiencing at least a 70% reduction in sBA levels from baseline to end of treatment or reaching a level of 70 µmol/L or less after 24 weeks between odevixibat 40 mcg/kg per day and placebo was 44.1% (95% CI, 23.6% to 64.6%; P = 0.0015) and between odevixibat 120 mcg/kg per day and placebo was 21.6% (95% CI, −0.5% to 43.8%; P = 0.0174). However, CDEC noted that pruritus and disease progression (i.e., need for surgical biliary diversion [SBD] or liver transplant, mortality) are more important outcomes to patients and clinicians. CDEC discussed that the relationship between sBA levels, disease progression, and pruritus has not been established.
- **Extension study:** CDEC considered evidence from PEDFIC 2, an ongoing phase III, nonrandomized, open-label extension study to investigate the long-term efficacy and safety of a 120 mcg/kg daily dose of odevixibat in patients with PFIC. However, the PEDFIC 2 study was limited by its open-label and noncomparative design. Some patients who received odevixibat at a dosage of 40 mcg/kg per day in the PEDFIC 1 trial received odevixibat at a dosage of 120 mcg/kg per day in the PEDFIC 2 trial. The sponsor reported that the percentage of patients who had a positive pruritis response increased in those who transitioned from 40 mcg/kg per day to 120 mcg/kg per day from PEDFIC 1 to PEDFIC 2 ([redacted]), suggesting that improvement in symptoms due to odevixibat may be delayed in some patients.
- **Dose escalation:** CDEC noted that patients enrolled in the PEDFIC 1 trial were assigned to receive odevixibat at a daily dose of either 40 mcg/kg or 120 mcg/kg, and patients who received odevixibat 40 mcg/kg did not have their dose escalated to 120 mcg/kg during this trial. CDEC also discussed the lack of a dose-dependent treatment response for patients because response for many end points was not greater for patients who received 120 mcg/kg per day of odevixibat compared to those who received 40 mcg/kg per day. In the CADTH pharmacoeconomic base case, patients were assumed to have their dose escalated to 120 mcg/kg per day if they had not responded after 12 weeks. Given the lack of evidence to support dose titration of odevixibat to 120 mcg/kg per day, CDEC discussed the

CADTH scenario analysis in which dose escalation was removed. In this scenario, a price reduction of 97.9% would be required for odevixibat to achieve an ICER of $50,000 per QALY gained compared to standard of care alone. Given the incongruent dose response in patients assigned to 40 mcg/kg per day compared to 120 mcg/kg per day in the PEDFIC 1 trial, and the limitations noted in the extension study, evidence to justify a higher cost to the health care system for daily doses higher than 40 mcg/kg is lacking.

- **Comparative evidence:** There was no direct evidence comparing odevixibat to other drugs used for treating PFIC, although such drugs are not indicated for the disease and are used off-label. As such, CDEC considered evidence from a matched cohort study (OvEC) comparing clinical outcomes in patients treated with odevixibat from the PEDFIC 1 and PEDFIC 2 trials to an external control cohort of children who had not undergone SBD from a retrospective natural history study (NAPPED) submitted by the sponsor to address this gap. Although the results suggested odevixibat may confer a benefit in event-free survival, native liver survival, SBD-free survival, and overall survival, CDEC noted the results were uncertain due to methodological limitations. The inverse probability of treatment weighting (IPTW) method was used to minimize the impact of confounding on the results. However, this method does not control for the different study designs for the 2 cohorts, insufficient description of data collection methods and patient characteristics, derivation of baseline covariates and likelihood of residual confounding, and handling of missing data. These methodological limitations reduce certainty in the results and precluded CDEC from drawing conclusions from this study.
- **Ethics and equity:** CDEC discussed ethical and equity considerations related to odevixibat, including the significant physical, psychosocial, and financial burdens of living with and caring for someone with PFIC, especially due to cholestatic pruritus. Surgical treatment options, such as a liver transplant, are invasive and life-altering. The committee also discussed how pediatric patients with PFIC may be considered particularly vulnerable because they are living with a severe and rare disease and depend on their parents or caregivers to facilitate access to their diagnosis and support for their condition and care transitions. The committee discussed how to weigh the relatively uncertain evidence of long-term safety and efficacy of odevixibat against the harm of not recommending odevixibat for reimbursement in the context of very limited treatment options for PFIC. CDEC also noted that health equity is an important consideration when assessing this uncertainty because PFIC is a rare and severe disease and odevixibat satisfies some important unmet needs for a vulnerable population with limited treatment options.

Background

PFIC is a rare, life-shortening, heterogeneous group of liver disorders of autosomal recessive inheritance that affects the production and/or composition of bile from the liver. PFIC is characterized by an early onset of cholestasis (usually during infancy) with severe pruritus and fat malabsorption which rapidly progresses and leads to liver failure. Elevated bile acid concentrations result in ongoing liver inflammation, fibrosis, cirrhosis, and eventually liver failure. Intractable pruritus is the most troubling symptom of PFIC. PFIC is categorized

into subtypes based on genetic defect, clinical presentation, laboratory findings, and liver histology. At least 6 subtypes of PFIC have been described in the literature. PFIC1 and PFIC2 represent approximately two-thirds of cases; PFIC3 represents a large portion of the remainder. PFIC is estimated to affect between 1 in every 50,000 to 100,000 children born worldwide. Although global or country-specific prevalence estimates are not available for PFIC, it is believed to be responsible for approximately 10% to 15% of cholestatic liver diseases in children and 10% to 15% of liver transplant indications in children. PFIC is a fatal disease. Survival in patients with PFIC who do not undergo SBD or liver transplant is 50% at age 10 and almost none at age 20.

The clinical experts consulted by CADTH for this review stated that although there are numerous anti-itch medications, including antihistamines and other drugs such as rifampicin that indirectly address itch, they may be effective for mild to moderate pruritus but are not effective therapies for severe pruritus. One clinical expert noted that accumulation of bile acids damages the liver; however, it is not clear whether a medication such as ursodeoxycholic acid (UDCA) is able to address this key aspect of the pathophysiology of PFIC. Surgery is also a key nonpharmacological approach, although it is not always successful, carries a high risk of morbidity, and is not suitable for a subset of patients who have cirrhosis.

Odevixibat has been approved by Health Canada for the treatment of pruritus in patients aged 6 months or older with PFIC. Odevixibat is an ileal bile acid transporter inhibitor. It is available as 200 mcg, 400 mcg, 600 mcg, and 1,200 mcg capsules. The dosage recommended in the product monograph is 40 mcg/kg administered orally once daily in the morning. If an adequate clinical response has not been achieved after 3 months of continuous therapy, the daily dose may be increased to 120 mcg/kg, with a maximum daily dose of 7,200 mcg.

Sources of Information Used by the Committee

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

- a review of a phase III, double-blind, randomized, placebo-controlled trial in children with PFIC1 and PFIC2; a nonrandomized, open-label extension study; and a matched cohort study
- patients' perspectives gathered by 1 patient group, the Canadian Liver Foundation (CLF)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- a panel of 4 clinical specialists with expertise diagnosing and treating patients with PFIC
- input from 1 clinician group, the Canadian Pediatric Hepatology Research Group (CPHRG)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to odevixibat from published literature.

Stakeholder Perspectives

Patient Input

Input was received from the CLF. They surveyed patients and caregivers living with PFIC and received 14 responses (4 of which were from Canada).

Families expressed feelings of helplessness, anguish, and frustration, noting that a diagnosis of PFIC has severely impacted the lives of their loved ones and also their own daily activities. Respondents highlighted the significant impact that constant itch has on their daily lives and how disrupted sleep leaves them and their loved ones chronically fatigued.

Respondents highlighted the importance of improving their quality of life as well as improving itch and sleep, achieving normal growth, maintaining energy, and slowing progression of their disease. The CLF emphasized the need to ensure equitable access to therapies for PFIC across the country.

Clinician Input

Input From Clinical Experts Consulted by CADTH

According to the clinical experts consulted by CADTH for this review, there is a major unmet need in PFIC for a drug that can address the underlying pathophysiology of the disease, effectively control pruritus (particularly severe pruritus), and potentially slow progression of the disease.

The clinical experts did not identify a specific subtype of PFIC that is more likely to benefit from odevixibat; however, they did highlight the fact that evidence from randomized controlled trials is only available for the PFIC1 and PFIC2 subtypes. The clinical experts indicated that the severity of pruritus should be the main determinant of when to initiate therapy, with signs such as excoriation and significant lack of sleep as key indicators of severe itch. The clinical experts noted that the key indicator of treatment response is a reduction in itch, and this should be accompanied by improvement in sleep, feeding, and, in older children, school performance, sports activities, and mood and energy levels. The clinical experts stressed that although sBA can also be used to assess response, it does not always correlate well with itch, and the assay is not widely available. According to the clinical experts, the main reason to discontinue odevixibat would be when a patient undergoes a liver transplant. Additional considerations would be tolerability or safety issues.

Clinician Group Input

The CPHRG, which functions under the aegis of the Canadian Association for the Study of the Liver provided input for this review.

The CPHRG agreed with the clinical experts consulted by CADTH that current pharmacological treatments have limited efficacy and do not address the underlying disease process, and surgical options carry a high risk of morbidity and mortality. They also agreed that a response to odevixibat would be indicated by improvement in pruritus and in sleep, and indications for discontinuation would include continued progression of disease (i.e., liver transplant) and drug intolerance.

The CPHRG did not state whether they had experience with odevixibat.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
PEDFIC 1 had a baseline requirement for elevated sBA levels. Would this be considered a clinical criterion when considering treatment initiation?	The clinical panel indicated that elevated sBA levels would not be a critical criterion for initiating treatment with odevixibat. The clinical panel emphasized that cholestatic pruritus is more important to consider. Furthermore, the panel noted that there may be challenges in accessing tests for sBA, and sBA levels do not always correlate with pruritus. CDEC noted that patients enrolled in the PEDFIC 1 trial were required to have elevated sBA levels, and thus this requirement is included in the recommended reimbursement criteria for initiation in Table 1.
PEDFIC 1 included patients aged from 6 months to 18 years. Would there be an upper limit to the age at which to initiate therapy (not included in indication)? What other criteria would be considered for initiation of therapy?	The clinical panel agreed that there should not be an upper age limit at which to initiate therapy. However, the panel reported that few patients with PFIC1 and PFIC2 with cholestatic pruritus requiring treatment with odevixibat would be older than 18 years at the time of treatment initiation. The clinical panel highlighted the need for patients to have continued access to treatment with odevixibat as they become older (i.e., from adolescent to adult) if they continue to benefit from the treatment. CDEC agreed with the clinical panel.
In the PEDFIC 1 study, most patients were on other therapies, such as UDCA and rifampicin (off-label for symptomatic relief). Would the clinical experts suggest that the criteria include a trial of other therapies before starting odevixibat?	The clinical panel indicated that it should not be required to try other therapies before starting odevixibat. The clinical experts noted that the therapies currently used off-label to treat cholestatic pruritus associated with PFIC have limitations to their efficacy (e.g., only provide symptomatic relief to patients with mild to moderate itch). In contrast to these therapies, the panel noted that odevixibat directly and mechanistically addresses the pruritus in PFIC. The clinical panel also noted that because odevixibat is the only treatment for severe itch and it can reverse some of the disease pathology within the liver, it would not be appropriate to require patients to try other treatments before initiating odevixibat.
Considerations for discontinuation of therapy	
What level of response would be considered clinically meaningful with respect to sBA and pruritus? What other assessments would be relevant to drug coverage?	The clinical panel noted that improvement in pruritus would be the outcome of most importance for assessing response. The panel noted that improvement in the condition of the skin and general well-being would also be important. In older children, additional variables of interest would include school performance, ability to participate in sports activities, and improvements in mood and energy levels. The clinical experts indicated that features of a clinically meaningful response to treatment would include decreasing pruritus to nonproblematic levels (i.e., able to sleep, able to focus on play and school, greater socialization), improved condition of skin, and good nutrition. The clinical experts noted that stabilization of

Implementation issues	Response
	symptoms would also be an acceptable outcome. The clinical experts agreed that routine monitoring of sBA is of less importance for assessing response. CDEC agreed with the clinical experts that pruritis is the most important outcome for assessing treatment response. Furthermore, CDEC noted that sBA response does not always correspond with a response in pruritis.
Considerations for prescribing of therapy	
What is the optimal starting dose and how would the dose be titrated?	The clinical panel noted that, as per the product monograph, the recommended dosage of odevixibat is 40 mcg/kg per day. The product monograph also states that if an adequate clinical response (improvement in pruritus and reduction of sBA levels) has not been achieved after 3 months of continuous therapy, the dosage may be increased to 120 mcg/kg per day, with a maximum daily dose of 7,200 mcg. The clinical panel indicated that they would start the patients at 40 mcg/kg, but they would not triple the dose to 120 mcg/kg at 12 weeks. Instead, they would assess response sooner and prefer to increase the dose in smaller increments if the patient was not deriving benefit at the 40 mcg/kg dose. The clinical panel reported they would first try doubling the dose (e.g., to 80 mcg/kg) or use an incremental approach to titrate the dose, noting that large dose increases can be associated with adverse effects (e.g., diarrhea, abdominal pain).
System and economic issues	
Price per 30-capsule pack is as follows: • $5,277.74 for 200 mcg • $10,555.4800 for 400 mcg • $15,833.22 for 600 mcg • $31,666.44 for 1,200 mcg Assuming 95% of eligible patients with PFIC will be treated with odevixibat by year 3, the model estimated that 69 children and 14 adults would receive odevixibat by year 3 in Canada. The estimated net budget impact of odevixibat over the model time horizon of 3 years is $137.9 million.	This is a comment from the drug plans to inform CDEC deliberations.
Should the potential to require surgical intervention be considered? How comfortable are you with the end point of lowering sBA levels and its potential correlation to increased native liver survival?	The clinical panel agreed with considering the potential to require surgical intervention as part of the cost analysis. The clinical panel noted that preventing bile duct diversion surgery or liver transplantation should be considered. The clinical panel noted that lower sBA levels do not necessarily correlate with itching, but they may correlate with increased native liver survival. CDEC agreed with the clinical panel.
Do you agree with the decision to not include PEBD in the cost comparison?	This question is addressed in the pharmacoeconomic report.

CDEC = Canadian Drug Expert Committee; PEBD = partial external biliary diversion; PFIC = progressive familial intrahepatic cholestasis; sBA = serum bile acid; UDCA = ursodeoxycholic acid.

Clinical Evidence

Systematic Review

Description of Studies

PEDFIC 1 (N = 62) was a phase III, multicentre (1 site in Canada), double-blind, randomized, placebo-controlled study to demonstrate the efficacy and safety of odevixibat 40 mcg/kg per day and 120 mcg/kg per day in children with PFIC1 and PFIC2. The study included up to an 8-week screening period, a 24-week treatment period, and a 4-week follow-up period. The primary outcome of the PEDFIC 1 trial was the proportion of patients who experienced at least a 70% reduction in sBA concentration from baseline to the end of treatment or reached a level of 70 µmol/L or lower after 24 weeks of treatment. This was the primary outcome used for submission to regulatory bodies outside of the US, including Canada, and therefore was considered the primary outcome of interest for the purposes of this report. Secondary outcomes included the proportion of positive pruritus assessments at the patient level over the 24-week treatment period based on the PRUCISION ObsRO instrument (note that this was the primary outcome for submission to the FDA), the change from baseline to week 24 in growth, change from baseline in sleep parameters (awakenings) measured with the PRUCISION PRO and ObsRO instruments by each 4-week interval over the 24-week treatment period, proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level from weeks 0 to 4 and weeks 0 to 12, and number of patients undergoing biliary diversion surgery or liver transplantation.

The median age of the patients in the PEDFIC 1 trial was 3.2 years and ranged from 6 months to 15.9 years. Most patients (47 of 62; 76%) were aged between 6 months and 5 years; 12 (19%) were between 6 and 12 years, and 3 (5%) were between 13 and 18 years; a limited number of patients [redacted] were older than 8 years. Median height-for-age and weight-for-age z scores were −1.70 and −0.95, respectively, indicating the patients were below their age-matched peers for growth. Most (45 patients; 73%) had PFIC2, and 17 (27%) had PFIC1. According to the investigator, almost all patients (n = 60; 97%) had a history of significant pruritus present and most (n = 42; 68%) had sBA levels of greater than 100 µmol/L (40.85 mcg/mL) within 6 months before enrolment in the study. At study entry, 50 patients (81%) were on UDCA and 41 (66%) were on rifampicin. Overall, 8 (13%) patients reported prior biliary tract surgeries (all reports of biliary diversion). Median sBA levels were elevated at baseline at 228.0 µmol/L, 188.5 µmol/L, and 254.5 µmol/L in the odevixibat 40 mcg/kg per day, odevixibat 120 mcg/kg per day, and placebo groups, respectively. Median levels of hepatic biochemical parameters were elevated at baseline, including alanine aminotransferase (ALT) (approximately 2 × upper limit of normal [ULN]), aspartate transferase (AST) (less than 2 × ULN), and total bilirubin (1.8 × ULN). Based on Child-Pugh classification, 41 patients (66%) had mild hepatic impairment and 21 (34%) had moderate hepatic impairment; no patients had severe impairment.

Efficacy Results

Mortality

Mortality was reported as a safety outcome in the PEDFIC 1 trial, and there were no deaths in the study.

Need for Surgery

The need for surgery was a secondary outcome in the PEDFIC 1 trial, and there were no surgeries for liver transplant or biliary diversion in the study.

Health-Related Quality of Life

HRQoL was assessed as an exploratory outcome using the Pediatrics Quality of Life (PEDSQL) instrument, scored on a scale of 0 to 100, with higher scores indicating improved quality of life. After 24 weeks, the least square (LS) mean difference versus placebo for the odevixibat 40 mcg/kg per day group was [redacted] and for the 120 mcg/kg per day group was [redacted].

Pruritus

The sponsor designed their own instrument for assessing pruritus. The assessment of the proportion of positive pruritus responses at 24 weeks was a secondary outcome of the study. After 24 weeks of treatment with odevixibat, the between-group differences in the LS means for the comparisons of the odevixibat 40 mcg/kg per day group to placebo was 28.23% (95% CI, 9.83% to 46.64%), and the odevixibat 120 mcg/kg per day group to placebo was 21.71% (95% CI, 1.87% to 41.54%). Differences versus placebo were also observed for weeks 0 to 12 with a LS mean difference versus placebo for the odevixibat 40 mcg/kg per day group of [redacted] and for the 120 mcg/kg per day group of [redacted]. At weeks 0 to 4, the differences versus placebo were smaller, particularly at the higher dose, with a LS mean difference versus placebo for the odevixibat 40 mcg/kg per day group of [redacted] and for the 120 mcg/kg per day group of [redacted].

Serum Bile Acid Levels

The primary outcome of the PEDFIC 1 trial was the proportion of patients who experienced at least a 70% reduction in fasting sBA levels from baseline to the end of treatment or reached a level of 70 µmol/L or less after 24 weeks. The adjusted difference in proportions between odevixibat 40 mcg/kg per day and placebo was [redacted]. Between-group differences were smaller for the same outcome when assessed at 12 weeks, with an adjusted difference in proportions between odevixibat 40 mcg/kg per day and placebo was [redacted] and between odevixibat 120 mcg/kg per day and placebo was [redacted].

Growth

Improvement in growth (height, weight, body mass index [BMI]) was assessed as a secondary outcome by comparing changes from baseline in z scores relative to a typical pediatric growth chart. For height, the LS mean between-group difference for odevixibat versus placebo after 24 weeks was 0.32 (95% CI, 0.00 to 0.65) for the 40 mcg/kg per day group and 0.15 (95% CI, −0.18 to 0.48) for the 120 mcg/kg per day group. For weight, the LS mean between-group difference was 0.28 (95% CI, −0.01 to 0.57) for the 40 mcg/kg per day group and 0.08 (95% CI, −0.22 to 0.37) for the 120 mcg/kg per day group. For BMI, the LS mean between-group difference was [redacted] for the 40 mcg/kg per day group and [redacted] for the 120 mcg/kg per day group.

Number of Awakenings

The changes over time in sleep parameters, specifically awakenings, was assessed as a secondary outcome using data derived from the PRUCISION pruritus instrument developed by the sponsor. The LS mean between-group difference in number of awakenings from baseline to weeks 21 to 24 was [redacted] in the 40 mcg/kg per day group and [redacted] in the 120 mcg/kg per day group.

Total Bilirubin

The change from baseline to week 24 in total bilirubin was an exploratory outcome. The LS mean between-group difference versus placebo in total bilirubin was [redacted] in the 40 mcg/kg per day group and [redacted] in the 120 mcg/kg per day group.

Harms Results

Adverse Events

Overall, 35 (83%) of the 42 patients who received odevixibat experienced at least 1 treatment-emergent adverse event (TEAE) as did 17 (85%) of 20 patients who received placebo; the overall incidence of TEAEs was similar in the odevixibat 40 mcg/kg per day and 120 mcg/kg per day treatment groups (83% and 84%, respectively). The most commonly reported types of events during the study were gastrointestinal disorders and infections. Overall, the most commonly reported TEAEs (≥ 10% overall) among patients who received odevixibat versus patients who received placebo were diarrhea (31% vs. |||%), pyrexia (29% vs. 25%), upper respiratory tract infection (19% vs. 15%), vomiting (17% vs. 0%), increased ALT (14% vs. 5%), and increased blood bilirubin (12% vs. 10%).

Serious Adverse Events

Treatment-emergent serious adverse events (SAEs) were reported in 3 (7%) of 42 patients who received odevixibat and in 5 (25%) of 20 patients who received placebo. No treatment-emergent SAEs were reported in the 40 mcg/kg per day treatment group. The most commonly reported types of treatment-emergent SAEs were infections, which were reported in 4 (20%) of 20 patients in the placebo group and in 1 (5%) of 19 patients in the 120 mcg/kg per day group. The only event reported in more than 1 patient overall was urinary tract infection, which was reported in 1 patient each in the placebo and 120 mcg/kg per day groups. None of the treatment-emergent SAEs led to discontinuation of treatment.

Withdrawals Due to Adverse Events

Dose interruptions due to TEAEs were reported at a higher incidence in patients who received odevixibat (9 of 42; 21%) compared with patients who received placebo (1 of 20; 5%). The highest incidence was reported among patients who received 120 mcg/kg per day (6 of 19; 32%), whereas 3 (13%) of the 23 patients in the group that received 40 mcg/kg per day had treatment interruptions due to TEAEs. In 7 of the 10 patients with treatment interruptions due to TEAEs, the events were related to elevations in hepatic biochemical test results, and treatment was interrupted as required by the protocol. All 7 cases with study drug interrupted due to hepatic biochemical test results underwent adjudication by the Data Safety Monitoring Board which assessed all events as related to the patient's underlying disease. All these patients completed the PEDFIC

1 trial and rolled over to the PEDFIC 2 trial to receive odevixibat, except 1 patient who discontinued the study due to the inability to attend clinic visits.

One patient who received odevixibat 120 mcg/kg per day discontinued the study drug due to a TEAE of diarrhea.

Critical Appraisal

The PEDFIC 1 trial was double-blinded with steps taken to maintain blinding and allocation concealment during the randomization process. Despite randomization, there were imbalances in several baseline characteristics, suggesting that prognostic balance was not achieved, which was likely the result of the small sample size. Given the small size of the trial, there were a relatively large number of patients who discontinued treatment and who were rolled into the extension study, in which all patients were given the higher dose (120 mcg/kg) of odevixibat. Although steps were taken to account for these missing data points for outcomes such as pruritus and sBA levels, a number of key outcomes, such as PEDSQL, had data missing for more than 20% of the patient population.

With respect to external validity, major issues included that the enrolled population was limited to patients with PFIC1 and PFIC2, whereas the proposed indication does not restrict based on subtype. Additionally, the PEDFIC 1 trial assessed 2 different daily doses of odevixibat, 40 mcg/kg and 120 mcg/kg, which differs from the proposed labelling that recommends all patients begin at 40 mcg/kg per day and then titrate up to 120 mcg/kg per day if there is a lack of response at 12 weeks. The trial was not of sufficient size or duration to adequately assess key clinical outcomes such as mortality or the need for surgical intervention.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for the Grading of Recommendations, Assessment, Development, and Evaluation (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:

- Clinical outcomes:
  - mortality
  - need for surgery (biliary diversion or liver transplant)
  - growth (change from baseline to week 24 in z scores for height, weight, and BMI)
- Patient-reported outcomes:
  - PEDSQL (change from baseline to week 24 in PEDSQL Parent Report and Family Impact Module)
  - pruritus (proportion of positive pruritus assessments at the patient level at week 24, weeks 0 to 4, and weeks 0 to 12)
  - sleep parameters (change from baseline to week 21 to 24 in number of awakenings)
- Lab parameters:
  - sBA (proportion of patients with at least a 70% reduction in fasting sBA after 24 weeks or a sBA of 70 µmol/L or less at week 24 plus the same outcome for week 12)

- liver function (change from baseline to week 24 in total bilirubin)

- Harms:
  - clinically significant diarrhea
  - adjudicated hepatic events

Table 3: Summary of Findings for Odevixibat Versus Placebo for Patients With PFIC1 and PFIC2

Outcome measure	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)		Difference	Certainty	What happens
			Placebo	Odevixibat 40 mcg/kg and 120 mcg/kg			
Mortality							
Deaths (safety end point) Follow-up: 24 weeks	Odevixibat 40 mcg/kg N = 23 Placebo N = 20	NR	0	0	0	Very low[a]	Both doses: The evidence is very uncertain about the effects of odevixibat on survival (mortality) when compared to placebo after 24 weeks follow-up.
	Odevixibat 120 mcg/kg N = 19	—	—	0	0	Very low[a]	
Need for surgery							
Liver transplants or biliary diversion surgery Follow-up: 24 weeks	Odevixibat 40 mcg/kg: N = 23 Placebo: N = 20	NR	0	0	0	Very low[b]	Both doses: The evidence is very uncertain about the effects of odevixibat on the need for surgery (liver transplant or biliary diversion) when compared to placebo after 24 weeks follow-up.
	Odevixibat 120 mcg/kg: N = 19	—	—	0	0	Very low[b]	
Health-related quality of life							
PEDSQL – Family Impact Module, mean (SE) change from baseline (scores are linearly transformed	Odevixibat 40 mcg/kg: N = 19	NA	5.64	40 mcg/kg: [redacted]	40 mcg/kg: [redacted]	Very low[c]	Both doses: The evidence is very uncertain about the effects of odevixibat on

Outcome measure	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)		Difference	Certainty	What happens
			Placebo	Odevixibat 40 mcg/kg and 120 mcg/kg			
to a 0 to100 scale; higher scores = improved HRQoL) Follow-up: 24 weeks	Placebo: N = 17						parent and family HRQoL (PEDSQL family impact module) after 24 weeks follow-up.
	Odevixibat 120 mcg/kg: N = 13	—	—	120 mcg/kg: [redacted]	120 mcg/kg: [redacted]	Very low[c]	
PEDSQL – Parent Report, mean (SE) change from baseline Follow-up: 24 weeks	Odevixibat 40 mcg/kg: N = 13 Placebo: N = 10	NA	0.48	40 mcg/kg: [redacted]	40 mcg/kg: [redacted]	Very low[c]	Both doses: The evidence is very uncertain about the effects of odevixibat on HRQoL, parent report, after 24 weeks follow-up.
	Odevixibat 120 mcg/kg: N = 9	—	—	120 mcg/kg: [redacted]	120 mcg/kg: [redacted]	—	
Pruritus assessments							
Proportion of positive pruritus assessments at the patient level (scratching score of ≤ 1 or at least a 1-point drop from baseline on the PRUCISION ObsRO instrument), mean (SE)[l] Follow-up: 24 weeks	Odevixibat 40 mcg/kg: N = 23 Placebo: N = 20	NR	28.7 per 100	40 mcg/kg: 58.3 per 100 (6.2 per 100)	40 mcg/kg: 28.2 more per 100 (9.8 to 46.6 more per 100)	Moderate[d]	Both doses: Odevixibat likely results in a reduction in pruritus after 24 weeks of follow-up. The clinical importance of the reduction is unclear.
	Odevixibat 120 mcg/kg: N = 19	NR	—	120 mcg/kg: 47.7 per 100 (8.1 per 100)	120 mcg/kg: 21.7 more per 100 (1.9 to 41.5 more per 100)	—	

Outcome measure	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)		Difference	Certainty	What happens
			Placebo	Odevixibat 40 mcg/kg and 120 mcg/kg			
Proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level from weeks 0 to 4, as reported on the PRUCISION ObsRO instrument, mean (SE)[l] Follow-up: 4 weeks	Odevixibat 40 mcg/kg: N = 23 Placebo: N = 20	NR	[redacted]	40 mcg/kg: [redacted]	40 mcg/kg: [redacted]	40 mcg/kg: Moderate[e]	40 mcg/kg: Odevixibat likely results in a reduction in pruritus after 4 weeks of follow-up. The clinical importance of the reduction is unclear.
	Odevixibat 120 mcg/kg: N = 19	NR	—	120 mcg/kg: [redacted]	120 mcg/kg: [redacted]	120 mcg/kg: Low[f]	120 mcg/kg: Odevixibat may result in a reduction in pruritus after 4 weeks of follow-up. The clinical importance of the reduction is unclear.
Proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level from weeks 0 to 12, respectively, as reported on the PRUCISION ObsRO instrument, mean (SE)[l] Follow-up: 12 weeks	Odevixibat 40 mcg/kg: N = 23 Placebo: N = 20	NR	—	40 mcg/kg: [redacted]	40 mcg/kg: [redacted]	40 mcg/kg: Moderate[d]	Both doses: Odevixibat likely results in a reduction in pruritus after 12 weeks of follow-up. The clinical importance of the reduction is unclear.
	Odevixibat 120 mcg/kg: N = 19	—	[redacted]	120 mcg/kg: [redacted]	120 mcg/kg: [redacted]	120 mcg/kg: Moderate[e]	
Serum bile acid							
Proportion of patients experiencing at least a 70% reduction in fasting sBA	Odevixibat 40 mcg/kg: N = 23	NR	0	40 mcg/kg: 43.5 per 100	40 mcg/kg: 44.1 more per 100 (23.6 to	40 mcg/kg: Low[g]	Both doses: Odevixibat may result in a reduction in sBA after 24

Outcome measure	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)		Difference	Certainty	What happens
			Placebo	Odevixibat 40 mcg/kg and 120 mcg/kg			
concentration from baseline to the end of treatment or reaching a level ≤ 70 µmol/L Follow-up: 24 weeks	Placebo: N = 20				64.6 more per 100)		weeks of follow-up. The clinical importance of the reduction is unclear.
	Odevixibat 120 mcg/kg: N = 19	NR	—	120 mcg/kg: 21.1 per 100	120 mcg/kg: 21.6 more per 100 (0.5 fewer to 43.8 more per 100)	120 mcg/kg: Low[h]	
Proportion of patients experiencing at least a 70% reduction in fasting sBA concentration from baseline to the end of treatment or reaching a level ≤ 70 µmol/L[l] Follow-up: 12 weeks	Odevixibat 40 mcg/kg: N = 23 Placebo: N = 20	NR	[redacted]	40 mcg/kg: [redacted]	40 mcg/kg: [redacted]	Low[h]	Both doses: Odevixibat may result in a reduction in sBA after 12 weeks of follow-up. The clinical importance of the reduction is unclear.
	Odevixibat 120 mcg/kg: N = 19	NR	—	120 mcg/kg: [redacted]	120 mcg/kg: [redacted]	—	—
Sleep parameters							
Mean (SE) change from baseline in sleep parameters measured with the PRUCISION PRO and ObsRO instruments by each 4-week interval over the 24-week treatment period – number of awakenings Follow-up: 24 weeks	Odevixibat 40 mcg/kg: N = 19 Placebo: N = 14	NA	[redacted]	40 mcg/kg: [redacted]	40 mcg/kg: [redacted]	Very low[c]	Both doses: The evidence is very uncertain about the effects of odevixibat on awakenings after 24 weeks of follow-up.
	Odevixibat 120 mcg/kg: N = 16	—	—	120 mcg/kg: [redacted]	120 mcg/kg: [redacted]	Very low[c]	

Outcome measure	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)		Difference	Certainty	What happens
			Placebo	Odevixibat 40 mcg/kg and 120 mcg/kg			
Growth parameters							
Mean (SE) change from baseline in growth, height z score Follow-up: 24 weeks	Odevixibat 40 mcg/kg: N = 17 Placebo: N = 12	NA	−0.16	40 mcg/kg: 0.05 (0.11)	40 mcg/kg: 0.32 more (no difference to 0.65 more)	40 mcg: Low[i]	40 mcg: Odevixibat may result in an improvement in height z score compared to placebo after 24 weeks of follow-up. The clinical importance is uncertain.
	Odevixibat 120 mcg/kg: N = 15	—	—	120 mcg/kg: 0.00 (0.16)	120 mcg/kg: 0.15 less (0.18 less to 0.48 more)	120 mcg/kg: Very low[c]	120 mcg/kg: The evidence is very uncertain about the effects of odevixibat on height after 24 weeks of follow-up.
Mean (SE) change from baseline in growth, weight z score Follow-up: 24 weeks	Odevixibat 40 mcg/kg: N = 18 Placebo: N = 12	NA	0.10	40 mcg/kg: [redacted]	40 mcg/kg: [redacted]	40 mcg/kg: Low[i]	40 mcg/kg: Odevixibat may result in an improvement in weight z score compared to placebo after 24 weeks of follow-up. The clinical importance is uncertain.
	Odevixibat 120 mcg/kg: N = 15	—	—	120 mcg/kg: [redacted]	120 mcg/kg: [redacted]	120 mcg/kg: Very low[c]	120 mcg/kg: The evidence is very uncertain about the effects of odevixibat on weight after 24 weeks of follow-up.
Mean (SE) change from baseline in growth, BMI z score Follow-up: 24 weeks	Odevixibat 40 mcg/kg: N = 17 Placebo: N = 12	NA	0.26	40 mcg/kg: [redacted]	40 mcg/kg: [redacted]	Very low[c]	Both doses: The evidence is very uncertain about the effects of odevixibat on BMI z score after 24 weeks of follow-up.

Outcome measure	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)		Difference	Certainty	What happens
			Placebo	Odevixibat 40 mcg/kg and 120 mcg/kg			
	Odevixibat 120 mcg/kg: N = 15	—	—	120 mcg/kg: [redacted]	120 mcg/kg: [redacted]	Very low[c]	
Laboratory parameters							
Mean (SE) change from baseline in total bilirubin, µmol/L Follow-up: 24 weeks	Odevixibat 40 mcg/kg: N = 17 Placebo: N = 11	NA	−9.6	40 mcg/kg: −23.7 (9.2)	40 mcg/kg: [redacted]	Very low[c]	Both doses: The evidence is very uncertain about the effects of odevixibat on total bilirubin after 24 weeks of follow-up.
	Odevixibat 120 mcg: N = 15	—	—	120 mcg/kg: −19.3 (13.6)	120 mcg/kg: [redacted]	Very low[c]	
Harms							
Clinically significant diarrhea	Odevixibat 40 mcg/kg: N = 23 Placebo: N = 20	NR	[redacted]	[redacted]	[redacted]	Low[j]	Both doses: Odevixibat may result in [redacted] in the risk of clinically significant diarrhea after 24 weeks follow-up.
	Odevixibat 120 mcg/kg: N = 19	—	—	[redacted]	[redacted]	Low[j]	
Adjudicated hepatic events	Odevixibat 40 mcg/kg: N = 23 Placebo: N = 20	NR	[redacted]	[redacted]	[redacted]	Low[k]	Both doses: Odevixibat may result in [redacted] risk of adjudicated hepatic events after 24 weeks follow-up.
	Odevixibat 120 mcg/kg: N = 19	—	—	[redacted]	[redacted]	Low[k]	

BMI = body mass index; CI = confidence interval; HRQoL = health-related quality of life; NR = not reported; sBA = serum bile acid; SE = standard error.

Note: Study limitations (which refers 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.

[a]Rated down 2 levels for very serious imprecision, as there were no events and a small sample size; rated down 1 level for serious indirectness because the follow-up for this outcome was determined to be insufficient in consultation with clinical experts.

[b]Rated down 2 levels for very serious imprecision because there were no events and a small sample size; rated down 1 level for serious indirectness because the follow-up for this outcome was determined to be insufficient in consultation with clinical experts.

[c]Rated down 1 level for serious concerns about risk of bias due to missing outcome data. Rated down 2 levels for very serious concerns regarding imprecision; there was no published between-group minimal important difference (MID) identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects; therefore, the null was used. The 95% CI for both doses overlapped with both benefit and harm.

[d]Rated down 1 level for serious concerns about imprecision. No published between-group MID was identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects; therefore, the null was used. Although the point estimate and entire CI excluded the null, the small sample size raises concern for potential overestimation of the true effect, and there is evidence of prognostic imbalance. Because the effect appeared plausible, the CADTH review team rated down only once.

[e]Rated down 1 level for serious concerns about imprecision. No published between-group MID was identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects; therefore, the null was used. Although the point estimate suggested a benefit, the 95% CI also included the potential for little to no difference.

[f]Rated down 2 levels for very serious concerns about imprecision. No published between-group MID was identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects; therefore, the null was used. Although the point estimate suggested a benefit, the 95% CI also included the potential for little to no difference and harm.

[g]Rated down 1 level for serious concerns about imprecision. No published between-group MID was identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects; therefore, the null was used. Although the point estimate and entire CI excluded the null, the small sample size raises concern for potential overestimation of the true effect and there is evidence of prognostic imbalance. Because the effect appeared plausible, the CADTH review team rated down only once. Rated down 1 level for serious concerns about indirectness; this is a surrogate outcome with unclear relationship to clinical outcomes of interest.

[h]Rated down 1 level for serious concerns about imprecision. No published between-group MID was identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects; therefore, the null was used. Although the point estimate suggested a benefit, the 95% CI also included the potential for little to no difference (based on the judgment of the CADTH team). Rated down 1 level for serious concerns about indirectness; this is a surrogate outcome with unclear relationship to clinical outcomes of interest.

[i]Rated down 1 level for serious concerns about risk of bias due to missing outcome data. Rated down 1 level for serious concerns regarding imprecision; there was no published between-group MID identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects; therefore, the null was used. The point estimate suggests a benefit but the lower bound of the 95% CI includes the potential for little to no difference.

[j]Rated down 2 levels for very serious imprecision, as there was only 1 event in each group and very wide CI which included the potential for both benefit and harm.

[k]Rated down 2 levels for very serious imprecision, as very wide CI included the potential for both benefit and harm.

[l]These analyses were not adjusted for multiplicity and are at increased risk of false-positive findings; therefore, they should be considered as supportive evidence.

[m]These analyses were not part of the statistical analysis plan and were requested by CADTH to facilitate the GRADE assessment.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence and the Clinical Study Report for the PEDFIC trial.

Long-Term Extension Studies

Description of Study

PEDFIC 2 is an ongoing phase III, multicentre, nonrandomized, open-label extension study to investigate the long-term efficacy and safety of a 120 mcg/kg daily dose of odevixibat in patients with PFIC (Figure 14). Cohort 1 (n = 56) consists of children with PFIC1 and PFIC2 who have participated in the PEDFIC 1 study. Cohort 2 (n = 58) consists of patients with PFIC who have elevated sBA levels and cholestatic pruritus and who either did not meet the eligibility criteria for the PEDFIC 1 trial or were eligible for enrolment in the PEDFIC 2 trial after recruitment to PEDFIC 1 was completed. The primary outcome of the PEDFIC 2 trial was change from baseline in sBA levels after 24 (or 72) weeks of treatment. Secondary outcomes included the proportion of positive pruritus assessments at the patient level over the 24-week (or 72-week) treatment period using the PRUCISION ObsRO instrument, change from baseline in sBA levels at various time points, proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level using the PRUCISION ObsRO at various time points, proportion of individual morning and evening assessments meeting the definition of a positive pruritus assessment at the patient level using the PRUCISION ObsRO instrument at various time points and the number of patients undergoing biliary diversion surgery or liver transplantation.

Efficacy Results

Serum Bile Acid Levels

[redacted].

Surgical Intervention

[redacted].

Pruritus

Among patients who had received active treatment in the PEDFIC 1 trial and those who were treatment-naive at study entry, the median (range) proportion of positive pruritus assessments was [redacted] over the 72-week treatment period.

Data were consistent when the analysis was performed based on morning and evening scores separately.

Harms Results

[redacted].

No deaths occurred during the study.

Critical Appraisal

The PEDFIC 2 study is limited by its open-label and noncomparative design. Because there is no comparator, it does not show the comparative benefit of odevixibat to relevant comparators. Furthermore, the small sample size of the PEDFIC 2 study leads to difficulties in drawing any firm conclusions about the efficacy and safety of odevixibat. Due to its open-label and nonblinding nature, the absence of blinding can lead to assessor bias, and patient and caregiver would be most likely in favour of the intervention (i.e., odevixibat) for efficacy outcomes. Moreover, the subjective outcomes (e.g., pruritus assessments at the patient level and individual assessments meeting the definition of a positive pruritus assessment at the patient level) are at risk of bias regardless of blinding.

Although there was an amendment to include a starting dose of 40 mcg/kg per day with the possibility to escalate the dose to 120 mcg/kg per day after 12 weeks if there is no improvement in pruritus, the rationale of the optimal starting dose and titration strategy still remained unclear. The PEDFIC 2 study had not assessed the long-term efficacy and safety of the lower starting dose regimen, 40 mcg/kg per day, as of July 31, 2022.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Study

The Odevixibat versus External Control (OvEC) study was conducted to evaluate the effect of odevixibat on clinical outcomes in children with SBD-naive PFIC1 and PFIC2 participating in the PEDFIC 1 and PEDFIC 2 studies (N = 69) compared to an external control cohort of children who had not undergone SBD from the NAPPED study (N = 80). The primary objective was to evaluate the effect of odevixibat on death, liver transplantation, or SBD in children with PFIC1 and PFIC2. The primary end point was event-free survival, and the secondary end points included native liver survival, SBD-free survival, and overall survival. NAPPED is a retrospective database investigating the natural history of PFIC. The OvEC study used probability of treatment weighting (IPTW) methods to reduce the impact of confounding in comparing the clinical outcomes. A cohort of 69 patients treated with odevixibat were compared with 80 patients in the NAPPED trial (controls). The median study duration in the odevixibat cohort was 22.6 months (range, 1.9 to 39.2 months). The follow-up duration in the NAPPED cohort was truncated accordingly.

Efficacy Results

Event-free survival: In total, 6 (9%) of patients in the odevixibat cohort had an event-free survival event versus 44 patients (55%) in the NAPPED cohort. The weighted hazard ratio (HR) was 0.20 (95% CI, 0.09 to 0.45; P = 0.0016).

Native liver survival: In total, 4 (6%) of patients in the odevixibat cohort had a native liver survival event versus 21 patients (26%) in the NAPPED cohort. The weighted HR was 0.33 (95% CI, 0.11 to 1.03; P = 0.0900).

SBD-free survival: In total, 2 (3%) of patients in the odevixibat cohort had SBD-free survival event versus 31 patients (39%) in the NAPPED cohort. The weighted HR was 0.13 (95% CI, 0.04 to 0.39; P = 0.0023).

Overall survival: In total, no patients died in the odevixibat cohort versus 4 (5%) patients died in the NAPPED cohort. The weighted HR was 0 (95% CI, 0 to not estimable [NE]; P = 0.0845).

Critical Appraisal

Patients in the PEDFIC 1 and 2 trials were compared to the NAPPED cohort using IPTW methods in attempt to minimize the impact of confounding on the results. This method cannot control for substantial differences resulting from different study designs between the 2 cohorts (randomized controlled trial versus retrospective registry review). Details of the NAPPED cohort were limited; it is not clear how patients were selected into the cohort (i.e., potential for selection bias is unknown), their characteristics before weighting, nor what treatments they received. Similarly, data collection methods for the NAPPED cohort, how missing data were accounted for, the number of losses to follow-up, and outcome definitions have not been reported. The authors appropriately used cohort eligibility criteria that were considered similar to those used for the PEDFIC studies. However, the characteristics of patients at baseline and overlap in covariates before weighting were not described. Thereafter, the primary method to compare the 2 cohorts was based on using stabilized weights computed from the propensity score model. The dosing used in the PEDFIC 1 and 2 trials did not align with the proposed product monograph for all patients because some started on 120 mcg/kg per day and others escalated to this dosage despite responding to the lower dose. The treatments used among patients in the registry were not described; therefore, it is not clear whether these would correspond to treatments currently used for PFIC in Canada (the date of inclusion of patients in the registry is also unclear). For some outcomes, the follow-up time was likely to be too short and/or the sample size too small to capture relevant events. Numerous methodological limitations within the study limits the generalizability of the findings.

Ethical Considerations

Patient group, clinician group, clinical expert, and drug program input gathered in the course of this CADTH review as well as relevant literature were reviewed to identify ethical considerations relevant to the use of odevixibat for PFIC. Ethical considerations identified in this review included those related to:

- **Diagnosis, treatment, and experiences of PFIC:** Ethical considerations in the context of PFIC highlighted that patients and caregivers experience a tremendous physical, psychosocial, and financial burden from unremitting pruritis (itching) that is associated with this disease. Addressing referral bias, in which referrals may be influenced by illness severity, and ensuring early diagnosis of PFIC when possible is important in preventing needless suffering and reducing the burden on the health care system. There is an unmet need for an effective disease-modifying treatment for pruritis in PFIC, given its devastating impact on patients and their families. Surgical treatment alternatives, such as a liver transplant, are invasive and life-altering.
- **Clinical and economic evidence use in the evaluation of odevixibat**: There are some clinically meaningful outcomes identified in the trials used to evaluate odevixibat, including a significant reduction in sBA levels and symptom relief. These studies also exhibit considerable evidentiary

uncertainty. Specifically, uncertainty arises when attempting to extend efficacy results beyond the PFIC subtype 1 and 2 study population in correlating sBA to pruritis, and when considering durations exceeding the study's 24-week time frame. Ensuring that patients are adequately informed of these evidentiary uncertainties in a shared decision-making process and that health care resources are distributed fairly and equitably are important steps in addressing these ethical concerns.

- **Clinical use and implementation of odevixibat:** Clinical experts indicated there was some promise in odevixibat given its potential to address some unmet needs for the treatment of PFIC-associated pruritis with a favourable safety profile. However, it is essential to emphasize the importance of equitable access regarding continuity of care and access as pediatric patients become adults.
- **Health systems**: The reimbursement of odevixibat brings to the forefront a complex array of ethical considerations, including those regarding opportunity costs and resource allocation in the context of uncertain evidence as well as those related to equitable access and ensuring infrastructures to support continuity of care and access.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients aged 6 months or older with PFIC
Treatment	Odevixibat plus SOC
Dose regimen	40 mcg/kg administered once daily. If an adequate clinical response has not been achieved after 3 months of continuous therapy, the dose may be increased to 120 mcg/kg per day, with a maximum daily dose of 7,200 mcg/kg.
Submitted price	Odevixibat, 200 mcg: $175.92 per capsule Odevixibat, 400 mcg: $351.85 per capsule Odevixibat, 600 mcg: $527.77 per capsule Odevixibat, 1,200 mcg: $1,055.55 per capsule
Treatment cost	The annual cost of odevixibat ranges from $64,256 to $771,078 for a 40 mcg/kg dose and from $192,769 to $2,313,233 for a 120 mcg/kg dose
Comparator	SOC alone (defined as off-label use of UDCA, rifampicin, antihistamines, and naltrexone)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (99 years)
Key data sources	PEDFIC 1, PEDFIC 2, NAPPED natural history study

Component	Description
Key limitations	• The sponsor's model is based on a surrogate outcome, sBA levels, which limits the appropriateness of the sponsor's model structure. Clinical experts indicated that pruritus may be the preferred measure of response instead of sBA because a reduction in pruritus is the primary goal of treatment and there is uncertainty regarding a clinically meaningful threshold for sBA reduction. • The assumption of increased risk of mortality with acute liver transplant and long-term post–liver transplant results in a survival benefit with odevixibat that has not been shown in clinical trials and is uncertain based on recent large registry data from the US and UK, and clinical expert feedback. The model includes additional risk of mortality associated with loss of response on pre–liver transplant health states that is also uncertain. • The anticipated dose escalation for odevixibat is uncertain due to limited clinical evidence to support dose escalation in the manner it is described in the product monograph. Clinical experts also indicated that if dose escalation were to occur, it would occur incrementally in practice (e.g., increase to 80 mcg/kg to start). The anticipated dose escalation to 120 mcg/kg is a key driver of drug acquisition costs and cost-effectiveness of odevixibat; the annual incremental costs associated with dose escalation are approximately $1.5 million per adult patient. • There is limited evidence on the long-term comparative clinical effectiveness of odevixibat plus SOC vs. SOC alone. The sponsor assumed that the clinical effects of odevixibat observed in 24-week trials would be maintained for approximately 40 years, minus an annual probability of discontinuation of 3.53%. • The utility values used by the sponsor did not meet face validity according to clinical experts consulted by CADTH. The sponsor's utilities indicate that achieving response after receiving PEBD results in reduced quality of life compared to a patient who does not receive PEBD and does not respond.
CADTH reanalysis results	• CADTH attempted to address the key limitations by adjusting the additional risk of mortality associated with acute liver transplant and long-term post–liver transplant using large registry data for pediatric liver transplant recipients, removing the additional risk of mortality associated with loss of response in pre–liver transplant health states, and adjusting the utility value for patients achieving response after PEBD. CADTH was unable to address issues related to the model structure and lack of long-term comparative data. • Results from the CADTH base case suggest that odevixibat plus SOC is associated with higher costs (incremental: $9,688,198) and higher QALYs (incremental: 2.80) compared with SOC alone over a lifetime time horizon, resulting in an ICER of $3,462,139 per QALY gained. In the CADTH base case, odevixibat plus SOC had a 0% probability of being cost-effective at a WTP threshold of $50,000 per QALY. • A price reduction of 98.6% for odevixibat would be required for odevixibat plus SOC to be cost-effective compared to SOC alone at a WTP threshold of $50,000 per QALY gained. • In the CADTH base case, results were driven by the high drug acquisition costs of odevixibat and the dose escalation of patients from 40 mcg/kg to 120 mcg/kg after response is not achieved after 3 months of initial treatment.
Key scenario analyses	• Scenario analyses were conducted in which treatment response was based on pruritus score rather than sBA level. In these analyses the ICER remained above $3 million; thus, the conclusions are broadly similar to the CADTH base case. • Dose escalation to 120 mcg/kg increases the annual drug acquisition costs of odevixibat from $771,078 to $2,313,233 for adult patients. A scenario analysis excluding dose escalation to 120 mcg/kg dosing resulted in a decreased ICER of $2,237,178 per QALY gained.

ICER = incremental cost-effectiveness ratio; LY = life-year; PEBD = partial external biliary diversion; PFIC = progressive familial intrahepatic cholestasis; QALY = quality-adjusted life-year; sBA = serum bile acid; SOC = standard of care; UDCA = ursodeoxycholic acid; WTP = willingness to pay.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the sponsor's epidemiological approach to estimating target population was uncertain, post–liver transplant disease recurrence that requires treatment with odevixibat was likely overestimated in adults and did not meet face validity according to clinical experts, uncertainty surrounding dose escalation from 40 mcg/kg to 120 mcg/kg dosing and how this may be considered in clinical practice, uncertainty in the definition of PFIC and its variation across disease subtypes, and the proportion of patients eligible for public drug plan coverage is uncertain. The CADTH reanalysis included adjusting the incidence of PFIC, revising the proportion of adult and pediatric patients with native liver survival, and reducing the proportion of patients who experience disease recurrence post-LT. CADTH's reanalysis found that funding odevixibat for the treatment of PFIC in patients 6 months or older resulted in a budget impact of $16,531,305 in year 1, $21,046,984 in year 2, and $22,429,894 in year 3, for a cumulative 3-year budget impact of $60,008,183.

CADTH's reanalysis found that the reimbursement of odevixibat is likely to result in substantially less costs than predicted by the sponsor's model. The key driver of budget impact estimates is dose escalation from 40 mcg/kg to 120 mcg/kg. If dose escalation does not occur and patients remain on the initial 40 mcg/kg dose of odevixibat for the full time horizon, the 3-year budget impact of funding odevixibat decreases to $29,573,995.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Meeting date: November 23, 2023

Regrets: One expert committee member did not attend.

Conflicts of interest: None

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