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Reimbursement Recommendation

Odevixibat (Bylvay)

Indication: For the treatment of cholestatic pruritus in patients aged 12 months and older with Alagille syndrome (ALGS)

Sponsor: Medison Pharma Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Bylvay?

Canada's Drug Agency (CDA-AMC) recommends that Bylvay be reimbursed by public drug plans for the treatment of cholestatic pruritus in patients aged 12 months and older with Alagille syndrome (ALGS), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Bylvay should only be covered to treat patients aged 12 months or older, with a diagnosis of ALGS, who experience significant itch symptoms and have elevated serum bile acid (sBA) levels. Patients must be currently taking or have already tried a systemic medication for itch.

What Are the Conditions for Reimbursement?

Bylvay should only be reimbursed if it is prescribed under the care of a specialist with experience in treating patients with ALGS. The price of Bylvay should be negotiated so that the total treatment cost of Bylvay plus standard of care (SOC) does not exceed the drug program cost of treatment with maralixibat plus SOC. Bylvay should be stopped if the patient receives a liver transplant or biliary diversion surgery.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial showed that, in patients with ALGS, treatment with Bylvay improves itching compared to placebo.
- ALGS is a rare disease, often accompanied by severe itching. Bylvay may meet a need identified by patients as important because it may reduce patients' itching.
- Based on CDA-AMC's assessment of the health economic evidence, Bylvay 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 Bylvay plus SOC compared with maralixibat plus SOC.
- Based on public list prices, Bylvay plus SOC is estimated to cost the public drug plans approximately $211 million over the next 3 years when compared to SOC. However, the actual budget impact is uncertain and will depend on the funding status of maralixibat across all CDA-AMC–participating jurisdictions.

Summary

Additional Information

What Is ALGS?

ALGS is a rare, inherited liver disease that disrupts the normal flow of bile acids. Patients experience severe itching and a buildup of bile acids in the body that damage the liver. The itch can be severe enough to consider surgery or a liver transplant as treatment. ALGS is estimated to affect approximately 1 in 30,000 to 1 in 100,000 individuals or births.

Unmet Needs in ALGS

Patients with ALGS need effective treatments that can relieve symptoms of itchiness, reduce the risk of liver transplant, reduce fatigue for patients and caregivers, and improve quality of life. Most existing treatments for itching are not approved by Health Canada and are not effective. Currently, maralixibat is the only approved treatment and is not reimbursed by most public drug plans.

How Much Does Bylvay Cost?

Treatment with Bylvay is expected to cost approximately $192,769 to $2,313,233 per patient per year, depending on the patient's weight (i.e., 4.0 kg to > 55.5 kg), based on Health Canada–recommended dosages.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that odevixibat be reimbursed for the treatment of cholestatic pruritus in patients aged 12 months and older with Alagille syndrome (ALGS), only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

ALGS is a rare, life-threatening genetic disorder that presents with a range of clinical features, including cholestatic liver disease. Cholestatic pruritus is a significant management challenge for patients with ALGS and their families; it has a considerable impact on sleep, growth, and school performance in children. The itch has been described by patient groups as debilitating, unrelenting, and impossible to alleviate. It is also a common reason for liver transplant in children living with ALGS. There are few treatment options available, including off-label treatments (ursodeoxycholic acid [UDCA], rifampin, sertraline, naltrexone, cholestyramine, and antihistamines) —which have limited efficacy — and maralixibat, which has been approved by Health Canada for patients with ALGS but is not reimbursed by most public drug plans at this time. Considering this, CDEC recognized that there is a significant unmet need in patients with cholestatic pruritus due to ALGS.

Evidence from a phase III, placebo-controlled, double-blind, randomized trial (the ASSERT trial, N = 52) with an open-label extension suggested that odevixibat plus standard of care (SOC) results in improvements in pruritus severity and serum bile acid (sBA) levels compared to placebo plus SOC in pediatric patients with ALGS. The ASSERT study showed a statistically significant improvement in the PRUCISION Observer-Reported Outcome (ObsRO) scratching score, with a least squares (LS) mean difference of −0.88 points (95% confidence interval [CI], −1.44 to −0.33) from baseline to month 6, favouring odevixibat plus SOC. CDEC concluded that the results of the ASSERT study corresponded to clinically meaningful improvements in pruritus with odevixibat treatment plus SOC relative to placebo plus SOC. CDEC was unable to draw conclusions regarding the comparative efficacy and safety between odevixibat and maralixibat, the most relevant comparator, as no direct or indirect evidence was submitted.

Patients identified a need for an effective treatment for cholestatic pruritus in ALGS that reduced the frequency and severity of pruritus, reduced patient and caregiver fatigue, and improved quality of life. CDEC concluded that odevixibat met a need identified by patients in terms of improving pruritus.

Based on the sponsor’s submitted price for odevixibat and publicly listed prices for all other drug costs, odevixibat plus SOC was more costly than maralixibat plus SOC. As no conclusions could be drawn regarding the relative efficacy of odevixibat plus SOC compared to maralixibat plus SOC, the total drug cost of odevixibat plus SOC should not exceed the total drug cost of maralixibat plus SOC.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients aged 12 months or older with a diagnosis of ALGS who have demonstrated the following: 1.1. significant pruritus defined as an itching or scratching score of 2 or higher on the PRUCISION PRO or ObsRO scale 1.2. sBA level greater than the ULN.	Evidence from the ASSERT study supported the efficacy of odevixibat in pediatric patients with a diagnosis of ALGS, elevated sBA levels, and moderate to severe itch, defined as an average score of 2 or higher on the PRUCISION ObsRO scratching severity scale or PRO itching severity scale in the 2 weeks before randomization.	The ASSERT study used PRUCISION instruments to assess pruritic severity, while the ICONIC trial used ItchRO or CSS to evaluate maralixibat. A harmonized instrument to evaluate itch severity and response may be considered for all patients who begin treatment with severe itch and are treated with IBAT inhibitors. Eligibility for initial reimbursement of odevixibat could be similar to maralixibat as per the initiation criteria used by each public drug plan.
2. Patients must be either currently receiving systemic therapy for pruritus or have previously undergone an adequate trial of such treatment before initiating odevixibat.	In the overall population enrolled in the ASSERT study, 88.5% reported a history of treatment with UDCA and 67.3% reported a history of treatment with rifampin. This aligns with clinical practice in Canada, based on input from the clinical experts who noted that most patients with cholestatic pruritus due to ALGS are likely to have received prior treatment with UDCA or rifampin. There is no evidence that odevixibat is clinically superior or inferior to any other off-label treatments or IBAT inhibitors currently reimbursed for the treatment of cholestatic pruritus in patients with ALGS.	An adequate trial was defined as a trial of 1 to 3 months with appropriate dosing of a systemic treatment for pruritus based on usual care. This may include UDCA, rifampicin, sertraline, naltrexone cholestyramine, or antihistamines.
3. Patients with any of the following should not be eligible for reimbursement of odevixibat: biliary diversion, previous liver transplant, decompensated liver disease, or history or presence of other concomitant liver disease.	There is insufficient evidence for efficacy or safety of odevixibat in patients with the specified comorbidities because they were excluded from the ASSERT trial.	—

Reimbursement condition	Reason	Implementation guidance
Renewal		
4. The duration of initial authorization is 6 months. For renewal after initial authorization, the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as an improvement in pruritus to minimal or no itch.	An improvement in pruritus was observed within 24 weeks in the ASSERT trial. Assessment of response within 6 months of initiating treatment was considered appropriate and aligned with clinical practice in Canada based on input from clinical experts.	A sponsor-defined MID of 1 was identified as a clinically meaningful change for the PRUCISION ObsRO; as such, an improvement in pruritus by a score of 1 from baseline on this instrument could be considered. The ASSERT study used PRUCISION instruments to assess pruritic severity while the ICONIC trial used ItchRO or CSS to evaluate maralixibat. A harmonized measure of beneficial clinical effect as it pertains to itch severity and response may be considered for all patients who begin treatment with severe itch and are treated with IBAT inhibitors. Eligibility for renewal of reimbursement of odevixibat could be similar to maralixibat as per the renewal criteria used by each public drug plan.
5. For subsequent renewal, the physician must provide proof of maintenance of the change in pruritus severity from baseline every 6 months.		—
Discontinuation		
6. Reimbursement of odevixibat should be discontinued if 1 or both of the following occurs: 6.1. patient receives liver transplant or biliary diversion surgery.	There is no evidence to support the continued use of odevixibat following liver transplant or biliary diversion surgery.	—
Prescribing		
7. The patient should be under the care of a hepatologist with experience in treating patients with ALGS.	Accurate diagnosis and treatment of patients with ALGS and cholestatic pruritus is important to ensure that odevixibat is prescribed for appropriate patients.	—
Pricing		
8. The price of odevixibat plus SOC should be negotiated so that it does not exceed the drug program cost of treatment with maralixibat plus SOC reimbursed for the treatment of cholestatic pruritus in patients aged 12 months or older with ALGS.	Due to lack of robust comparative evidence, the comparative efficacy and safety of odevixibat plus SOC relative to maralixibat plus SOC is unknown. As such, there is insufficient evidence to justify a cost premium for odevixibat plus SOC over maralixibat plus SOC for the treatment of cholestatic pruritus in patients aged 12 months or older with ALGS.	—

Reimbursement condition	Reason	Implementation guidance
Feasibility of adoption		
9. The feasibility of adoption of odevixibat plus SOC 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 the CDA-AMC estimate(s).	—

ALGS = Alagille syndrome; CDEC = Canadian Drug Expert Committee; CSS = Clinician Scratch Scale; IBAT = ileal bile acid transporter; ICER = incremental cost-effectiveness ratio; ItchRO = Itch Reported Outcome; MID = minimal important difference; PRO = patient-reported; ObsRO = observer-reported outcome; QALY = quality-adjusted life-year; SOC = standard of care; UDCA = ursodeoxycholic acid; ULN = upper limit of normal.

Discussion Points

- **Significant unmet need:** CDEC deliberated on odevixibat considering the criteria for significant unmet need, which are described in section 11.3.2.3 of the Canada's Drug Agency (CDA-AMC) Procedures for Reimbursement Reviews. ALGS is a rare and chronic disease with significant mortality and morbidity. The available off-label therapies have limited efficacy in controlling pruritus in patients with severe symptoms. Maralixibat has demonstrated efficacy in reducing pruritus and is the only approved treatment currently available. Given the rarity of the condition and the medical need for additional treatment options to control pruritus, CDEC concluded that the available evidence reasonably suggests that odevixibat has the potential to reduce morbidity in patients with cholestatic pruritus associated with ALGS.
- **Efficacy:** The Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty of evidence assessment resulted in a rating of "low" for observer-reported pruritus severity and "moderate" for sBA levels. Weighing the uncertainty in the pruritus outcomes against the rarity of the disease and the notable impact that pruritus has on patients' quality of life — an impact highlighted by both patients and clinicians — CDEC concluded that the available evidence meets a patient need, based on clinically meaningful improvements in pruritus with odevixibat plus SOC compared to maralixibat plus SOC.
- **Adverse events**: CDEC discussed the safety profile observed with odevixibat. While the ASSERT trial did not provide direct comparative evidence regarding the adverse events (AEs) associated with odevixibat versus a relevant comparator (e.g., maralixibat), CDEC noted that, overall, treatment-emergent adverse events (TEAEs) appeared with similar frequency in patients treated with odevixibat and placebo. The most common AEs in the odevixibat group were diarrhea, pyrexia, and abdominal pain. CDEC noted that the diarrhea AEs were not serious, and no deaths or withdrawals due to AEs occurred in either group over the total study duration. CDEC agreed with the clinical experts that, overall, the incidence and severity of AEs appeared manageable; however, uncertainty remains due to the small sample size and limited follow-up duration.
- **Long-term extension study:** CDEC considered the data from the 72-week extension period of the ASSERT study, which suggested sustained benefits up to 72 weeks, and a safety profile of odevixibat

that was consistent with the randomized controlled period of the trial. However, interpretation of the long-term results was limited by the small sample size; missing data; and the open-label, noncomparative, and descriptive nature of the extension study, and CDEC considered it to be supportive evidence.

- **Health-related quality of life:** CDEC noted that patients expect new treatments for cholestatic pruritus in ALGS to improve quality of life; however, no conclusion could be reached regarding the effects of odevixibat on health-related quality of life (HRQoL) because of the limitations of the available evidence.
- **Relevant comparators:** At the time of writing of the review by CDA-AMC, CDEC had recommended that maralixibat be reimbursed with criteria and conditions, but it had not been listed by CDA-AMC–participating jurisdictions. After the draft reports were submitted to the sponsor, CDEC noted that the pan-Canadian Pharmaceutical Alliance (pCPA) had concluded negotiations for maralixibat with a letter of intent (LOI). CDEC is aware that at least 1 CDA-AMC–participating drug program has listed maralixibat on its drug formulary.
- **Comparative evidence:** CDEC discussed the lack of comparative evidence for odevixibat versus maralixibat. No indirect evidence was submitted because the sponsor-conducted feasibility assessment concluded that an indirect treatment comparison was unlikely to provide robust results. CDEC acknowledged the study heterogeneity and the feasibility issues for conducting an indirect treatment comparison; however, they noted the lack of comparative efficacy and safety data for odevixibat versus maralixibat as an evidence gap. CDEC further noted that the study heterogeneity resulted in differing reimbursement criteria for odevixibat compared to maralixibat. Given that there is no comparative evidence to support either agent over the other, the jurisdictions may wish to consider aligning reimbursement criteria for odevixibat and maralixibat.
- **Economic implications on the appropriateness of the comparator:** CDEC noted that the report by CDA-AMC was written before maralixibat was listed by CDA-AMC–participating drug programs. While CDEC acknowledged that at least 1 jurisdiction has listed maralixibat, it noted that in jurisdictions that do not list maralixibat, SOC remains the appropriate comparator. The review by CDA-AMC noted that the incremental cost-effectiveness ratio (ICER) for odevixibat plus SOC was estimated to be $5,678,772 per QALY gained compared to SOC alone, although this estimate was associated with uncertainty. Based on this analysis, price reductions greater than 90% would be required for odevixibat plus SOC to achieve an ICER of $50,000 per QALY gained compared to SOC alone. The review by CDA-AMC also noted that there would be a larger incremental budget impact if odevixibat plus SOC does not displace maralixibat plus SOC.

Background

ALGS is a rare, life-threatening, autosomal-dominant genetic disorder that presents with a range of features, including cholestatic liver disease, failure to thrive, cardiovascular disease, skeletal abnormalities, ocular abnormalities, renal and vascular abnormalities, and distinct facial features. In most cases, the liver

dysfunction associated with ALGS is an early and serious feature of this genetic condition and typically presents within the first 3 months of life. Elevated levels of sBA and jaundice (elevated bilirubin) are hallmarks of ALGS and indicate the presence of impaired bile flow, also known as cholestasis. Clinically, the hepatic manifestations may range from mild cholestasis to progressive liver failure, and usually include severe pruritus and, later, progression to cirrhosis. Cholestatic pruritus may be debilitating and intractable, and have a considerable impact on sleep, growth, and school performance in children.

ALGS prevalence and incidence are estimated between 1 in 30,000 to 1 in 100,000 individuals or births. Long-term follow-up studies report premature mortality rates of 7.5% to 35%, with median age of death between 2.3 years and 4 years. Diagnosis typically requires that at least 3 of the following 5 criteria are fulfilled: cholestatic liver disease, congenital heart disease, skeletal anomalies, ocular anomalies, or facial anomalies. While genetic testing (*JAG1* or *NOTCH2* mutations) supports diagnosis and is publicly funded in Canada, it is not required, as a small subset of patients lack detectable mutations despite meeting clinical criteria.

In Canada, several drugs are prescribed off-label to manage symptoms of ALGS, although many of these treatments have limited or transient efficacy and may cause undesirable adverse effects. The clinical experts consulted by CDA-AMC noted that UDCA is typically used early in cholestasis management to promote bile excretion, which may indirectly improve pruritus. Other antipruritic treatments prescribed include rifampin, cholestyramine, antihistamines, sertraline, and naltrexone. The clinical experts consulted by CDA-AMC noted that these drugs are often ineffective, have drug interactions and poor tolerability in pediatric patients. Surgical interventions include biliary diversion procedures and liver transplant, which are associated with significant morbidity or mortality. Maralixibat, an ileal bile acid transporter (IBAT) inhibitor like odevixibat, was approved in 2023 for the treatment of cholestatic pruritus in pediatric patients with ALGS. This novel class of drugs inhibits the absorption of bile acids in the small intestine. Maralixibat received a recommendation for reimbursement with conditions from CDEC in April 2024. Maralixibat recently received an LOI indicating the completion of pCPA negotiations, but it is not yet reimbursed by public drug plans at the time of this review.

Odevixibat has been approved by Health Canada for the treatment of cholestatic pruritus in patients aged 12 months or older with ALGS. The dosage recommended in the product monograph is 120 mcg/kg administered orally once daily in the morning with a meal. A temporary dose reduction to 40 mcg/kg/day may be considered if tolerability issues occur in the absence of other causes. Odevixibat is available as 200 mcg, 400 mcg, 600 mcg and 1,200 mcg capsules that may be swallowed whole, opened and sprinkled on soft food, or added to a liquid.

Sources of Information Used by the Committee

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

- a review of 1 phase III, randomized, double-blind, placebo-controlled trial in patients with ALGS and 1 long-term extension study
- patients' perspectives gathered by 1 patient group, the Alagille Syndrome Alliance (ALGSA)

- input from public drug plans that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with ALGS
- input from 1 clinician group, the Canadian Pediatric Hepatology Research Group (CPHRG)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Input for this review was submitted by 1 patient group, the ALGSA, a global nonprofit organization that supports the global ALGS community through resources, programs, and research and support initiatives. The ALGSA gathered information for this submission through direct interviews with patients and caregivers and responses to an international survey in September 2020, which included respondents living in Canada. Through interactions with patients and families in international ALGSA support networks, some of whom were living in Canada, the patient group provided feedback from those with firsthand experience with odevixibat.

The patient group highlighted ALGS as a complex, multisystem genetic disorder that profoundly impacts the day-to-day lives and emotional well-being of patients and caregivers. The most burdensome symptom of ALGS is chronic liver disease, resulting in symptoms such as jaundice, severe itch (pruritus), loss of sleep, discomfort, and malabsorption. The itch is described as “relentless, consuming, and life-altering,” and results in open wounds from scratching, sleep disruption, difficulty concentrating, and mental health challenges. Patients often face lengthy diagnostic journeys, involving invasive diagnostic procedures and misdiagnoses. Beyond liver complications, ALGS can affect the heart, kidney, bones, eyes, and thyroid, sometimes requiring invasive interventions such as open-heart surgery, dialysis, and catheterizations. Nutritional challenges — including malabsorption, poor growth, and feeding issues — introduce further emotional and time burdens on patients and caregivers. The patient groups noted that families often feel trapped in “survival mode,” managing complex medical regimens, frequent appointments, and financial stress.

Before the approval of maralixibat and odevixibat in the US, itch was typically managed through the systemic antibiotic rifampin, combined with medications like hydroxyzine, cholestyramine, naltrexone, or UDCA, alongside nonprescription remedies such as oatmeal baths, melatonin, and diphenhydramine. However, patients indicated that these approaches rarely provide significant relief from itch, and the risks of long-term use of antibiotics remain unclear. The patient group noted that the Health Canada approval of maralixibat improved treatment options for ALGS, and that the approval of odevixibat would offer patients greater flexibility in administration methods and serve as an alternative treatment option if treatment efficacy is lost over time.

According to the patient group, an “ideal treatment” would provide meaningful and consistent relief from severe itch, reduce the need for multiple medications, avoid major adverse effects (particularly sedation, “liver strain,” and serious infection), minimize disruption to daily life, and offer a convenient administration

method. Patients noted that they would be willing to accept mild adverse effects if the treatment significantly improves itching and quality of life, while treatments with more substantial risks would only be considered as a last resort.

Overall, families who have had experience with odevixibat report substantially reduced or eliminated pruritus; improved appetite and weight gain; and reduced stress, anxiety, and depression. Reported adverse effects were primarily related to mild to moderate gastrointestinal discomfort, including cramping and diarrhea, which typically improved within 1 to 2 weeks of treatment. Families indicated that the benefit of itch relief offered by odevixibat outweighed the initial adverse effects. Families who discontinued odevixibat reported a rapid return of pruritus, which they felt emphasized its importance for maintaining quality of life.

Clinician Input

Input From Clinical Experts Consulted for This Review

According to the clinical experts consulted by CDA-AMC, the main treatment goals for a patient with cholestasis are to reduce the severity of symptoms (specifically pruritus), to support normal growth and development, and to delay disease progression and liver transplant. The clinical experts emphasized the importance of pruritus to patients, which impacts sleep, school attendance and performance, and the overall quality of life of patients and their families. According to the clinical experts, the current standard treatment options for pruritus (sedatives, antihistamines, cholestyramine, rifampicin, naltrexone, and, rarely, sertraline) are of limited effectiveness, have adverse effects, and do not address the mechanism of cholestatic pruritus. Given the lack of effective pruritus treatments, biliary diversion surgery or liver transplant may be performed to manage symptoms in patients with severe symptoms. In such cases, liver transplant may be performed before the onset of liver failure. Maralixibat has recently been approved for the management of cholestatic pruritus in patients with ALGS; however, the majority of patients lack access due to cost and reliance on inconsistent private insurance coverage. According to the clinical experts, there are currently no specific treatments that have been demonstrated to modify the natural history of ALGS, although they noted that longer-term data for IBAT inhibitors are still developing.

The clinical experts stated that odevixibat would be used in combination with standard treatment options to control cholestatic pruritus. The patients who are best suited to treatment with odevixibat are those with ALGS who have significant or severe pruritus and consequent impairment in patient and family quality of life, according to the clinical experts consulted by CDA-AMC. These patients would be identified based on the clinical history provided by the patient and/or their family. Other criteria may include high sBA levels. Patients with ALGS and any of the genetic mutations involved (*JAG1* or *NOTCH2*) would be suitable for odevixibat therapy. One clinical expert suggested that odevixibat would be used as second-line or third-line therapy, after starting UDCA (which may improve cholestasis) and a trial of rifampin (to manage pruritus). The other clinical expert identified specific cases in which first-line IBAT inhibitor therapy may be warranted.

In clinical practice, the experts identified improvement in pruritus, sleep, and quality of life, and improved growth as the most important outcomes for assessing response to therapy. Improved liver function on lab testing would also be important. Patients are typically assessed every 3 to 6 months, or more frequently

in patients with advanced liver disease. The clinical experts expected that early treatment response would be evaluated in the first month or 2 after initiating odevixibat. The clinical experts noted that inadequate symptomatic response, intolerance to the drug (such as intolerable diarrhea) or disease progression necessitating liver transplant would require discontinuation of the drug.

The clinical experts agreed that odevixibat should be prescribed and monitored by a pediatric gastroenterologist or hepatologist on an outpatient basis in a specialty pediatric gastroenterology or liver clinic. One of the clinical experts noted that patients living in remote areas could be treated by a general pediatrician in collaboration with a pediatric hepatologist or gastroenterologist.

Clinician Group Input

Input for this review was submitted by 1 clinician group, the CPHRG of the Canadian Association for the Study of the Liver (CASL). CASL is the national professional organization for hepatology in Canada, which aims to eliminate liver disease through research, education, and advocacy. The CPHRG is a committee within CASL, comprised of representatives from all pediatric hepatology services in Canada. Information was gathered for the input submission through published literature, conferences, and collective expert opinions within the CPHRG, based on experience treating patients with ALGS.

The clinician group input was generally consistent with that provided by the consulted clinical experts regarding the limitations of currently available therapies for cholestatic pruritus. Both sources noted that existing pharmacologic options (i.e., antihistamines, cholestyramine, rifampin, naltrexone, and sertraline) are associated with adverse effects and limited efficacy, and do not address the underlying pathophysiology of cholestatic pruritus. The clinician group also confirmed that, in the absence of effective symptom control, liver transplant may be considered as a last resort, although this route has associated risks and a lifelong treatment burden.

With respect to the place in therapy, both the clinician group and clinical experts anticipated that odevixibat would be used as an adjunct to existing therapies rather than a replacement. The clinician group added that some patients may be able to taper other medications after starting treatment. Both the experts and clinician group identified patients with moderate to severe pruritus not adequately controlled on standard therapy as the population most likely to benefit from treatment with odevixibat. The clinician group also noted that those with moderate to severe pruritus and elevated bile acids would be considered most likely to respond.

In terms of treatment monitoring, both the clinician group and clinical experts highlighted improvements in pruritus and sleep as clinically meaningful indicators of treatment benefit. The clinician group expressed concerns regarding the practicality of implementing the pruritus assessment tools used in the odevixibat clinical trial (e.g., the PRUCISION instrument) in real-world practice settings, instead suggesting the Clinician Scratch Score, while the experts noted that similar domains are assessed routinely through clinical history. Both groups agreed that treatment with odevixibat should be discontinued in cases of liver disease progression, transplant, or intolerable AEs. Both the clinical experts and the clinician group indicated that odevixibat should be prescribed and monitored by a pediatric hepatologist or gastroenterologist within a specialized care setting.

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	
The ASSERT study was a phase III, double-blind, randomized, placebo-controlled trial of odevixibat in children with ALGS. No comparative evidence was submitted by the sponsor for odevixibat vs. maralixibat. Maralixibat is indicated for the treatment of cholestatic pruritus in patients with ALGS and received a CDEC recommendation to reimburse with conditions.	The clinical experts consulted by CDA-AMC agreed that SOC (e.g., UDCA, rifampin, and antihistamines) and maralixibat were relevant comparators to odevixibat. CDEC acknowledged the clinical experts' response.
Considerations for initiation of therapy	
The instruments used to assess pruritus in the maralixibat and odevixibat clinical trials were different. The ICONIC trial (and CDEC recommendation) used the ItchRO or the CSS for maralixibat. The ASSERT trial for odevixibat used the PRUCISION ObsRO scratching score. Question: Is there a way to harmonize itch scoring tools across both drugs for ALGS so that clinicians must only be versed in 1 tool?	The ItchRO and PRUCISION ObsRO pruritus instruments are similar, with scores ranging from 0 (no itching or scratching), to 4 ("worst" or "very severe" itching or scratching). The experts did not have an opinion on whether the pruritus scales could be considered interchangeable in clinical practice, as they were not aware of evidence comparing the 2 instruments. CDEC suggested that a harmonized itch assessment tool could be considered for IBAT inhibitors.
Consider aligning with the maralixibat initiation criteria if possible: Maralixibat initiation criteria: 1. Evidence of cholestasis (must include at least 1 of the following): 1.1. total sBA > 3 × ULN for age 1.2. conjugated bilirubin > 1 mg/dL 1.3. fat-soluble vitamin deficiency otherwise unexplainable 1.4. GGT > 3 × ULN of age 1.5. intractable pruritus explainable only by liver disease.	The experts noted that the ASSERT study inclusion criteria were different from the criteria used for the pivotal maralixibat trial, and did not require patients to meet the bilirubin, vitamin deficiency, or GGT criteria listed. In addition, the sBA criteria in the ASSERT trial was above the ULN, not 3 times the ULN. Despite the differences in the criteria, the clinical experts anticipated that most patients with ALGS and moderate to severe pruritus would meet the reimbursement initiation criteria listed based on bilirubin levels or intractable pruritus. The experts expected that odevixibat and maralixibat would be used in the same patient population and emphasized the need for more than 1 IBAT inhibitor, given that not all patients will show an adequate response with the initial IBAT received. CDEC acknowledged that the inclusion and exclusion criteria for the odevixibat and maralixibat trials were different. CDEC recommended reimbursing odevixibat as per the inclusion and exclusion criteria of the ASSERT study. CDEC noted that it may also be appropriate to align the initiation criteria of odevixibat with those of maralixibat used by each drug plan.
Consider aligning the prerequisite medications with the maralixibat recommendation: An adequate trial of 1 to 3 months with appropriate dosing of a systemic treatment for pruritus based on usual care. This may include: • UDCA	The clinical experts stated that most patients with moderate to severe pruritus will have been treated with 1 of the drugs listed, and it would be reasonable to apply these criteria to the reimbursement of odevixibat. They noted that SOC treatment options may control symptoms in some patients with mild pruritus. For patients with severe pruritus, the clinical experts

Implementation issues	Response
• rifampicin • sertraline • naltrexone • cholestyramine • antihistamines.	noted that a requirement to use off-label antipruritic treatments before odevixibat would delay many patients from receiving an effective therapy. CDEC agreed that a trial with current SOC would be appropriate as per the maralixibat reimbursement criteria, and considering that 88.5% of patients in the ASSERT study had received UDCA and 67.3% had received rifampin before trial entry.
Can patients switch between maralixibat and odevixibat?	The experts stated that patients may switch between odevixibat and maralixibat if they have an inadequate response to either of these drugs. CDEC acknowledged the clinical experts' response.
Considerations for continuation or renewal of therapy	
Consider aligning with maralixibat renewal criteria, if possible, given that the submitted studies used different pruritus grading tools.	The clinical experts stated that the response threshold specified in the maralixibat renewal criteria (i.e., an improvement in pruritus to minimal or no itch [a score of 1 or lower] on the ItchRO or CSS scale) was too stringent and suggested that a 1-point improvement on a 0-to-4 pruritus severity scale would be clinically important. In practice, patients would continue to receive therapy if they reported any subjective improvement in pruritus, and a partial response may be clinically important to patients, according to the experts. The clinical experts also noted that numerical rating scales are not commonly used in clinical practice to assess pruritus symptoms, but these instruments could be adopted if required for reimbursement. CDEC considered it appropriate to align the renewal criteria of odevixibat with those of maralixibat as per the renewal criteria used by each public drug plan.
Considerations for prescribing of therapy	
Odevixibat is given orally at a dose of 120 mcg/kg once daily in the morning. The dose may decrease to 40 mcg/kg/day if tolerability issues occur in the absence of other causes.	This is a comment from the drug plans to inform CDEC deliberations.
Odevixibat and maralixibat have the same mechanism of action. Question: Would the 2 drugs be prescribed together?	The clinical experts did not anticipate the IBAT inhibitors would be prescribed concurrently. CDEC noted that there is currently insufficient evidence to guide a recommendation on the concurrent use of maralixibat and odevixibat; therefore, odevixibat should be used as monotherapy.
Consider aligning prescribing criteria with maralixibat.	The clinical experts stated that odevixibat should be prescribed and monitored by a pediatric gastroenterologist or hepatologist on an outpatient basis in a specialty pediatric gastroenterology or liver clinic. One of the clinical experts noted that patients living in remote areas could be treated by a general pediatrician in collaboration with a pediatric hepatologist or gastroenterologist. CDEC agreed with the clinical experts and supported alignment of prescribing conditions for IBAT inhibitors reimbursed for cholestatic pruritus in patients with ALGS.

Implementation issues	Response
System and economic issues	
The sponsor's base-case analysis assumed the following market share distribution: • year 0: [redacted] standard of care and [redacted] maralixibat • year 1: [redacted] standard of care, [redacted] maralixibat, and [redacted] odevixibat • year 2: [redacted] standard of care, [redacted] maralixibat, and [redacted] odevixibat. The budget impact assessment resulted in varying annual cost estimates for odevixibat depending on dosing assumptions. Over the first 3 years after the introduction of odevixibat, the total budget impact was estimated to range from −$15,063,908 to $11,713,715. The cost per capsule of odevixibat ranges from $175.92 for the 200 mcg capsule to $1,055.55 for the 1,200 mcg capsule. The annual cost by body weight ranges from $192,768 for less than 4 kg to $2,313,238 for 55.5 kg or greater.	This is a comment from the drug plans to inform CDEC deliberations.

ALGS = Alagille syndrome; CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; CSS = Clinician Scratch Scale; IBAT = ileal bile acid transporter; ItchRO(Obs) = Itch Reported Outcome (Observer); ObsRO = observer-reported outcome; pCPA = pan-Canadian Pharmaceutical Alliance; sBA = serum bile acid; UDCA = ursodeoxycholic acid; ULN = upper limit of normal.

Clinical Evidence

Systematic Review

Description of Studies

The systematic review included 1 phase III, double-blind, parallel design, randomized controlled trial (RCT), the ASSERT trial, which compared the efficacy and safety of odevixibat with placebo in patients with ALGS, elevated sBA, and significant pruritus. Patients were randomized to once-daily oral odevixibat 120 mcg/kg/day (N = 35) or a matching placebo (N = 17), for up to 24 weeks. During the trial, patients were permitted to continue with standard antipruritic therapies they had been receiving before randomization. The primary end point was the change from baseline to month 6 in the PRUCISION Observer-Reported Outcome (ObsRO) scratching severity score. Other key outcomes were the PRUCISION Patient-Reported Outcome (PRO) itching severity score, the Pediatric Quality of Life Inventory (PedsQL), and sBA levels.

The mean age of enrolled patients was [redacted] years (standard deviation [SD] = [redacted]; range, [redacted] to [redacted] years) in the odevixibat group and [redacted] years (SD = [redacted]; range, [redacted] to [redacted]) in the placebo group. In the odevixibat group, 60% of patients were male and 40% were female, while in the placebo group, 64.7% of patients were female and 35.4% were male. According to the National Cancer Institute Organ Dysfunction Working Group classification system, [redacted] and [redacted] of patients had mild hepatic impairment, [redacted] and [redacted] had moderate impairment, and [redacted] and [redacted] of patients had severe impairment at baseline in the odevixibat and placebo groups, respectively. The mean ObsRO scratching score was 2.80 points (SD = 0.52) and 3.01 points (SD = 0.64), and the mean sBA level was 237.4 µmol/L

(SD = 114.9) and 246.1 µmol/L (SD = 120.5) in the odevixibat and placebo groups, respectively. Most patients were receiving UDCA, including 30 patients (85.7%) in the odevixibat group and 16 patients (94.1%) in the placebo group. All patients were on antipruritic medications at baseline, except for 1 patient randomized to the odevixibat group.

Efficacy Results

The primary outcome in the ASSERT trial was the change from baseline to month 6 (average of week 21 to week 24) in the scratching severity score (morning and evening scores combined) measured using the PRUCISION ObsRO questionnaire. Caregivers reported the observed scratching behaviours on a scale from 0 to 4 (ranging from no scratching to worst possible scratching) twice daily, covering the nighttime (AM score) and daytime symptoms (PM score). The LS mean difference in the change from baseline was −0.88 points (95% CI, −1.44 to −0.33; 1-sided P = 0.0012) favouring odevixibat versus placebo. The sponsor identified a 1.0-point to 1.5-point reduction as the clinically relevant within-patient threshold for change. The proportion of patients who achieved at least a 1.0-point or 1.5-point reduction in PRUCISION ObsRO scratching scores from baseline to month 6 also favoured odevixibat over placebo, with point estimates of 44.7% and 36.6%, respectively, for the between-group difference.

Patients aged 8 years or older (N = 15) self-reported itching severity using the PRUCISION PRO questionnaire (with a scale from 0 to 4). No statistical difference was detected between the odevixibat and placebo groups based on the change from baseline to month 6 in the itching severity score (LS mean difference 0.18 points; 95% CI, −0.65 to 1.00; 1-sided P = 0.678).

HRQoL was assessed using the PedsQL questionnaire. The parent-reported instrument includes 23 items and 4 domains: physical, emotional, social, and school. The PedsQL is scored on a scale from 0 to 100, with higher scores indicating improved HRQoL. The estimated within-group minimal important difference (MID) in children with chronic health conditions (asthma, ADHD, depression, diabetes, or “other”) was 4.5 points for the Parent Proxy-Report. For odevixibat versus placebo, the LS mean difference in the change from baseline to week 24 in the PedsQL total score was 2.78 points (95% CI, −6.31 to 11.87; 1-sided P = 0.27).

The change from baseline to month 6 in sBA levels favoured odevixibat over placebo, with the study reporting a LS mean difference of −112.7 µmol/L (95% CI, −178.8 to −46.7; 1 sided P = 0.0006). For patients with ALGS, the MID for the change in sBA levels is unknown.

No deaths were reported, and no patients underwent liver transplant during the 24-week study.

Harms Results

Overall, 26 (74.3%) of the 35 patients who received odevixibat experienced at least 1 TEAE, as did 12 (70.6%) of the 17 patients who received placebo. The most common TEAEs (≥ 10%) among patients who received odevixibat, with corresponding frequency in patients who received placebo, were diarrhea (28.6% versus 5.9%), pyrexia (22.9% versus 23.5%), COVID-19 (14.3% versus 23.5%), and abdominal pain (11.4% versus 5.9%). Treatment-emergent serious adverse events (SAEs) were reported in 5 patients (14.3%) who received odevixibat and in 2 patients (11.8%) who received placebo (proportion difference = 2.5%; 95% CI, −23.0% to 21.6%, for odevixibat versus placebo).

No patients discontinued treatment due to a TEAE. Interruptions and dose reductions due to TEAEs were reported in 3 patients (8.6%) and 1 patient (2.9%) in the odevixibat group, respectively; none of the patients in the placebo group had an interruption in dosing or a dose reduction due to TEAEs.

Diarrhea TEAEs were reported in 10 patients (28.6%) in the odevixibat group and 1 patient (5.9%) in the placebo group (proportion difference = 22.7%; 95% CI, −3.3% to 41.7%, for odevixibat versus placebo). No cases were rated as SAEs and none led to treatment discontinuation. Six patients (17.1%) in the odevixibat group and 1 patient (5.9%) in the placebo group met the criteria for clinically significant diarrhea (defined as 1 of the following: diarrhea with duration of 3 or more days without other etiology, diarrhea of grade 3 intensity or reported as an SAE, or diarrhea with concurrent dehydration requiring treatment with rehydration and/or other treatment intervention).

Critical Appraisal

The ASSERT study was a randomized, double-blind, placebo-controlled trial. No major sources of bias were identified by the CDA-AMC review team in the methods used to randomize and conceal allocation of patients to treatment groups. However, due to the small sample size (N = 52), there is an increased risk that prognostic balance was not achieved, as evidenced by imbalances in patients' baseline disease and demographic characteristics (age, sex, growth, medical and surgical history, time since diagnosis, extent of hepatic impairment, liver enzymes, and bilirubin levels). As such, it is possible that the observed effects were either overestimated or underestimated and may have been driven by prognostic differences between the 2 groups (i.e., may not be reflective of the true treatment effect). The extent of bias, however, is unclear. Although the trial was double-blind, patients who experienced diarrhea, a known adverse effect of IBAT inhibitors, may have been able to infer the treatment group to which they were assigned. Subjective outcomes like pruritus, HRQoL, and harms may be biased if treatment allocation is known or suspected. Given that diarrhea was reported more frequently in the odevixibat group than the placebo group (29% versus 6%, respectively), the possibility of reporting bias cannot be ruled out.

No major issues were identified by the CDA-AMC review team in the statistical methods used in the study. A multiple testing procedure was employed for the change from baseline in the PRUCISION ObsRO scratching score and sBA levels. The study assessed pruritus and HRQoL, which were identified as important outcomes based on patient and clinician input. The PRUCISION instrument used to assess pruritus and sleep-related outcomes was developed by the sponsor for patients with cholestatic liver diseases, including ALGS. The CDA-AMC review team noted that the instrument has not been validated externally, and has only been assessed within the sponsor's own trials and in a small number of patients. The sponsor estimated a 1.0-point to 1.5-point decrease in ObsRO scratching score as representing a clinically important within-patient change. However, no data were provided on the MID for between-group differences. Thus, the clinical relevance of the mean differences between groups in the change in ObsRO scratching score was difficult to assess. No MIDs were available for the pruritus responder analyses or individual sleep-related outcome measures.

HRQoL was evaluated using the PedsQL, which has evidence to support its validity, reliability, and responsiveness in pediatric patients with various chronic health conditions; however, the evidence in children

with liver diseases was limited. The sponsor relied heavily on proxy reports to assess HRQoL. There is evidence supporting the validity of using this proxy approach with the PedsQL in pediatric populations. Of note, however, there may be a difference between what the proxy thinks and what the child thinks with respect to HRQoL and symptoms. For the PedsQL total score analysis, [redacted] and [redacted] of patients were missing or excluded in the odevixibat and placebo groups, respectively. Given the magnitude of the missing data, the CDA-AMC review team considered this an important limitation of this outcome.

Change in sBA levels was a key secondary outcome in the trial. It has not yet been defined what sBA level or reduction can be associated with improved long-term outcomes in patients with ALGS. Thus, it is difficult to interpret the sBA level results given that the surrogate threshold effect is unclear.

According to the clinical experts consulted by CDA-AMC, the patients enrolled in the ASSERT study were consistent with pediatric patients with ALGS in Canada. The experts noted that some patients excluded from the trial may be treated with odevixibat in practice, such as those with ascites or those waiting for liver transplant, but overall, the patients enrolled were generalizable. The dose of odevixibat used in the study matched the product monograph. During the trial, patients were allowed to continue the standard antipruritic medications they had been receiving before randomization, which aligns with the anticipated use of odevixibat in practice. The clinical experts confirmed that the use of antipruritic co-interventions during the trial was consistent with clinical practice.

Limitations to the external validity include the relatively small sample size (N = 52) of the study, the focus on shorter-term end points, and the lack of head-to-head data with maralixibat. Liver transplant and mortality were identified as key clinical outcomes for patients with ALGS. While no deaths were reported and no patients underwent liver transplant during the 24-week study, the study was not designed to test the comparative effectiveness of odevixibat versus placebo for these end points. In addition, the lack of data for these key clinical outcomes is a limitation of the systematic review. The trial's sample size and duration were likely insufficient to assess the impact of odevixibat on patients' growth, or on safety, except for the most common TEAEs.

GRADE Summary of Findings and Certainty of the Evidence

For the RCT 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 the RCT started as high-certainty evidence and could be rated down for concerns related to study limitations (which refer 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. For the PRUCISION ObsRO and PRO, sBA levels, and harms, the

presence or absence of any (non-null) effect was used, and for the PedsQL, the target of the certainty of evidence assessment (presence or absence of an important effect) was based on thresholds identified in the literature.

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. Table 3 lists the key outcomes that were finalized in consultation with expert committee members.

Table 3: Summary of Findings for Odevixibat vs. Placebo for Patients With ALGS

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Odevixibat	Difference		
Pruritus outcomes							
LS mean CFB in the observer-reported scratching severity score (PRUCISION ObsRO)[a] Follow-up: 24 weeks	50 (1 RCT)	NA	−0.80 (SE = 0.23)	−1.69 (SE = 0.17)	−0.88 (95% CI, −1.44 to −0.33)	Low[b]	Odevixibat may result in a reduction in the ObsRO scratching severity score when compared with placebo.
LS mean CFB in the patient-reported itching severity score (PRUCISION PRO)[a] Follow-up: 24 weeks	15 (1 RCT)	NA	−1.58 (SE = 0.31)	−1.40 (SE = 0.21)	0.18 (95% CI, −0.65 to 1.00)	Low[c]	Odevixibat may result in little to no difference in the PRO itching severity score when compared with placebo.
HRQoL							
LS mean CFB in PedsQL Parent Report total score[d] Follow-up: 24 weeks	39 (1 RCT)	NA	10.72 (SE = 3.96)	13.50 (SE = 2.54)	2.78 (95% CI, −6.31 to 11.87)	Very low[e]	The evidence is very uncertain about the effect of odevixibat on the change in PedsQL Parent Report total score when compared with placebo.
sBA							
LS mean CFB in sBA (µmol/L)[f] Follow-up: 24 weeks	52 (1 RCT)	NA	22.4 (SE = 28.5)	−90.4 (SE = 21.3)	−112.7 (95% CI, −178.8 to −46.7)	Moderate[g]	Odevixibat likely results in a reduction in sBA levels when compared with placebo. The clinical importance of the decrease is unclear.
Other efficacy outcomes							
Liver transplant[h]	NR	NR	NR	NR	NR	—	There is no evidence to assess the effect of odevixibat on the need for liver transplant

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Odevixibat	Difference		
							when compared with placebo.
Mortality[h]	NR	NR	NR	NR	NR	—	There is no evidence to assess the effect of odevixibat on mortality when compared with placebo.
Harms							
Patients with any SAEs Follow-up: 24 weeks	52 (1 RCT)	RR 1.19 (95% CI, 0.26 to 5.45)	118 per 1,000	143 per 1,000	25 more per 1,000 (230 fewer to 216 more per 1,000)	Very low[i]	The evidence is very uncertain about the effect of odevixibat on SAEs when compared with placebo.
Patients with diarrhea TEAEs Follow-up: 24 weeks	52 (1 RCT)	RR 4.71 (95% CI, 0.67 to 33.15)	59 per 1,000	286 per 1,000	227 more per 1,000 (33 fewer to 417 more per 1,000)	Low[j]	Odevixibat may result in an increase in diarrhea TEAEs when compared with placebo. The clinical importance of the increase is unclear.

AE = adverse event; CDA-AMC = Canada's Drug Agency; CFB = change from baseline; CI = confidence interval; HRQoL = health-related quality of life; LS = least squares; NA = not applicable; NR = not reported; ObsRO = observer-reported outcome; PedsQL = Pediatric Quality of Life Inventory; PRO = patient-reported outcome; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; sBA = serum bile acid; SE = standard error; TEAE = treatment-emergent adverse event; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), 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]PRUCISION ObsRO scratching scores and PRO itching scores range from 0 (no itching or scratching) to 4 (worst itching or scratching). The estimates were based on the AM and PM scores combined, with baseline levels calculated as the average scores for the 14 days before the start of treatment, and 24-week results based on the average of scores between week 21 and 24.

[b]The ObsRO scratching score was rated down 2 levels for very serious concerns about imprecision. The sponsor identified a 1.0-point to 1.5-point decrease as the clinically important within-patient difference based on an analysis of data from the sponsor's own trials; however, no data were submitted for the between-group MID and the clinical experts consulted by CDA-AMC were unable to estimate a between-group threshold for clinically important effects. Given the uncertainty in the between-group MID, the null was used. The small sample size raises concern for potential overestimation of the true effect and there is evidence of prognostic imbalance. The potential for reporting bias was identified by the CDA-AMC review team. Due to the differential frequency of known AEs potentially leading to patients being able to infer their assigned treatment, and the subjectivity of the outcome, the possibility of reporting bias could not be ruled out; however, the outcome was not downrated due to this risk of bias.

[c]The PRO itching score was rated down 2 levels for very serious concerns about imprecision. No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. The small sample size raises concern for potential overestimation of the true effect and there is evidence of prognostic imbalance. The potential for reporting bias was identified by the CDA-AMC review team. Due to the differential frequency of known AEs potentially leading to patients being able to infer their assigned treatment, and the subjectivity of the outcome, the possibility of reporting bias could not be ruled out; however, the outcome was not downrated due to this risk of bias.

[d]The PedsQL is an HRQoL instrument that is scored from 0 to 100, with higher scores indicating better HRQoL. The data are based on parent-reported assessment.

[e]The PedsQL outcome was rated down 1 level due to serious concerns with risk of bias due to missing data. In addition, the potential for reporting bias, due to the differential frequency of known AEs, could not be ruled out. The outcome was rated down 2 levels due to very serious imprecision. The estimated within-group MID was 4.5 points based on the literature (no between-group MID was submitted by the sponsor). Based on the available within-group threshold, the 95% CI includes the potential for improvement, little to no difference, and worse HRQoL.

[f]The 24-week sBA levels were based on the average of week 20 and week 24 results. sBA levels were measured by a central laboratory and the results were concealed from study participants to maintain study blinding.

[g]sBA levels were rated down 1 level for serious concerns about imprecision. No published between-group MID was identified, and the clinical experts consulted by CDA-AMC 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 CDA-AMC review team rated it down only once.

[h]No patients died or required a liver transplant in either treatment group during the study. However, the trial was not designed (in sample size or in length of follow-up) to provide information on these outcomes.

[i]The risk of SAEs outcome was rated down 2 levels due to very serious imprecision. No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. Although the point estimate suggests an increase, the 95% CI includes the potential for both no difference and a decrease. The risk of SAEs outcome was rated down 1 level due to serious indirectness. The follow-up duration and sample size were insufficient to evaluate safety of the study drug except for common AEs that occur shortly after initiating treatment.

[j]The risk of diarrhea TEAEs outcome was rated down 2 levels due to very serious imprecision. No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. Although the point estimate suggests an increase, the 95% CI includes the potential for no difference and a decrease.

Source: Clinical Study Report for the ASSERT study; additional data supplied by the sponsor on April 28, 2025.

Long-Term Extension Studies

Description of Studies

The ASSERT-EXT study (N = 50) was a phase III, multicentre, open-label, long-term extension study designed to evaluate the long-term safety and efficacy of odevixibat 120 mcg/kg once daily in patients with ALGS. The study consisted of a 72-week primary treatment period, followed by a 4-week safety follow-up period. In the ASSERT-EXT study, eligibility criteria, intervention protocols, and evaluated outcomes were identical to those of the ASSERT RCT. Patients in the active treatment arm of the ASSERT RCT continued to be treated with odevixibat using the same dose and protocol (i.e., the continued-treatment group), and those receiving placebo were switched to odevixibat (i.e., the treatment-naive group). As in the ASSERT RCT, SOC antipruritic treatments were permitted in both groups.

Efficacy Results

ObsRO Scratching Severity

At weeks 69 to 72, PRUCISION ObsRO scratching score data were available for 28 patients (85%) and 13 patients (76%) in the odevixibat continued-treatment and treatment-naive groups, respectively. The mean change from baseline in ObsRO scratching severity score at weeks 69 to 72 was −0.54 (SD = 0.82) in the continued-treatment group and −1.66 (SD = 0.82) in the treatment-naive group.

From the baseline of the ASSERT trial, at weeks 69 to 72 of the ASSERT-EXT study, 93% of patients in the continued-treatment group had at least a 1.0-point reduction in scratching severity score and 73% had at least a 1.5-point reduction.

From the ASSERT-EXT study baseline, at weeks 69 to 72, 77% of patients in the treatment-naive group had at least a 1.0-point reduction in scratching severity score and 54% had at least a 1.5-point reduction; 23% of patients in the continued-treatment group had at least a 1.0-point reduction in scratching severity score and 10% had at least a 1.5-point reduction.

PRO Itching Severity

At weeks 69 to 72, PRUCISION PRO itching score data were available for 8 patients (67%) and 2 patients (33%) in the odevixibat continued-treatment and treatment-naive groups, respectively. The mean change from baseline in itching severity score at weeks 69 to 72 baseline was −0.50 (SD = 0.62) in the odevixibat continued-treatment group and −0.90 (SD = 0.14) in the treatment-naive group.

HRQoL Outcomes

For the PedsQL total score, data at week 72 were available for [redacted] patients and [redacted] patients in the continued-treatment and treatment-naive groups, respectively. Data were available for [redacted] patients and [redacted] patients in the continued-treatment and treatment-naive groups, respectively, for the Family Impact Module at week 72.

The mean change from baseline to week 72 in the PedsQL total score was [redacted] (SD = [redacted]) in the continued-treatment group and [redacted] (SD = [redacted]) in the treatment-naive group. For the Family Impact Module, the mean change from baseline in the continued-treatment group and treatment-naive group, respectively, was [redacted] (SD = [redacted]) and [redacted] (SD = [redacted]).

sBA Levels

The mean change from baseline to week 72 in sBA levels was −36.0 µmol/L (SD = 90.76) in the continued-treatment group and −138.6 µmol/L (SD = 101.17) in the treatment-naive group. At 72 weeks, sBA data were available for 30 patients (91%) in the continued-treatment group and 13 patients (76%) in the treatment-naive group.

Harms Results

Overall, [redacted] of patients in the ASSERT-EXT study experienced at least 1 TEAE, including [redacted] of patients in the continued-treatment group and all patients in the treatment-naive group. Across both groups, the most common TEAEs were [redacted]; [redacted]; [redacted]; and [redacted] and [redacted]. Most TEAEs were grade 1 or 2, with no grade 4 or 5 TEAEs. Treatment-emergent SAEs were reported in 22% of patients overall, including 12% of patients in the continued-treatment group and 41% of patients in the treatment-naive group.

As patients with ALGS are known to have multiple comorbidities, specific AEs of special interest included clinically significant diarrhea, new or worsening fat-soluble vitamin deficiency refractory to clinically recommended vitamin supplementation, potential sequelae of the deficiency, and hepatic events. Overall, [redacted] of patients had clinically significant diarrhea (most due to being more than 3 days in duration), although all were nonserious and assessed as grade 1 or 2; [redacted] had fat-soluble vitamin deficiency refractory to clinically recommended vitamin supplementation; [redacted] reported possible sequelae of fat-soluble vitamin deficiency; and [redacted] had liver-related TEAEs.

Overall, [redacted], and [redacted] and [redacted]. There were no deaths during the study period.

Critical Appraisal

The ASSERT-EXT study was a phase III, multicentre, open-label study to evaluate the long-term safety and efficacy of odevixibat in patients with ALGS. The open-label design could bias the magnitude of treatment effect for subjective efficacy outcomes (pruritus and HRQoL), and reporting of safety parameters due to

unblinded exposure to the study drug. The direction and magnitude of the potential biases remain unclear. In addition, the absence of statistical hypothesis testing and a control group (i.e., no active comparator or placebo arm) limits the ability to draw definitive conclusions on whether the observed effects can be attributed to natural history, the placebo effect, or effects of the drug.

The extension study consisted of patients who took part in the ASSERT study, and it is therefore reasonable to expect that the same strengths and limitations related to generalizability apply to the extension period. There were considerable data missing at week 72 for most efficacy outcomes in the continued-treatment and treatment-naive groups, [redacted] A complete case analysis was used, which assumes that the missing data were missing completely at random. As this assumption is unlikely to be reasonable, there is a risk of bias due to missing outcomes data for these efficacy outcomes. The magnitude and direction of the bias cannot be predicted.

Economic Evidence

Cost and Cost-Effectiveness

- Odevixibat is available as 200 mcg, 400 mcg, 600 mcg, and 1,200 mcg oral capsules (swallowed whole or sprinkled on food). At the submitted price of $175.92 per 200 mcg, $351.84 per 400 mcg, $527.77 per 600 mcg, and $1,055.55 per 1,200 mcg capsule, the annual cost of odevixibat is expected to range from $192,769 to $2,313,233 per patient depending on the patient's weight (i.e., 4.0 kg to > 55.5 kg), based on Health Canada–recommended dosages. The daily dose may be reduced to 40 mcg/kg/day if tolerability issues occur.
- Clinical efficacy in the economic analysis for odevixibat plus SOC was derived from the ASSERT trial, which suggested that odevixibat plus SOC may result in a reduction in caregiver-reported pruritus severity at 6 months compared with SOC alone for patients with cholestatic pruritus and ALGS. No indirect evidence comparing odevixibat to maralixibat, the main comparator, was submitted because a feasibility assessment conducted by the sponsor concluded an indirect treatment comparison was unlikely to provide robust results. The sponsor undertook an unadjusted, naive comparison of odevixibat and maralixibat. Therefore, the comparative efficacy and safety of odevixibat plus SOC relative to maralixibat plus SOC is unknown.
- The results of the CDA-AMC base case suggest the following:
  - Odevixibat plus SOC will be associated with higher costs to the health care systems than SOC alone (incremental costs = $14,171,485), primarily driven by increased drug acquisition costs associated with odevixibat.

    - Odevixibat plus SOC is predicted to be associated with a gain of 2.85 life-years compared to SOC alone. When the impact on HRQoL is also considered, odevixibat plus SOC is predicted to result in a gain of 2.50 quality-adjusted life-years (QALYs) compared to SOC alone.
    - The ICER of odevixibat plus SOC compared to SOC alone was $5,678,772 per QALY gained in the CDA-AMC base case. The estimated ICER was highly sensitive to dosing assumptions, such as the distribution of patients across different dose levels and the associated caregiver burden captured using disutility.
- Given the lack of direct comparative evidence and limitations with the sponsor's submitted naive comparison of odevixibat and maralixibat, there is insufficient evidence to justify a price premium for odevixibat plus SOC compared to maralixibat plus SOC.
- CDA-AMC estimates that the budget impact of reimbursing odevixibat plus SOC for the treatment of cholestatic pruritus in patients with ALGS will be approximately $211 million over the first 3 years of reimbursement compared to the amount currently spent on SOC alone, with an estimated expenditure of $212 million on odevixibat plus SOC over this period. The actual budget impact of reimbursing odevixibat plus SOC will depend on the dosing of odevixibat in clinical practice and reimbursement status of maralixibat, as the CDA-AMC estimate is based on the currently available situation, in which maralixibat is not funded. 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.
- At the time of writing, maralixibat was not listed by public drug plans in Canada and is under active pan-Canadian Pharmaceutical Alliance (pCPA) negotiations for the treatment of cholestatic pruritus in patients aged 12 months or older with ALGS.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Ran Goldman, 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: July 23, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.