6.10 ODEVIXIBAT,
Capsule 200 micrograms,
Capsule 400 micrograms,
Capsule 600 micrograms,
Capsule 1200 micrograms
Bylvay®,
Ipsen PTY LTD.

1 Purpose of submission

1.1 The Category 2 submission requested a Section 85, Authority Required, Restricted Benefit listing for odevixibat for the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged six months and older.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard of care (SoC) including biliary diversion surgery (SBD) and liver transplant (LT).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with cholestatic pruritus in Alagille Syndrome (ALGS).
Intervention	Odevixibat 120 µg/kg administered orally once daily in the morning. Dose reduction to 40 µg/kg/day may be considered if tolerability issues occur in the absence of other causes.
Comparator	Standard of care (SoC) including biliary diversion surgery (SBD) and liver transplant (LT).
Outcomes	Pruritus response, serum bile acid (sBA) response, sleep parameters, growth parameters, quality of life and safety.
Clinical claim	Superiority in terms of efficacy (pruritus response, sBA response and sleep parameters). Non-inferiority in terms of safety.

Source: Table 1-1, p14, p24 and p105 of the submission.

2 Background

Registration status

2.1 Odevixibat is not Therapeutic Goods Administration (TGA) registered for the treatment of ALGS. The submission was made under the TGA/Pharmaceutical Benefits Advisory Committee (PBAC) Parallel Process. The application has been submitted under the Comparable Overseas Regulator (COR) pathway. However, at the time of evaluation, confirmation of the acceptability of inclusion within the COR pathway was pending. This confirmation, along with the evaluation plan (including expected time frames for related TGA documents), and outcome of the first-round evaluation was not available at the time of PBAC consideration.

2.2 Odevixibat was TGA registered in March 2025 for the treatment of Progressive Familial Intrahepatic Cholestasis (PFIC) in patients aged six months or older and was

recommended by the PBAC for the treatment of PFIC at the July 2025 PBAC meeting and listed on the PBS on 1 January 2026. Odevixibat is orphan drug designated for the treatment of ALGS and PFIC.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Max. qty packs	Max. qty units	№. of Rpts	DPMQ	Available brands
Odevixibat 200 micrograms capsules bottle	12	360	5	Published: $67,122.93 Effective: $[redacted]	Bylvay
Odevixibat 400 micrograms capsules bottle	6	180	5	Published: $67,122.93 Effective: $[redacted]	Bylvay
Odevixibat 600 micrograms capsules bottle	12	360	5	Published: $201,042.93 Effective: $[redacted]	Bylvay
Odevixibat 1200 micrograms capsules bottle	6	180	5	Published: $201,042.93 Effective: $[redacted]	Bylvay

Source: Table 1-9, p36 of the submission

Abbreviations: DPMQ = dispensed price per maximum quantity

[a] In Table 1-9 of the submission, the maximum quantity of units was shown to be 30, which was the number of units per pack.

Initial

Category / Program: Section 85 – General Schedule
Restriction type: ☒Restricted benefit ☒Authority Required (in writing only via post/HPOS upload or Online PBS Authorities system)
Indication: The treatment of cholestatic pruritus in Alagille syndrome (ALGS)
Treatment Phase: Initial
Clinical criteria: Patient must not have received prior PBS-subsidised treatment with this drug for this condition AND Patient must have a clinical diagnosis of ALGS AND The patient must have elevated serum bile acids at treatment initiation with this drug AND Patient must be experiencing itch at treatment initiation with this drug, with other factors causing pruritus excluded through both:(i) physical examination and (ii) patient history AND Patient must have had an average pruritus score of ≥2 on the Prucision™ ObsRO Pruritus Scale assessed on three occasions over a one-week period prior to treatment initiation with this drug.
Treatment criteria: Must be treated by a specialist experienced in the management of ALGS, who is either a: (i) gastroenterologist, (ii) hepatologist
Population criteria: Patient must be aged 6 months or older
Prescribing Instructions: The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include: (1) details of the pruritus score using the Prucision™ ObsRO Pruritus scale (2) details of serum bile acids (date and micromol/L)
Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) details of the proposed prescription; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
Prescribing Instructions: Prescriber must exclude any other causes of pruritus which include any of the following: (i) drug related (e.g., opioid-related pruritus) (ii) drug hypersensitivity or adverse effect; contact dermatitis; allergy (iii) differential diagnoses (e.g., xerosis; infestations; iron deficiency; chronic kidney disease; polycythaemia vera/leukemia/lymphoma; hypothyroidism; uncontrolled diabetes, eczema, scabies).
Prescribing Instructions: At the time of the authority application, the prescriber should request the appropriate strength(s) and quantity based on the patients' weight, according to the dosing schedule in the TGA approved Product Information to provide sufficient drug for one month's supply with 5 repeats. A separate authority approval is required for each strength requested
Prescribing Instructions: All diagnostic reports/tools must be documented in the patient's medical records.
Prescribing Instructions: Eligible patients must not be recommencing treatment directly through this treatment phase
Patients who have demonstrated an adequate clinical response and have ceased treatment for reasons other than a lack of response may recommence treatment through the continuing treatment phase.

Administrative Advice:
The Prucision™ ObsRO Pruritus Scale is available as a downloadable document at: Prucision ™ ObsRO Pruritus Scale

Grandfather arrangements:

Category / Program: Section 85 – General Schedule
Restriction type: ☒Restricted benefit ☒Authority Required (in writing only via post/HPOS upload or Online PBS Authorities system)
Indication: The treatment of cholestatic pruritus in Alagille syndrome (ALGS)
Treatment Phase: Grandfather
Clinical criteria: Patient must not have received prior PBS-subsidised treatment with this drug for this condition AND Patient must have a clinical diagnosis of ALGS AND The patient must have elevated serum bile acids at treatment initiation with this drug or maralixibat AND Patient must have been experiencing itch at treatment initiation with this drug or maralixibat with other factors causing pruritus excluded through both:(i) physical examination and (ii) patient history AND Patient must have had an average pruritus score of ≥2 on the Prucision™ ObsRO Pruritus Scale prior to initiation of treatment initiation with this drug or maralixibat AND Patient must have demonstrated an adequate clinical response to the most recent course of treatment with this drug or maralixibat
Treatment criteria: Must be treated by a specialist experienced in the management of ALGS, who is either a: (i) gastroenterologist, (ii) hepatologist
Population criteria: Patient must be aged 6 months or older
Prescribing Instructions: An adequate clinical response under this treatment phase is defined as maintenance of an average ≥1 grade improvement in pruritus score, versus baseline measurement, on the Prucision™ ObsRO Pruritus Scale, assessed on 3 occasions over a one-week period prior to assessment of response
Prescribing Instructions: The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include: (1) details of the pruritus score using the Prucision™ ObsRO Pruritus scale (2) details of serum bile acids (date and micromol/L)
Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) details of the proposed prescription; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
Prescribing Instructions: Prescriber must exclude any other causes of pruritus which include any of the following: (i) drug related (e.g., opioid-related pruritus) (ii) drug hypersensitivity or adverse effect; contact dermatitis; allergy (iii) differential diagnoses (e.g., xerosis; infestations; iron deficiency; chronic kidney disease; polycythaemia vera/leukemia/lymphoma; hypothyroidism; uncontrolled diabetes, eczema, scabies).

Prescribing Instructions: At the time of the authority application, the prescriber should request the appropriate strength(s) and quantity based on the patients' weight, according to the dosing schedule in the TGA approved Product Information to provide sufficient drug for one month's supply with 5 repeats. A separate authority approval is required for each strength requested
Prescribing Instructions: All diagnostic reports/tools must be documented in the patient's medical records.
Prescribing Instructions: Eligible patients must not be recommencing treatment directly through this treatment phase
Patients who have demonstrated an adequate clinical response and have ceased treatment for reasons other than a lack of response may recommence treatment through the continuing treatment phase.
Administrative Advice:
The Prucision™ ObsRO Pruritus Scale is available as a downloadable document at: Prucision ™ ObsRO Pruritus Scale

Continuing:

Category / Program: Section 85 – General Schedule
Restriction type: ☒Restricted benefit ☒Authority Required (telephone/online PBS Authorities system)
Indication: The treatment of cholestatic pruritus in Alagille syndrome (ALGS)
Treatment Phase: Continuing
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must have demonstrated an adequate clinical response to the most recent course of treatment
Treatment criteria: Must be treated by a specialist experienced in the management of ALGS, who is either a: (i) gastroenterologist, (ii) hepatologist OR Must be treated by a medical practitioner under the supervision of a specialist experienced in the management of ALGS
Population criteria: Patient must be aged 6 months or older
Prescribing Instructions: An adequate clinical response under this treatment phase is defined as an average ≥1 grade improvement in pruritus score, versus baseline measurement, on the Prucision™ ObsRO Pruritus Scale, assessed on 3 occasions over a one-week period prior to assessment of response.
Prescribing Instructions: Dose reduction to 40 µg/kg/day may be considered if tolerability issues occur in the absence of other causes. Once tolerability issues stabilize, increase to 120 µg/kg/day
Administrative Advice:
The Prucision™ ObsRO Pruritus Scale is available as a downloadable document at: Prucision ™ ObsRO Pruritus Scale
Administrative Advice:
Patients who have demonstrated an adequate clinical response and have ceased treatment for reasons other than a lack of response may recommence treatment through the continuing treatment phase.

3.1 The proposed effective pricing was the same as the approved effective price for PFIC (approved ex- manufacturer price per 30 capsule pack $[redacted] for 200 mcg, $[redacted] for 400 mcg, $[redacted] for 600 mcg and $[redacted] for 1,200 mcg). However, the recommended odevixibat dosage for patients with ALGS is 120 µg/kg/day (with de-escalation to 40 µg/kg/day if

tolerability issues) compared to 40 µg/kg/day (with escalation to 120 µg/kg/day in the case of inadequate response) for patients with PFIC. The ESC considered that the restrictions should allow patients who demonstrate an adequate clinical response (via ObsRO score) at a dose lower than 120mcg/kg/day to continue treatment at that lower dose.

3.2 The requested listing for initial treatment for ALGS, with five repeats, differed to the odevixibat initial listing for the treatment of PFIC with two repeats, suggesting a three-month initial course of treatment for PFIC.

3.3 The proposed restriction did not require genetic testing as a requirement for initial treatment. This was inconsistent with the clinical management algorithm, and the inclusion criteria for ASSERT which required a genetically confirmed diagnosis. The ESC considered that confirmed genetic test results should not be a prerequisite for treatment as obtaining results in Australia can take several months. The PBAC considered that genetic test results are not required for the initial restriction criteria.

3.4 The requested listing for initial treatment included a clinical criterion of elevated serum bile acids (sBAs), with no minimal level of elevation specified. This was consistent with the odevixibat initial listing for the treatment of PFIC. The Pre-Sub-Committee Response' (PSCR) considered that (as accepted with PFIC listing), "elevated SBAs with significant pruritus appropriately defined the eligible patient population". Further, the PSCR (table 1) noted "the goal of therapy is relief of pruritus and therefore SBA measure are not appropriate measures to assess efficacy".

3.5 The requested listing for initial treatment did not exclude patients with prior LT, consistent with the odevixibat listing for the treatment of PFIC. However, this was inconsistent with the clinical trial evidence from ASSERT, in which patients were excluded if they had SBD within six months prior to screening or prior LT or planned LT within six months of randomisation.

3.6 An adequate clinical response was defined as an average ≥1 grade improvement in the observer-reported outcome (ObsRO) pruritus scratching scale, versus baseline measurement, assessed on three occasions over a one-week period prior to assessment of response. The ObsRO Pruritus (scratching) scale has been previously considered by the PBAC for the odevixibat submission for the treatment of PFIC. The PBAC previously noted that "the clinical experts considered that the ObsRO Pruritus Scale was an appropriate tool to measure response to treatment." (paragraph 13.2, odevixibat Public Summary Document [PSD], March 2025 PBAC Meeting with Addendum July 2025). The PBAC reiterated its previous concern regarding the validation of the ObsRO (paragraph 7.8, odevixibat PSD, July 2024 PBAC meeting).

3.7 The Secretariat noted that assessment of response was required only for the first continuing prescription when a patient transitions from initial to continuing treatment, but was not specified for each subsequent continuing script.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 ALGS is a rare autosomal dominant disorder caused by defects in the Notch signalling pathway, primarily characterised by hepatic involvement manifesting as cholestasis (reduced flow of bile from the liver) with variable extrahepatic clinical features. Hepatic manifestations range from mild cholestasis to progressive liver failure and usually include severe pruritus. Extrahepatic features are highly variable and include cardiac defects, renal abnormalities, skeletal malformations, vascular abnormalities, and ophthalmologic manifestations. The ESC noted odevixibat does not impact on extrahepatic features of AGLS. The submission emphasised the significant morbidity associated with pruritus, including skin lesions, pruritic self-mutilation, scarring, sleep disruption, chronic debilitating fatigue, and a negative impact on physical and psychosocial health.

4.2 In ALGS, disrupted Notch signalling is associated with abnormal development of intrahepatic bile ducts, resulting in malformed and narrowed or a paucity of bile ducts and chronic cholestasis in the majority of patients. Paucity of bile ducts often appears to be progressive, observed in 60% of biopsies from patients aged less than 6 months, and ~95% those aged 6 months and older[1]. The evaluation noted that progression may not occur in all cases. Infants with ALGS and substantial cholestasis may have either spontaneous improvement, progression to end-stage liver disease, or persistent symptomatic cholestasis. Mouzaki 2016[2] reports that the potential to have mild hepatic outcomes later in life despite cholestasis during the first few years of life should be considered in decision-making regarding evaluation for LT or surgery for the treatment of pruritus. No well validated prognostic marker is described in the literature which could effectively predict which patients will develop chronic liver failure, versus an indolent course. Similarly, no genotypic, histological, or radiological predictive markers have been developed to confidently predict the severity of liver disease.

4.3 Mutations in two genes associated with Notch signalling pathways are known to cause ALGS: JAG1 (encoding the jagged canonical Notch ligand 1, or Jagged1) in the majority (>90%[3]) of ALGS cases; and NOTCH2 (encoding the Notch2 receptor) being second most common (5%). Jagged1 and Notch2 are both single-pass transmembrane proteins; direct communication between the two proteins occurs via interaction of the extracellular domain of JAG1 (ligand) with NOTCH2 (receptor).

[1] Singh SP, Pati GK. Alagille Syndrome and the Liver: Current Insights. Euroasian J Hepatogastroenterol, 2018;8(2):140-147
[2] Mouzaki et al. Early life predictive markers of liver disease outcome in an International, Multicentre Cohort of children with Alagille syndrome. Liver Int. 2016 May;36(5):755-60. doi: 10.1111/liv.12920.
[3] Zhou et al. (2022) Notch signalling pathway: architecture, disease, and therapeutics. Signal Transduct Target Ther, 7, 95.

4.4 Diagnosis of ALGS is supported by genetic testing for mutations in JAG1 or NOTCH2. However, a small portion of patients fulfilling the classic clinical criteria for ALGS do not appear to have either a mutation or deletion involving JAG1 or NOTCH2[4], and conversely, the presence of mutations in these genes often doesn't result in clinical presentation of ALGS. A study by Kamath 2003[5] of 53 mutation positive relatives aged 5 to 66 years of 34 ALGS probands (mean age 14 years) found that only eleven of 53 (21%) mutation positive relatives had clinical features that would have led to a diagnosis of ALGS. The submission claimed results from genetic evaluations in Australia can take two to six months, and that 'haematologist' [or hepatologist] advisors at a recent advisory board concurred that whilst they always perform such genetic tests as they are informative (especially in relation to undiagnosed family members), they do not wait for results for diagnosis or commencement of treatment. The submission did not provide any evidence regarding the overall reliability of diagnosis of ALGS or the diagnostic test methods used.

4.5 The submission claimed that in Australia, the diagnosis of ALGS in children is typically made by paediatric hepatologists, particularly when children present with cholestasis. The submission stated that diagnoses in adults are considerably less frequent and generally occur when patients present to 'haematologists' [or hepatologists] with hepatic symptoms. The PBAC noted that AGLS may occasionally be identified in adulthood in some individuals who are completely asymptomatic.

4.6 The Global ALagille Alliance (GALA) study (Vandriel 2022); a retrospective review of 1,433 patients with ALGS across 67 paediatric centres from 29 countries represents the largest and most recent analysis of ALGS natural history, reporting:

- Median age of diagnosis was 4.1 years (IQR 1.5 – 8.3) (Vandriel 2022[6]).
- Liver involvement was observed in 95% (n=1321/1387) of children, and 85% (n=1184/1387) presented with neonatal cholestasis. Pruritus was reported in 74% (n=761/1028), with median age of onset at 12 months. The Sponsor's advisory board survey indicated that the age of diagnosis is unclear, as it depends on the presenting features.
- Overall survival at 5, 10 and 18-years was 92.8%, 91.2%, and 88.1%, respectively.

[4] Turnpenny 2012. Alagille syndrome: pathogenesis, diagnosis and management. European Journal of Human Genetics (2012) 20, 251–257. doi:10.1038/ejhg.2011.181

[5] Kamath BM, Bason L, Piccoli DA, Krantz ID, Spinner NB. Consequences of JAG1 mutations. J Med Genet. 2003 Dec;40(12):891-5. doi: 10.1136/jmg.40.12.891.

[6] Vandriel et al. Global ALagille Alliance (GALA) Study Group. Natural history of liver disease in a large international cohort of children with Alagille syndrome: Results from the GALA study. Hepatology. 2023 Feb 1;77(2):512-529. doi: 10.1002/hep.32761.

- Median age of death was 2.6 years (1.2 – 4.7), due to liver and cardiac complications (22% and 18%, respectively), multi-organ failure (15%), and non-cardiac vascular complications (15%).
- Native liver survival (defined as either LT or death) in patients with a history of neonatal cholestasis at 5, 10 and 18-years was 66.8%, 54.4% and 40.3%, respectively.

4.7 There is scarce epidemiology data on ALGS. The submission claimed many sources give a figure of 1/70,000 births which goes back to a large study from Victoria, Australia (Danks 1977) of 790,385 children born in Victoria during 1963-1974. The Alagille Syndrome Alliance (ALGSA) reports the current estimated incidence of ALGS is between 1/30,000 and 1/70,000 with no difference in gender.

4.8 Odevixibat is a reversible, potent, selective inhibitor of the ileal bile acid transporter (IBAT), also identified as the apical sodium-dependent bile acid transporter (ASBT). Odevixibat acts locally in the distal ileum to decrease the reuptake of bile acids and increase the clearance of bile acids through the colon, reducing the concentration of bile acids in the serum.

4.9 The submission noted that the European Association for the Study of the Liver (EASL) guidelines[7] recommend that, when available, IBAT inhibitor treatment should be offered to ALGS patients with cholestatic pruritus.

4.10 Odevixibat will not replace any TGA approved and/or PBS-listed medicines. The submission's proposed clinical algorithm includes odevixibat as an additional first-line treatment for ALGS, either with or without medicines commonly used off-label such as ursodeoxycholic acid (UDCA) and rifampicin. The submission claimed odevixibat will not replace surgical procedures, according to the proposed clinical algorithm. The submission however claimed that treatment with odevixibat is expected to potentially delay or prevent LT in patients who might otherwise progress to cirrhosis or end stage liver disease. However, the incidence of SBD or LT was not an outcome in the odevixibat ASSERT trial or its extension study, ASSERT-EXT.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated SoC as the comparator, including medicines used off-label (UDCA, rifampicin and cholestyramine) and surgical procedures (SBD and LT), which are also proposed to be used alongside odevixibat in Australian clinical practice (see paragraph 4.10). The evaluation noted that this was similar to the nominated SoC comparator in the PFIC submission (i.e. off-label UDCA and rifampicin, and LT and

[7] Verkade, Henkjan J. et al. EASL Clinical Practice Guidelines on genetic cholestatic liver diseases. Journal of Hepatology, Volume 81, Issue 2, 303 - 325

SBD). The evaluation considered that the nominated comparator of SoC was reasonable, however, the comparative clinical evidence did not include patients with SBD or previous or planned LT. Also, cholestyramine was not permitted as an off-label medication in ASSERT and ASSERT-EXT, though EASL clinical practice guidelines note marginal efficacy in ALGS[8]. Medications including UDCA, rifampicin, antihistamines, and topical treatments were permitted in ASSERT.

5.2 LT is an effective treatment option for ALGS and is required by many patients experiencing disease progression despite treatment. The primary indications of LT in ALGS are multifactorial but can be broadly classified as end-stage liver disease (owing to progressive cholestasis or portal hypertension) or intractable pruritus. The 2025 Australia and New Zealand Liver and Intestinal Transplant Registry (ANZLITR 2025) reported that in 1,168 paediatric patients who underwent their first LT in Australia or New Zealand up to December 2023, the primary diagnosis was ALGS in 44 (3.8%) patients, and one additional patient had ALGS as a secondary diagnosis. ALGS was also a primary diagnosis in 11 of 6,135 adults that underwent first LT (0.2%).

5.3 The submission stated it should be recognised that LT is a complicated surgery associated with significant risks including infection and rejection and is not always curative. ANZLITR 2025 reported a 1-year and 5-year post LT survival rate of 91.0% at both timepoints for ALGS patients (N=44). Though patients with previous LT were excluded from ASSERT, there have been case series of IBAT inhibitors (including odevixibat) in patients after LT.

5.4 The submission claimed that Australian clinical experts reported SBD is rarely practiced in Australian patients with ALGS, owing to poor acceptance of such a procedure in a very young patient group. In the GALA study, SBD was reported in 5% (n=56/1184) of children with ALGS, at a median age of 2.4 years (IQR 1.9 – 4.4; n=53).

5.5 Maralixibat is an IBAT inhibitor approved by the FDA in September 2021 for use in the treatment of cholestatic pruritus in ALGS patients aged ≥1 year old. Maralixibat was later granted marketing authorisation by the European Commission in December 2022. To the Sponsor's knowledge, maralixibat has not been submitted to the TGA for evaluation and as such is not considered as a near market comparator in this submission. The evaluation noted that maralixibat is referred to in the proposed grandfather restriction.

For more detail on PBAC's view, see section 7 PBAC outcome.

[8] Verkade, Henkjan J. et al. EASL Clinical Practice Guidelines on genetic cholestatic liver diseases. Journal of Hepatology, Volume 81, Issue 2, 303 - 325

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer input

6.2 The PBAC noted and welcomed input from health professionals (4), medical organisations (1) and consumer organisations (1) via the Office of Health Technology Assessment Consultation Hub, describing the burden of cholestatic pruritus in ALGS, emphasising that persistent, severe itch can dominate daily life, impair sleep, schooling, development, family functioning and mental health, and is a common reason children are listed for liver transplantation despite not yet having liver failure. Input from healthcare professionals considered that current therapies are ineffective, and that odevixibat is "game-changing", with the potential to improve long-term NLS, profound effects of pruritis and the equity gap in access to therapies between adults and children.

6.3 The PBAC noted advice from the National Paediatric Medicines Forum (NPMF) which highlighted the significant unmet need, and early evidence supporting odevixibat's benefit in reducing pruritus and SBAs. The NPMF advised that existing treatments for cholestatic pruritus offer minimal benefit, and that odevixibat has the potential to avoid liver transplantation in children where refractory pruritus is the primary reason for transplant listing. The PBAC also noted the Liver Foundation's view that relieving severe itch would allow children with ALGS to better engage in normal life, and that access would reduce the burden on families. Input suggested that access to odevixibat would offer meaningful relief and improve quality of life for both patients and carers.

6.4 The PBAC considered that input was informative to understanding the natural history of disease and progression.

Clinical studies/trials

6.5 The submission was based on one head-to-head Phase 3 randomised trial, ASSERT, comparing odevixibat to placebo, in addition to the 72-week open-label extension study (ASSERT-EXT). The submission also presented a pooled analysis of ASSERT and ASSERT-EXT data.

6.6 Details of the trial and extension study presented in the submission are provided in Table 2.

Table 2: Trials/studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ASSERT NCT04674761	Clinical Study Report (A4250-012) Ovchinsky N, et al. Efficacy and safety of odevixibat in patients with Alagille syndrome (ASSERT): a phase 3, double-blind, randomised, placebo-controlled trial. (2024) Ovchinsky, N, et al. Efficacy and Safety Outcomes with Odevixibat Treatment: Pooled Data from the Phase 3 ASSERT and ASSERT-EXT Studies in Patients with Alagille Syndrome. (2023) Ovchinsky, N, et al. Fat-soluble vitamin levels in patients with Alagille syndrome treated with odevixibat in the phase 3 assert study (2023) Ovchinsky, N, et al. Changes in hepatic parameters in patients with Alagille syndrome treated with odevixibat: pooled data from the phase 3 ASSERT and ASSERT-EXT studies. (2023)	Clinical Study Report Lancet Gastroenterol Hepatol. 2024 Jul;9(7):632-645 Journal of hepatology. 2023. 78: S965–S966. The Liver Meeting AASLD. Poster 4615-C Journal of pediatric gastroenterology and nutrition. 2023b. 77(1), S256-S257
ASSERT-EXT NCT05035030	Clinical Study Report (A4250-015) Ovchinsky, N, et al. Poster 2599: ASSERT-EXT: final data from an open-label, phase 3 study of odevixibat in patients with Alagille syndrome. (2024)	Clinical Study Report 2024b. The Liver Meeting, San Diego, California, Nov 15-19, 2024.

Source: Table 2-3, p45 of the submission.

6.7 The key features of the direct randomised trial and extension study are summarised in Table 3.

Table 3: Key features of the included evidence

Trial/Study	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
ASSERT	ODX = 35 Placebo = 17	R,DB, MC 24 weeks	Low	Genetically confirmed ALGS (any age) with significant pruritus and elevated sBA	Pruritus score[a] (primary), sBA levels, sleep parameters, growth parameters, QoL, Safety	Treatment response rate, responder/non-responder utility
ASSERT-EXT	ODX/ODX = 33 PBO/ODX = 17	SA, OL 72 weeks	High	Patients rolled over from ASSERT [b]	Pruritus score[a] (primary), sBA levels, sleep parameters, QoL, Safety	Discontinuation

Source: Compiled from Section 2 of the submission

Abbreviations: DB = double blind; MC = multi-centre; ODX = odevixibat; OL = open label; PBO = placebo; QoL = quality of life; R = randomised; SA = single arm; sBA = serum bile acids

[a] Change from baseline in average AM and PM scratching severity (pruritus) scores as measured by the observer-reported outcomes (ObsRO) caregiver instrument

[b] ASSERT-EXT (N=50) recruited patients who rolled over from ASSERT, both odevixibat-treated patients (defined as the ODX/ODX group, N=33) and placebo (PBO) patients (defined as the PBO/ODX, group, N=17).

6.8 ASSERT provided information regarding the comparative efficacy of odevixibat with the nominated comparator of SoC over 24 weeks.

6.9 The evaluation considered ASSERT had a low risk of bias overall, however the reliability of the observer-reported outcome (ObsRO) pruritus scratching severity score, which was used to measure the primary outcome was uncertain. The submission claimed

that the assessment of reliability, validity, and sensitivity to change were established through the analysis of the final data from ASSERT.

6.10 In addition, the evaluation considered it may not be reasonable to have used data from ASSERT to validate results from the same trial. The same concern was noted in regard to the July 2024 PFIC submission, in which the ESC noted it was not appropriate that the data from PEDFIC 1 (the key trial) be used to validate results from the same trial with no independent validation (paragraph 6.22, odevixibat PSD, July 2024 PBAC Meeting).

6.11 The PBAC previously noted concern that the ObsRO Pruritus (scratching) Scale was highly variable and may not provide a meaningful measure, particularly in terms of assessment of response for continuing therapy (paragraph 11.1, odevixibat PSD, March 2025 PBAC Meeting with Addendum July 2025).

6.12 ASSERT-EXT was a single arm, open-label study and was considered at high risk of bias. Of the 17 patients treated with placebo who rolled over into ASSERT-EXT (defined as the PBO/ODX group), four (23.5%) discontinued early from the extension study. In comparison, 6.1% (2/33) of patients treated with odevixibat in ASSERT (defined as the ODX/ODX group) discontinued early from the extension study. Reasons for early treatment discontinuation included adverse event (n=1), withdrawal of consent (n=1), caregiver did not think the study medication was working (n=1); switched medications (n=1); underwent LT (n=1); and one patient whose family withdrew consent due to patient's itchiness.

Comparative effectiveness

Change in pruritus scratching severity score (ObsRO instrument)

6.13 Results for the ASSERT primary endpoint, the mean change in ObsRO pruritus scratching severity scores from baseline over the 24-week treatment period is shown in Table 4. The proposed minimal clinically important difference (MCID) for change in the ObsRO scratching severity score in ALGS was defined as a decrease between 1.0 and 1.5 points.

6.14 Based on the mixed-effect model for repeated measures (MMRM), the least square (LS) mean change from baseline to Weeks 21-24 in the ObsRO pruritus scratching severity score was -1.69 and -0.80 in the odevixibat and placebo groups, respectively. The LS mean difference of -0.88 (95% CI: -1.44, -0.33) between the groups was statistically significant (two-sided p = 0.00242). The submission did not specify a between-group MCID. Therefore, while statistically significant, the evaluation considered it difficult to determine whether there was a clinically meaningful difference in scratching between the groups. The PSCR argued that, although no between-group MCID was formally established, the proposed within-patient MCID reflects clinically meaningful improvement. The PBAC considered that, although the

between group LS mean difference (-0.88) did not meet the within-individual MCID, it still likely represented a clinically important difference.

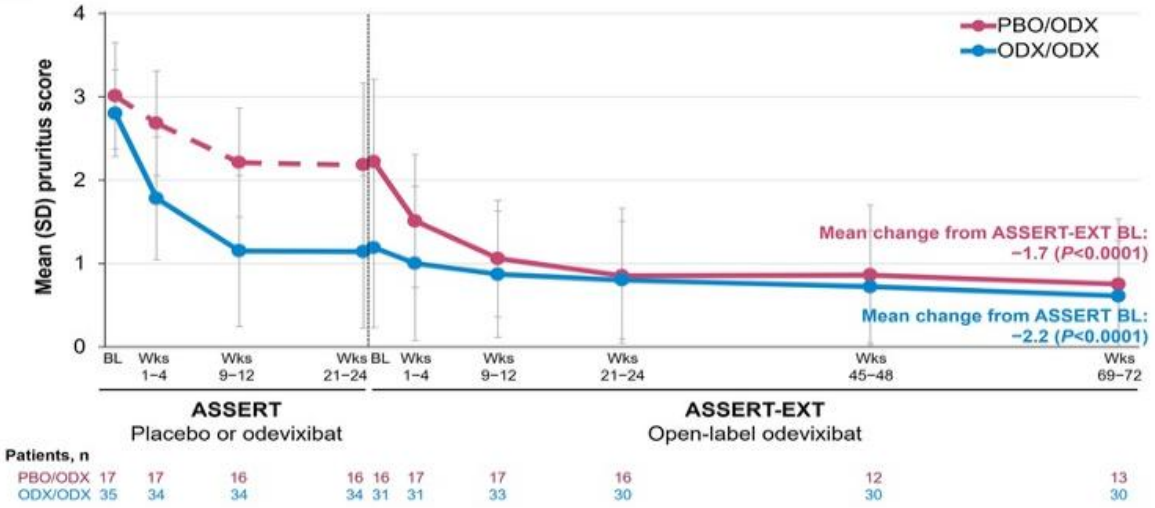
6.15 The mean change in the ObsRO pruritus scratching score from the ASSERT baseline to the end of the ASSERT-EXT treatment period is shown in Figure 1.

Table 4: Pruritus scratching score (ObsRO, morning and evening combined): Baseline, Weeks 21-24, and Change at Weeks 21-24 – ASSERT FAS

	ObsRO pruritus (scratching) score	
Visit Statistic	**Placebo (N=17)**	**Odevixibat (N=35)**
Baseline		
n	17	35
Mean (SD)	3.01 (0.64)	2.80 (0.52)
Median	3.18	2.71
Minimum, maximum	2.1, 4.0	1.9, 4.0
Average of Weeks 21-24		
n	16	34
Mean (SD)	2.18 (0.98)	1.14 (0.91)
Median	2.17	0.99
Minimum, maximum	0.7, 4.0	0.0, 3.0
Change from Baseline to Month 6 (Weeks 21-24)		
n	16	34
Mean (SD)	-0.76 (0.82)	-1.66 (0.97)
Median	-0.65	-1.59
Minimum, maximum	-2.3, 0.7	-3.3, 0.7
LS Mean (SE) [a]	-0.80 (0.23) 95% CI (-1.27, -0.33)	-1.69 (0.17) 95% CI (-2.04, -1.34)
LS Mean Difference (SE) (odevixibat-placebo) [a]	**-0.88 (0.28)** **95% CI (-1.44, -0.33), p=0.00242 [b]**	

Source: Table 2-20, p69 of the submission, Table 23, ASSERT CSR
CI = confidence interval; FAS = full analysis set; LS = least square; MMRM = mixed-effect model for repeated measures; ObsRO = observer-reported outcomes; SD = standard deviation; SE = standard error of the mean.
[a] The analysis is based on a MMRM using a restricted maximum likelihood with baseline score as a covariate, and baseline age stratification, baseline direct bilirubin, treatment group, time (in months), and treatment-by-time interaction as fixed effects. Unstructured covariance matrix is used in the analysis. The Kenward-Roger approximation is used to estimate denominator degrees of freedom.
[b] 2-sided p-value is presented.

Figure 1: Mean change in pruritus scratching score (ObsRO) from ASSERT baseline (Baseline 1) during ASSERT and ASSERT-EXT (FAS)



Source: Figure 2-9, p71 of the submission
Abbreviations: BL = baseline; FAS = full analysis set; ODX/ODX = received odevixibat in ASSERT and ASSERT-EXT; PBO/ODX = received placebo in ASSERT and odevixibat in ASSERT-EXT; wk = week.
Dashed pink line indicates period of placebo administration in ASSERT. Error bars represent standard deviations (SDs). Values shown for ASSERT time points represent data from all ASSERT patients with available data at the indicated time point (odevixibat, n=35; placebo, n=17); values shown for ASSERT-EXT time points represent only the patients in ASSERT-EXT with available data at the indicated time point (ODX/ODX, n=33; PBO/ODX, n=17). Pruritus scores range from 0 to 4; higher scores indicate worse symptoms.

Proportion of patients with a clinically meaningful decrease in the ObsRO pruritus scratching severity score (pruritus responders)

6.16 The proportion of pruritus responders (≥1.0 or ≥1.5-point reduction in ObsRO pruritus score from baseline) was a secondary outcome of ASSERT and ASSERT-EXT and is shown in Table 5.

6.17 The submission claimed that there was a statistically significant greater proportion of pruritus responders with a ≥1.5-point drop in pruritus from baseline for patients who received odevixibat compared with those who received placebo at both Weeks 9–12 (difference 54.1%, odds ratio [OR] 23.97, p <0.05) and Weeks 21–24 (difference 36.7%, OR 5.15, p <0.03). However, the evaluation noted that the difference in the proportion of pruritus responders (≥1.0 or ≥1.5-point reduction in ObsRO) was a secondary outcome of ASSERT and was not adjusted for multiplicity.

6.18 The submission claimed that some odevixibat-treated patients from ASSERT, with improvements in scratching scores of >1.5 or >1.0 at the start of ASSERT-EXT (from ASSERT baseline), showed further improvement with long-term odevixibat treatment.

6.19 The ASSERT-EXT clinical study report (CSR) stated that, based on the ASSERT baseline, for those patients who received odevixibat in both studies (i.e. ODX/ODX group) following 48 weeks of treatment (ASSERT-EXT Weeks 21-24), 21 (70.0%) of 30 patients had a ≥1.5-point reduction in scratching severity score as did 22 (73.3%) of 30 patients after 96 weeks (ASSERT-EXT Weeks 69-72).

Table 5: Proportion of pruritus responders (≥1.0 or ≥1.5-point reduction in ObsRO pruritus score from baseline) – ASSERT and ASSERT-EXT (average of morning and evening scores)

Visit, Statistic	% (n/N)	% (n/N)	% difference
ASSERT	**Placebo (N=17)**	**Odevixibat (N=35)**	
≥1.0 point drop from ASSERT baseline to Week 9-12	35.3 (6/17)	74.3 (26/35)	39.0 OR 5.27 (95% CI 1.28, 21.31) p<0.01
≥1.0 point drop from ASSERT baseline to Week 21-24	35.3 (6/17)	80.0 (28/35)	44.7 OR 8.31 (95% CI 1.82, 44.48) p<0.01
≥1.5 point drop from ASSERT baseline to Week 9-12	5.9 (1/17)	60.0 (21/35)	54.1 OR 23.97 (2.80, 996.25) p<0.01
≥1.5 point drop from ASSERT baseline to Week 21-24	17.6 (3/17)	54.3 (19/35)	36.7 OR 5.15 (95% 1.17, 34.16) p<0.03
ASSERT-EXT	**PBO/ODX (n=17)**	**ODX/ODX (n=33)**	
≥1.0 point drop from ASSERT-EXT baseline to Week 21-24	50.0 (8/16)	16.7 (5/30)	-
≥1.0 point drop from ASSERT-EXT baseline to Week 45-48	75.0 (9/12)	16.7 (5/30)	-
≥1.0 point drop from ASSERT-EXT baseline to Week 69-72	76.9 (10/13)	23.3 (7/30)	-
≥1.5 point drop from ASSERT-EXT baseline to Week 21-24	43.8 (7/16)	10 (3/30)	-
≥1.5 point drop from ASSERT-EXT baseline to Week 45-48	50.0 (6/12)	10 (3/30)	-
≥1.5 point drop from ASSERT-EXT baseline to Week 69-72	53.8 (7/13)	10 (3/30)	-

Source: Table 2-27, p78 and Figure 2-16, p79 of the submission, Table 14.2.11.1.1 and 14.2.11.1.2 of ASSERT CSR.
p = p-value; OR = odds ratio; PRO = patient-reported outcome; SD = standard deviation.
Notes: Two-sided p-values are presented. Bold represents statistical significance at p<0.05 level.

6.20 The submission also presented a post-hoc pooled analysis of ASSERT and ASSERT-EXT showing the proportion of patients who achieved a ≥1.0 point pruritus reduction in morning pruritus scores from ASSERT baseline (Baseline 1) to week 24, 48 and 72 (Table 6). The pooled patient numbers and morning pruritus scores could not be verified from the CSR. the evaluation also noted that use of only the morning pruritus scores differed to the primary outcome reported in ASSERT, in which the morning and evening scores were combined.

Table 6: Proportion of pruritus responders (≥1.0 point reduction in morning pruritus score from ASSERT baseline (Baseline 1)) – ASSERT and ASSERT-EXT

Treatment	Odevixibat; n/N (%)	Placebo (SoC); n/N (%)
Week 24	28/34 (82.4)	6/15 (40.0)
Week 48	23/26 (88.5)	-
Week 72	28/31 (90.3)	-

Source: Table 2-28, p79 of the submission
Abbreviations: n = number of patients with event; N = total number of patients in group; SoC = standard of care

6.21 The Week 24 pooled pruritus response (82.4%) was applied in the submission's economic model, whilst the Week 48 pooled response (88.5%) was applied in the submission's financial estimates. The evaluation considered it may not be reasonable

for differing response rates to be applied in the economic and financial models, both of which were higher than rates reported in the odevixibat arm in ASSERT (80%) and in patients that commenced odevixibat (PBO/ODX) in ASSERT-EXT (50%) (Table 5).

Change in sBA levels

6.22 Change in baseline in serum bile acid (sBA) levels over 24 weeks in ASSERT is shown in Table 7.

6.23 The LS mean changes from baseline to Weeks 20–24 in sBA levels were -90.35 and +22.39 µmol/L in the odevixibat and placebo groups respectively, and the LS mean difference of -112.74 (95% CI: -178.78, -46.69) µmol/L between the groups was statistically significant (p=0.001).

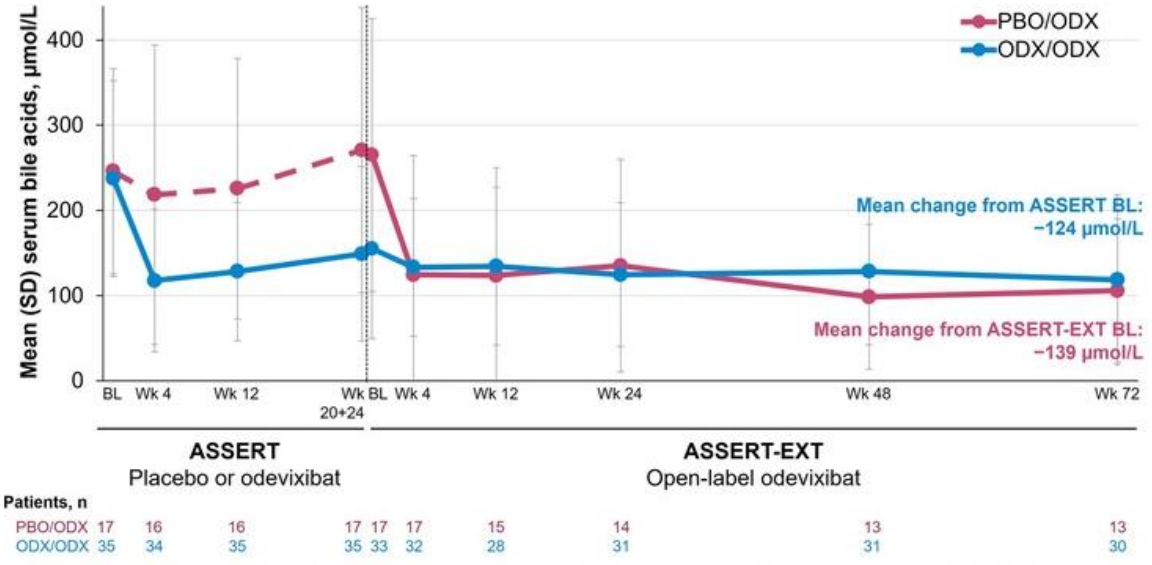
6.24 Change from ASSERT baseline (Baseline 1) in sBA levels over ASSERT and ASSERT-EXT is shown in Figure 2.

Table 7: Serum bile acid (sBA) levels: Baseline, Weeks 20-24, and Change at Weeks 20–24 – ASSERT FAS

	Serum bile acids (µmol/l)	
Visit Statistic	**Placebo (N=17)**	**Odevixibat (N=35)**
Baseline		
n	17	35
Mean (SD)	246.1 (120.53)	237.4 (114.88)
Median (min, max)	*232.0*	*210.5*
Minimum, maximum	56, 428	96, 510
Average of Weeks 20 and 24		
n	17	35
Mean (SD)	270.7 (166.93)	149.0 (102.30)
Median	*261.0*	*126.0*
Minimum, maximum	42, 647	26, 377
Change from Baseline to Weeks 20 and 24		
n	17	35
Mean (SD)	24.6 (131.63)	-88.4 (120.27)
Median	*17.5*	*-91.0*
Minimum, maximum	-246, 291	-350, 252
LS Mean (SE)[a]	22.39 (28.463) 95% CI (-34.75, 79.52)	-90.35 (21.336) 95% CI (-133.14, -47.56)
LS mean difference (SE) (odevixibat-placebo)	**-112.74 (32.864) 95% CI (-178.78, -46.69), p = 0.001**	

Source: Table 2-22, pp72-73 of the submission, ASSERT CSR Table 25
Italicised text reflects values extracted from the CSR during evaluation.
CI = confidence interval; FAS = full analysis set; L = litre; LS = least square; n = number of patients; N = total number of patients in group; SE = standard error; µmoL = micromole.
[a] The analysis is based on a MMRM using a restricted maximum likelihood with baseline score as a covariate, and baseline age stratification, baseline direct bilirubin, treatment group, time (in months), and treatment-by-time interaction as fixed effects. Unstructured covariance matrix is used in the analysis. The Kenward-Roger approximation is used to estimate denominator degrees of freedom.

Figure 2: Mean change in sBA from Baseline 1 during ASSERT and ASSERT-EXT (FAS)



Source: Figure 2-13, p75 of the submission
BL = baseline; L = litre; ODX/ODX received odevixibat in ASSERT and ASSERT-EXT; PBO/ODX received placebo in ASSERT and odevixibat in ASSERT-EXT; sBA = serum bile acids; SE = standard error; µmoL = micromole; wk = week
Note: Dashed pink line indicates period of placebo administration in ASSERT.
Note: Error bars represent standard deviations (SDs).
Note: Values shown for ASSERT time points represent data from all ASSERT patients with available data at the indicated time point (odevixibat, n=35; placebo, n=17); values shown for ASSERT-EXT time points represent only the patients in ASSERT-EXT with available data at the indicated time point (ODX/ODX, n=33; PBO/ODX, n=17).

6.25 For ODX/ODX patients, the submission claimed that further reductions in sBA levels were observed in ASSERT-EXT with continued treatment. At Week 24 of ASSERT-EXT, mean changes from the ASSERT-EXT baseline in sBA levels were -32.7 (SD 88.72) µmol/L and at Week 72, were -36.0 (SD 90.76) µmol/L. The overall mean change from ASSERT baseline to 72 weeks ASSERT-EXT (or 92-96 weeks from ASSERT baseline) was -124 µmol/L for ODX/ODX patients.

6.26 For patients who received placebo in ASSERT, a reduction in sBA levels was observed after the initiation of treatment with odevixibat in ASSERT-EXT. By Week 4 of odevixibat treatment, the mean change in sBA was -140.5 (SD 92.66) µmol/L. At Week 24 of ASSERT-EXT, the mean change from ASSERT-EXT baseline in sBA levels was -123.6 (SD 94.95) µmol/L and at Week 48 was -145.8 (SD 91.49) µmol/L. The reduction in sBA was sustained at Week 72, with mean change from ASEERT-EXT baseline of -138.6 (SD 101.17) µmol/L.

6.27 The submission did not propose a MCID for changes in sBA levels. However, the submission claimed that data from the GALA study provides evidence of sBA being an independent predictive factor for native liver survival in children with ALGS (Perez 2025)[9]. Perez 2025 assessed a prognostic threshold of sBA 102 µmol/L for native liver

[9] Perez CFM et al., Elevated Serum Bile Acids Predict Poor Liver Outcomes in Children With Alagille Syndrome: Results From the GALA Study Group. Liver Int. 2025 Dec;45(12):e70423. doi: 10.1111/liv.70423. PMID: 41250932; PMCID: PMC12625800.

survival (NLS) and found sBA below 102 µmol/L was a significant predictor of outcomes (NLS: HR = 3.78, 95% CI 2.39–5.99, p < 0.001; event-free survival [EFS]: HR = 3.44, 95% CI 2.35–5.04, p < 0.001). The authors noted that the patients studied did not receive IBAT inhibition, however the data suggests that lowering sBA may improve important clinical outcomes. In the PFIC odevixibat clinical trial PEDFIC 1, sBA response was defined as a ≥70% reduction in fasting sBA concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L.

6.28 For context, changes in mean sBA levels observed in the ASSERT/ASSERT-EXT and PEDFIC 1/PEDFIC 2 were compared. The PEDFIC 1 trial and its associated extension study, PEDFIC 2, were presented in the July 2024 odevixibat submission for the treatment of patients with PFIC. All PFIC patients in PEDFIC 2 were treated with odevixibat 120 µg/kg/day. Prior to commencing treatment with odevixibat, baseline sBA levels were 237.4 µmol/L and 248.11 µmol/L in the odevixibat arm of ASSERT (N=35) and the odevixibat arm of PEDFIC 1 (N=37), respectively. Following approximately 96 weeks of treatment (i.e. Week 72 of ASSERT-EXT and the Week 70/72 average for PEDFIC 2), the mean change in sBA levels was -124 µmol/L (Figure 2) and -139.84 µmol/L for the ALGS and PFIC patients, respectively. With acknowledgment of patient and trial heterogeneity, there was a similar degree of sBA reduction observed with odevixibat treatment across ALGS and PFIC patients. A comparison of pruritus outcomes was not feasible due to differences in how pruritus outcomes were reported.

Quality of Life

6.29 The Paediatric Quality of Life Inventory (PedsQL) was used to measure quality of life (QoL) in ASSERT and ASSERT-EXT, however, only results from ASSERT were presented in the submission. The specific instrument used was not specified in the submission. However, the evaluation noted that the PedsQL 4.0 Generic Core Scales instrument is the last version of PedsQL and contain 23-items, consisting of: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). Likert scores for each question are linearly transformed to a 0–100 scale in which high score means better condition. Change in the total score of the PedsQL is shown in Table 8.

Table 8: Paediatric Quality of Life Inventory (Full Analysis Set): Baseline, Week 24, and Change at Week 24– ASSERT

	PedsQL score	
Visit, Statistic	**Placebo (N=17)**	**Odevixibat (N=35)**
Baseline: Mean (SD)	67.1 (13.5) N=11	67.8 (16.3) N=30
Week 24: Mean (SD)	76.6 (10.6) N=11	80.5 (14.7) N=30
Change from Baseline to Week 24		
Mean (SD)	9.5 (9.3) N=11	12.8 (17.8) N=28
LS mean (SE) [a]	10.7 (4.0) 95% CI: 2.7, 18.8	13.5 (2.5) 95% CI: 8.3, 18.7
LS mean difference (SE) (odevixibat-placebo)[a]	2.8 (4.5) 95% CI: -6.3, 11.9, p=0.54 [b], *One-sided p-value = 0.269*	

Source: Table 2-31, p82 of the submission
Abbreviations: CI, confidence interval; LS, least square; SD, standard deviation; SE, standard error of the mean.
Note: Higher scores represent better quality of life. Data are based on parent report.
[a] The analysis was based on an analysis of covariance (ANCOVA) model at each visit with baseline score as a covariate, and treatment group and age category (<5, 5–7, 8–12, 13–18) as fixed effects.
[b] The p-value reported in the submission (0.54) differed from Table 31 in the CSR (0.2691).

6.30 The LS mean changes to Week 24 were 13.50 and 10.72 for the odevixibat and placebo groups, respectively. The LS mean difference between groups of 2.78 (95% CI: 6.31, 11.87) was not statistically significant (one-sided p = 0.2691). PedsQL results from ASSERT were used to derive health-state utility values in the submission's economic model.

Sleep and growth parameters

6.31 Changes in sleep parameters from baseline to Weeks 20-24 in ASSERT are shown in Table 9.

Table 9: Change from baseline in sleep parameter items (ObsRO) at Weeks 21–24 (Full Analysis Set) – ASSERT

Sleep parameter	LS mean change (SE)		LS difference (95% CI)
	Placebo (N=17) [a]	Odevixibat (N=35) [a]	
Proportion days with help falling asleep, %	-10.1 (9.2)	-43.4 (6.7)	-33.4 (-54.9, -11.9) p=0.003
Proportion days with soothing, %	-6.3 (7.9)	-46.7 (5.8)	-40.4 (-58.8, -22.0) p<0.001
Proportion days sleeping with caregiver, %	-8.3 (7.2)	-34.5 (5.4)	-26.3 (-43.3, -9.2) p=0.0034
Tiredness [b]	-0.5 (0.2)	-1.1 (0.2)	-0.6 (-1.1, -0.1) p=0.012
Proportion days seeing blood, %	-19.0 (6.0)	-28.0 (4.5)	-9.0 (-23.3, 5.4) p=0.215
Number of awakenings	0.2 (1.3)	-2.7 (0.9)	-2.9 (-6.1, 0.3) p=0.078
Proportion days taking medication to induce sleep, %	4.3 (5.8)	-2.8 (4.3)	-7.1 (-21.0, 6.7) p=0.306

Source: Table 2-29, p80 of the submission

CI, confidence interval; MMRM, mixed-effect model for repeated measures; ObsRO, observer-reported outcome; SE, standard error.

[a] At Weeks 21-24, the number of placebo respondents was n=16, and the number of odevixibat respondents was n=33 (Table 12.2.12.1 ASSERT CSR).

[b] Tiredness was measured with the ObsRO item "How tired did your child seem to be today?", with caregiver response options of 0 = not tired at all, 1 = a little tired; 2 = medium tired; 3 = very tired; 4 = very, very tired.

6.32 The submission claimed that from baseline to Weeks 21–24, the LS mean change was significantly greater with odevixibat versus placebo for several sleep parameters: proportion of days needing help falling asleep (odevixibat −43% vs placebo −10%; LS difference −33%); proportion of days sleeping with a caregiver (odevixibat −35% vs placebo −8%; LS difference −26%); proportion of days needing soothing (odevixibat −47% vs placebo −6%; LS difference −40%); and daytime tiredness score (odevixibat −1.1 points vs placebo −0.5; LS difference −0.6 [95% CI: −1.1 to −0.1]). However, the evaluation considered that as changes in sleep parameter outcomes were not adjusted for multiplicity, there was an increased risk of Type I error. In addition, a higher proportion of patients in the placebo arm were aged <2 years (29.4%, 5/17) compared with the odevixibat group (8.6%, 3/35), and the evaluation considered it uncertain whether this could potentially confound differences in sleep parameter outcomes.

6.33 Changes in growth parameters were an exploratory outcome of ASSERT. After 24 weeks of treatment, small LS mean changes baseline to Week 24 were noted in height (0.12 odevixibat vs -0.15 placebo; difference 0.27 (95% CI: 0.00, 0.54)) and weight (0.05 odevixibat vs 0.23 placebo; difference -0.28 (95% CI: -0.53, -0.04)) z-scores in both treatment groups. The submission noted the imbalance across age groups at baseline (paragraph 6.32) which may confound measurement of growth parameters.

6.34 The PBAC recalled that some limited evidence of benefit for odevixibat for EFS (time to first surgical biliary diversion, liver transplant or death), was presented for PFIC (see table 8, odevixibat PSD, July 2025 PBAC meeting), but noted that no such evidence was presented for ALGS.

Comparative harms

6.35 A summary of treatment emergent adverse events (TEAEs) reported in ASSERT and ASSERT-EXT is shown in Table 10.

Table 10: Summary of key adverse events – ASSERT and ASSERT-EXT

	ASSERT		
	Placebo (N=17) n (%); E	**Odevixibat (N=35) n (%); E**	**RD (95% CI) Difference in % patients with an AE [a]**
TEAE	12 (70.6); 42	26 (74.3); 104	3.7 (-22.4, 29.8)
Drug-related TEAE	3 (17.6) / 4	8 (22.9); 17	5.2 (-17.6, 28.1)
TEAEs by maximum intensity			
Grade 1	7 (41.2); 32	11 (31.4); 70	-9.7 (-37.7, 18.3)
Grade 2	3 (17.6); 7	10 (28.6); 26	10.9 (-12.6, 34.4)
Grade 3	2 (11.8); 3	5 (14.3); 8	2.5 (-16.7, 21.7)
Grade 4	0	0	0.0 (0.0, 0.0)
Grade 5	0	0	0.0 (0.0, 0.0)
Serious TEAE	2 (11.8); 5	5 (14.3); 8	2.5 (-16.7, 21.7)
Drug-related serious TEAE	0	1 (2.9); 2 [b]	2.9 (-2.7, 8.4)
TEAE leading to death	0	0	0.0 (0.0, 0.0)
TEAE leading to: drug discontinuation drug interruption drug dose reduction	 0 0 0	 0 3 (8.6) / 4 1 (2.9) / 2	 0.0 (0.0, 0.0) 8.6 (-0.7, 17.8) 2.9 (-2.7, 8.4)
	ASSERT-EXT		**ASSERT / ASSERT-EXT (Pooled)**
	PBO/ODX N=17 n (%); E	**ODX/ODX N=33 n (%); E**	**ODX N=52 n (%); E**
TEAE	17 (100); 161	30 (90.9); 200	50 (96.2); 465
Drug-related TEAE	7 (41.2); 20	6 (18.2); 10	19 (36.5); 47
TEAEs by maximum intensity			
Grade 1	4 (23.5); 83	10 (30.3); 107	
Grade 2	6 (35.3); 65	14 (42.4); 79	
Grade 3	7 (41.2); 13	6 (18.2); 14	
Grade 4	0	0	16 (30.8); 35
Grade 5	0	0	
Serious TEAE	7 (41.2); 8	4 (12.1); 7	
Drug-related serious TEAE	0	0	13 (25.0); 23
TEAE leading to death	0	0	1 (1.9); 2
TEAE leading to: drug discontinuation drug interruption drug dose reduction	 1 (5.9); 1 [c] 1 (5.9); 2 1 (5.9); 3	 0 4 (12.1); 5 2 (6.1); 2	1 (1.9); 1 [c] 8 (15.4); 11 3 (5.8); 6

Source: Table 2-33 and Table 2-38, p85-89 of the submission

E = number of events; TEAE = treatment-emergent adverse event

[a] *Calculated during evaluation using normal approximation to the binomial (Gardner and Altman 1997)*

[b] One patient in the odevixibat group had serious TEAE of haematemesis and increased International Normalized Ratio (INR) that were assessed as related to study drug.

[c] Discontinued due to blood bilirubin increased

6.36 Overall, 26 (74.3%) of the 35 patients who received odevixibat experienced at least one TEAE as did 12 (70.6%) of the 17 patients who received placebo. Most TEAEs were Grade 1 to 2 in intensity and assessed as unrelated to study drug. The most common drug-related TEAE was diarrhoea, occurring in 11.4% (4/35) and 5.9% (1/17) of patients in the odevixibat and placebo arm, respectively. All reports of diarrhoea were

Grade 1 or 2 in intensity and non-serious. Grade 3 abdominal pain, constipation and haematemesis was reported in one patient (2.9%) each.

6.37 In ASSERT, the incidence of serious TEAEs was similar in the odevixibat (14%, 5/35) and placebo (12%, 2/17) groups. One patient had serious TEAEs considered by the investigator to be study drug-related during treatment with odevixibat in ASSERT. The patient experienced haematemesis and increased international normalised ratio (INR) requiring hospitalisation.

6.38 The most commonly reported types of serious TEAEs in ASSERT-EXT were infections, reported in four (8.0%) of the 50 patients, including one report each of enterovirus infection, gastroenteritis, rotavirus gastroenteritis, and chronic otitis media. In most patients, treatment with odevixibat was continued unchanged; none of the serious TEAEs led to treatment discontinuation. One patient had treatment interrupted for rotavirus gastroenteritis.

6.39 There were 11 (21%) of 52 patients in the pooled patient group (i.e. over the ASSERT and ASSERT-EXT study period) that experienced liver-related TEAEs. The most common TEAEs were INR increased (four patients, 8%), alanine transaminase (ALT) increased (three patients, 6%), and aspartate aminotransferase (AST) increased, blood bilirubin increased, gamma-glutamyl transferase (GGT) increased, and hepatomegaly (two patients each, 4%). Most liver-related events were Grade 1 or 2 in severity and non-serious. No liver decompensation events were reported during the studies, nor did any patient report new or worsening portal hypertension, hepatic cirrhosis, hepatic encephalopathy, or variceal haemorrhage. The EMA assessment report[10] stated that overall, it was considered that increases in blood bilirubin, ALT, AST, and CGT with odevixibat treatment were mostly mild in severity and non-serious, and that increases were not indicative of drug-induced liver injuries.

6.40 In ASSERT-EXT, one patient (aged 14 years and nine months), who received placebo in ASSERT, discontinued odevixibat after 3.5 months in ASSERT-EXT and underwent LT five days after the last dose. The case report form documented advanced disease at ASSERT baseline, including cholelithiasis and splenomegaly, oesophageal varices, vitamin A deficiency, and portal hypertensive gastropathy. Both the investigator and the Sponsor assessed the LT as unrelated to odevixibat.

6.41 Adverse events of special interest reported in ASSERT are summarised in Table 11.

[10] https://www.ema.europa.eu/en/documents/variation-report/kayfanda-h-c-006462-ii-0001-g-epar-assessment-report-variation_en.pdf

Table 11: Patients with adverse events of special interest – ASSERT (Safety Analysis Set)

Patients with:	Placebo (N=17) n (%) / E	Odevixibat (N=35) n (%) / E
Any clinically significant diarrhoea	1 (5.9) / 1	6 (17.1) / 6
Any FSV deficiency refractory to clinically recommended vitamin supplementation	1 (5.9) / 1	1 (2.9) / 1
Any possible sequelae of FSV deficiency	3 (17.6) / 4	5 (14.3) / 7
Any liver-related TEAEs	2 (11.8) / 3	4 (11.4) / 5
Hepatobiliary disorders	0	1 (2.9) / 1
Jaundice	0	1 (2.9) / 1
Investigations	2 (11.8) / 3	3 (8.6) / 4
Alanine aminotransferase increased	0	1 (2.9) / 1
Gamma-glutamyltransferase increased	0	1 (2.9) / 1
Hepatic enzyme increased	1 (5.9) / 1	1 (2.9) / 1
International normalised ratio increased	2 (11.8) / 2	1 (2.9) / 1
Any liver decompensation	0	0

Source: Table 2-37, p87 of the submission, Table 14.3.1.18 ASSERT CSR.
E = number of events; FSV = fat-soluble vitamin; n = number of patients with events; N = total number of patients in group; TEAE = treatment-emergent adverse event

6.42 Overall, the evaluation and the *ESC* noted that consistent with the current TGA Prescribing Information for PFIC, the safety profile of odevixibat appeared to be primarily characterised by Grade 1 or 2 gastrointestinal disturbances, primarily reports of diarrhoea. The EMA assessment report considered that the safety profile emerging form the long-term extension is more or less in line with the adverse events profile observed in the initial placebo-controlled studies.

Benefits/harms

6.43 A summary of the comparative benefits and harms for odevixibat versus placebo is presented in Table 12. No statistically significant differences between odevixibat and placebo with respect to adverse events were observed.

Table 12: Summary of comparative benefits for odevixibat and placebo - ASSERT

	Placebo			Odevixibat			LS Mean difference: odevixibat vs. placebo (95% CI)
	N	Mean Δ baseline	SD	N	Mean Δ baseline	SD	
Change from baseline to Weeks 21-24 in ObsRO pruritus scratching score							
ObsRO score	17	-0.80	0.23	35	-1.69	0.17	**-0.88 (-1.44, -0.33)**
Change from baseline to Weeks 20-24 in sBA levels (µmol/l)							
sBA	17	22.39	131.63 (SE)	35	-90.35	21.34 (SE)	**-112.74 (-178.78, -46.69)**

Proportion of pruritus responders at Weeks 21-24 (average of morning and evening scores)					
	Placebo n/N	Odevixibat n/N	OR (95% CI)	Event rate / 100 patients	
				Placebo	Odevixibat
≥1.0 ObsRO score reduction	6/17	28/35	**8.31 (1.82, 44.48)**	35.3	80.0
≥1.5 ObsRO score reduction	3/17	19/35	**5.15 (1.17, 34.16)**	17.6	54.3

Source: Table 2-20, Table 2-27, p69 and p78 of the submission
CI = confidence interval; LS = least square; OR = odds ratio; SD = standard deviation; SE = standard error

6.44 Based on direct comparative evidence presented by the submission, the comparison of odevixibat (120 µg/kg/day) and placebo resulted in:

- Approximately an 0.88 point reduction in ObsRO pruritis scratching score over a 24 week duration of exposure. and
- Approximately a -112.74 µmol/L reduction in sBA levels over a 20-24 week duration of exposure.

6.45 For every 100 patients treated with odevixibat in comparison with placebo over a duration of exposure of 21-24 weeks:

- Approximately 45 additional patients would have a >1.0 reduction in the ObsRO pruritus scratching score; and
- Approximately 37 additional patients would have a >1.5 reduction in the ObsRO pruritus scratching score.

Clinical claim

6.46 The submission described odevixibat as superior in terms of effectiveness compared to SoC. The evaluation considered that this claim was partially supported by direct evidence from ASSERT, i.e.:

- Odevixibat treatment led to a statistically significant decrease in the ObsRO pruritus scratching score over 24 weeks compared with placebo (LS mean difference - 0.88 [95% CI: -1.44, -0.33] p=0.0024).
- There was a statistically significant difference in the proportion of patients with a ≥1.5-point ObsRO scratching score reduction from baseline for odevixibat treated patients compared with placebo at Weeks 9–12 (difference 54.1%, odds ratio [OR] 23.97, p <0.05) and Weeks 21–24 (difference 36.7%, OR 5.15, p <0.03).
- Odevixibat treatment led to a statistically significant reduction in sBA levels over 24 weeks, with an LS mean change at Weeks 20–24 of -90.35 µmol/L versus +22.39 µmol/L for placebo (LS mean difference: -112.74 µmol/L, 95% CI: -178.78, -46.69; p <0.01). However, the evaluation considered that as the submission did not propose an MCID for reduced sBA levels, the clinical significance of the observed difference was uncertain.
- From ASSERT baseline to Weeks 21–24, LS mean change was greater with odevixibat versus placebo for the proportion of days needing help falling asleep, days sleeping with a caregiver, days needing soothing, and daytime tiredness (refer to Table 9). However, the evaluation considered that as changes in sleep parameters were not adjusted for multiplicity; and a higher proportion of placebo patients were aged <2 years compared with odevixibat (29.4% and 8.6%, respectively), the impact on sleep parameters was considered uncertain.

6.47 The submission described odevixibat as non-inferior in terms of safety compared to SoC. The evaluation considered that this claim was not well supported by comparative evidence from ASSERT, given: The small sample sizes (n=17 and n=35 for the placebo and odevixibat groups, respectively); and limited comparative data (up to 24 weeks). However, the evaluation noted that:

- discontinuation of odevixibat due to TEAEs was uncommon, and a similar rate of serious TEAEs were demonstrated in the odevixibat and placebo arm of ASSERT (14.3% and 11.8%, respectively); and
- the PBAC previously considered that for patients with PFIC, a claim of comparable safety between odevixibat and SoC was reasonable (paragraph 6.46, odevixibat PSD, July 2024 PBAC Meeting).

6.48 Overall, the ESC considered that the submission's claim of superior effectiveness and non-inferior safety was supported.

6.49 The PBAC considered that the claim of superior comparative effectiveness was reasonable; however the magnitude of clinical benefit (i.e. pruritis reduction) was uncertain.

6.50 The PBAC considered that the claim of non-inferior comparative safety was reasonable, but noted the limited data in terms of small population and limited follow-up. The PBAC noted the increase of mild gastrointestinal adverse events, especially diarrhoea associated with odevixibat, but considered that safety appears manageable, with no new safety signals.

Economic analysis

6.51 The type of economic evaluation presented was a cost-utility analysis, using quality-adjusted life years (QALYs) as the final health outcome. The key components of the economic evaluation are shown in

6.52

6.53 Table 13. The model structure was similar to the model submitted for the PBAC July-2025 resubmission of odevixibat in PFIC, which the ESC previously considered unreliable for decision making because of both implausible structural assumptions and continuing uncertainty in data inputs (see Odevixibat PFIC PBAC July-2025 PSD, paragraphs 6.63 and 13.3).

Table 13: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Odevixibat vs SoC (off-label pharmaceutical treatments and LT)
Outcomes	Total and disaggregated costs, total quality-adjusted life years (QALYs), QALYs by health state, and life-years gained (LYGs).
Perspective	Health care system perspective Base Case 1: Patient and Carer QoL considered

<table>
<tr><th>Component</th><th colspan="3">Summary</th></tr>
<tr><td></td><td colspan="3">Base Case 2: Patient QoL only</td></tr>
<tr><td>Discounting</td><td colspan="3">5% applied for costs and clinical outcomes</td></tr>
<tr><td>Time horizon</td><td colspan="3">50 years (versus 24 weeks of comparative trial data)</td></tr>
<tr><td>Methods used to generate results</td><td colspan="3">Markov state transition model</td></tr>
<tr><td>Health states</td><td colspan="3">1. Cholestasis with response
2. Cholestasis with loss of response
3. Cirrhosis
4. Portal hypertension (PHT)
5. Ascites
6. Liver transplant (LT)
7. Post-LT
8. Death
A scenario analysis was also included which added two additional health states, SBD and post-SBD</td></tr>
<tr><td>Cycle length</td><td colspan="3">12 weeks</td></tr>
<tr><td rowspan="25">Transition probabilities</td><td colspan="3"></td></tr>
<tr><td>Transition</td><td>Input</td><td>Source</td></tr>
<tr><td>Response to ODX</td><td>82.4%</td><td>Post-hoc pooled ASSERT/ASSERT-EXT patient data conducted by the Sponsor</td></tr>
<tr><td>Response to SoC</td><td>0%</td><td>Assumption</td></tr>
<tr><td>Response to SBD</td><td>0%</td><td>Assumption</td></tr>
<tr><td>Discontinuation of ODX</td><td>5/50 (10%) at 92.6 weeks)</td><td>Post-hoc analysis at 92.6 weeks conducted by the Sponsor.</td></tr>
<tr><td>Discontinuation of SoC</td><td>Same as ODX discontinuation</td><td>Assumption</td></tr>
<tr><td>Loss of response of SBD</td><td>–</td><td>–</td></tr>
<tr><td>Unresponsive → Cirrhosis</td><td>41/94 (44%) at 10 years</td><td>Lykavieris 2001 (maralixibat NICE submission)</td></tr>
<tr><td>Cirrhosis → PHT</td><td>40% at 30 years</td><td>Kamath 2020b (maralixibat NICE submission)</td></tr>
<tr><td>PHT → Ascites</td><td>36% at 30 years</td><td>Kamath 2020b (maralixibat NICE submission)</td></tr>
<tr><td>Unresponsive → LT</td><td>47% at 4 years</td><td>Quiros-Tejeira 1999</td></tr>
<tr><td>Cirrhosis → LT</td><td>7.27% at 1 year</td><td>Hagstrom 2021</td></tr>
<tr><td>PHT → LT</td><td>23% at 1 year</td><td>Krasinskas 2005</td></tr>
<tr><td>Ascites → LT</td><td>–</td><td>Assumption</td></tr>
<tr><td>Post-SBD → LT</td><td>0% in base-case / 36% at 18 years</td><td>NAPPED (Gonazles and Filiere de Sante Maladies Rares du Foie de L’Adulte et de L’Enfant, 2018) (maralixibat NICE submission)</td></tr>
<tr><td>LT → LT (Re-transplantation)</td><td>22% at 1 year</td><td>Adam 2012 (maralixibat NICE submission)</td></tr>
<tr><td>Unresponsive → SBD</td><td rowspan="4">50% at 29 months</td><td rowspan="4">Foroutan 2020 (maralixibat NICE submission)</td></tr>
<tr><td>Cirrhosis → SBD</td></tr>
<tr><td>PHT → SBD</td></tr>
<tr><td>PHT → SBD</td></tr>
<tr><td>Mortality</td><td colspan="2"></td></tr>
<tr><td>Responder
Non-responder</td><td>KM data (base case)
Log-logistic extrapolation</td><td>GALA study (Hansen 2021; Vandriel 2022) - Mortality in children with ALGS presenting with neonatal cholestasis</td></tr>
<tr><td>Cirrhosis</td><td>0.92% per cycle</td><td>D'Amico 2006</td></tr>
<tr><td>PHT</td><td>2.18% per cycle</td><td>Santambrogio 2013</td></tr>
<tr><td>Ascites</td><td>4.50% per cycle</td><td>Tonon et al., 2021</td></tr>
<tr><td>LT (once off)</td><td>25.17% per cycle</td><td>Emerick 1999</td></tr>
<tr><td>Post-LT (per cycle)</td><td>0.92% per cycle</td><td>Hou 2021</td></tr>
<tr><td>SBD (scenario only)</td><td>0.12% per cycle</td><td>Assumed equal non-responder</td></tr>
</table>

Component	Summary		
	Post-SBD (scenario only)	0.12% per cycle	Assumed equal non-responder
Extrapolation method	Responder/non-responder health state mortality values were informed in the base case by extrapolating digitised Kaplan-Meier from the GALA study (Vandriel 2022, Hansen 2021).		
Health related quality of life	**Health state**	**Utility**	**Source**
	Responder	0.881	ASSERT and ASSERT-EXT pooled data (Sponsor data on file)
	Non-responder	0.734	ASSERT and ASSERT-EXT pooled data (Sponsor data on file)
	Cirrhosis	0.734	Assumed equal to non-responder
	PHT	0.734	Assumed equal to non-responder
	Ascites	0.734	Assumed equal to non-responder
	LT *(one cycle only)*	0.710	'Severe pruritus patients' from Kini 2011
	Post-LT	0.820	NICE EAG preference from maralixibat submission
	SBD (scenario only)	0.734	Assumed equal to non-responder
	Post-SBD (scenario only)	0.734	Assumed equal to non-responder
Healthcare resource use and costs	The base case model included costs associated with:		
	Resource use or cost	**Source used in model**	
	Odevixibat drug acquisition	Dosage was based on the average patient weight for a given age (ABS National Health Survey 2022) and corresponding capsule strengths (200, 400, 600 and 1200 µg). All patients were on a dosage of 120 µg/kg/day with 100% compliance assumed. Odevixibat costs are only incurred in the 'responder' health state.	
	SoC drug costs (only applied to SoC arm in the base case)	UDCA, cholestyramine, rifampicin, and naltrexone usage was sourced from PBS usage data, consistent with the PBAC July-2025 resubmission of odevixibat in PFIC. Ondansetron and SSRI usage was additionally sourced from PBS usage data for this submission.	
	LT costs (pre-transplant, surgery, post-transplant monitoring and complications)	Transplant costs were sourced from the National Efficient Price Determination 2025-26. Pre-transplant and post-transplant costs were consistent with the PBAC July-2025 resubmission of odevixibat in PFIC.	
	ALGS management	The model includes costs for severe illness events associated with ALGS (informed by Vandriel 2022, Blue 2007 and Bales 2010) in addition to costs associated with routine monitoring and management of ALGS patients (*reportedly* aligned with the NICE 2024 maralixibat submission; and HCD economics 2021 burden of illness study)	
	AE	The submission stated no AE disutility (or costs) was included in the model given most AEs are low grade and would have a negligible impact on QoL.	

Source: Table 3-1, Table 3-9, Table 3-10, Table 3-15, Table 3-16, Table 3-18, Table 3-21, Table 3-22, of the submission
ABS = Australian Bureau of Statistics; AE = adverse events; ALGS = Alagille syndrome; EAG = external assessment group; LT = liver transplant; LYG = life years gained; NICE = U.K. National Institute for Health and Care Excellence; ODX = odevixibat; PBAC = Pharmaceutical Benefits Advisory Committee; PFIC = progressive familiar intrahepatic cholestasis; PHT = portal hypertension; QALY = quality adjusted life years; SBD = biliary diversion surgery; SoC = standard of care

6.54 The evaluation and the ESC considered that the inclusion of caregiver disutility was not appropriate in the base case. Therefore, the following discussion is in reference to Base Case 2 which does not include caregiver disutility, unless otherwise specified. Results from Base Case 1 (i.e. including caregiver disutility) is presented alongside, as a sensitivity analysis.

6.55 A 50-year time horizon was modelled in the base-case versus 24 weeks of comparative data from ASSERT, and 72 weeks of single-arm data from ASSERT-EXT. The submission claimed that this aligns to the time horizon presented in the July 2025 odevixibat PFIC resubmission. However, the PBAC had considered that the base case economic model presented in the PFIC resubmission could not be used to assess the cost-effectiveness of odevixibat (paragraph 7.11, odevixibat PSD, March 2025 PBAC Meeting with Addendum July 2025). The evaluation and the ESC considered it highly uncertain whether clinical benefit observed in the 24 week treatment period from ASSERT would be maintained for the model horizon.

6.56 In the base case, treatment response was defined as the proportion of patients with a ≥1.0 point reduction in the ObsRO morning pruritus score from baseline. The 24 week response rate from the Sponsor's post-hoc pooled analysis was applied (82.4%, Table 6). A response rate of 0% was assumed for the SoC arm which the evaluation and the ESC considered was not reasonable as this was not supported by results from ASSERT, which observed pruritus reduction in the SoC arm (40% at 24 weeks).

6.57 The model structure did not permit patients receiving odevixibat (i.e. responsive to treatment) to develop cirrhosis, ascites, PHT or require LT. The evaluation and the ESC considered that this was not reasonable as it was inconsistent with ASSERT-EXT, which showed one patient discontinued odevixibat in order to undergo LT, and no patients in either arm developed cirrhosis, ascites or PHT. As patients receiving odevixibat were assumed in the model to not be at risk of disease progression, a reduction in LT and overall survival benefit from odevixibat treatment was indirectly assumed. The PSCR argued that the treatment discontinuation rate applied in the model includes loss of response; thereby allowing patients receiving odevixibat to experience disease progression. However, this implies that patients cannot progress while still on treatment, as progression can only occur after treatment discontinuation. The evaluation and the ESC considered it was not reasonable for native liver survival, nor an overall survival benefit (see also paragraph 6.69) to be modelled, as this was not supported by the presented clinical evidence and likely results in an overestimation of the incremental benefits of odevixibat.

6.58 The baseline patient age was six months. The submission claimed that a starting age of six months was clinically reasonable as chronic cholestasis typically manifests within the first three months of life, often with jaundice and/or cardiac symptoms. The evaluation and the ESC considered that the baseline age of six months may not be reasonable, as this was younger than the ASSERT trial cohort (mean 6.29 years, median 5.45 years) and the Australian early access program (mean 4.4 years, median 2.8 years). In addition, in the GALA study (N=1433) the median age of diagnosis was 4.1 years (IQR 1.5 – 8.3) (Vandriel 2022). The evaluation and the ESC considered that use of a baseline age of 6 months may underestimate odevixibat acquisition costs as it assumed that patients commenced odevixibat on the lowest possible dosage (due to weight-based dosing), particularly as a discontinuation rate derived from ASSERT-EXT (which had a mean baseline age of 6.6 years) was applied to patients commencing

treatment at six months. The PBAC considered a starting age of 6 months in the model was not reasonable and would underestimate odevixibat acquisition costs.

6.59 Patients who discontinue odevixibat treatment were assumed to lose response, transitioning from the responder to non-responder state. The base case modelled median and mean time on treatment (ToT) was 7.59 years and 12.63 years, respectively. The longer mean ToT was due to a long tail of odevixibat responders. For example, at the end of the 50-year time horizon, 4% of odevixibat patients remained on treatment in the 'responder' health state.

6.60 Responder and non-responder health state mortality was informed in the base case via log-logistic parametric extrapolation of digitised Kaplan-Meier data from the GALA study (Vandriel 2022, Hansen 2021). The submission's base case survival analysis showed median survival for the selected log-logistic curve was not reached with 66.1% of patients alive at 100 years, which the evaluation noted was not plausible.

6.61 The base case model assumed patients post LT would have a higher risk of mortality compared with patients in the responder health state (receiving odevixibat). The 0.92% per 12-week cycle risk of death was based on an 80% five-year survival reported in Hou 2021, which was a meta-analysis (n=22 studies) of LT in infants (aged <12 months). The reasons for transplant were 'biliary atresia/cholestatic disease' and 'acute hepatic failure/metabolic disorder'. The study did not report the number of patients represented by the pooled data, though noted that most of the included studies had limited sample size. The evaluation considered it unclear whether the survival rate of infants that were indicated for LT would be applicable to the ALGS PBS population, as these patients may likely reflect more severe disease to have been indicated for LT at infancy. The GALA study (Vandriel 2022) and ANZLITR both report a five-year survival post LT of 91%, versus 80% applied in the base case. The evaluation also noted that NICE considered that, based on clinical expert advice, certain patients may achieve near-normal life expectancies post LT. As such, the ESC considered it was not reasonable for the post-LT health state to have lower survival rates than the responder/non-responder health states.

6.62 The base case additionally applied a once-off mortality risk of 25.17% for patients at the time of LT surgery, based on Emerick 1999 (US based retrospective study from 1974 to 1997 of 92 patients with ALGS). LT was required in 19/92 patients, with four deaths recorded after LT at a mean age of 71 months. The PBAC considered it was highly unlikely this historical rate would be applicable to current Australian practice. In addition, as an increased per cycle mortality risk was already applied for patients post-LT, this once-off risk of death likely double-counted the mortality risk associated with LT. The PSCR claimed that the GALA study showed 52% of patients die within 30 days post-LT; however, the ESC considered this was incorrect. Patient survival rates in the GALA study following LT at 5, 10, and 20 years were 92.0%, 91.0%, and 88.0%, respectively. The source of '52% within 30 days' stated in Vandriel 2022 is not

described in the text, though may refer to the proportion of deaths post LT which occurred within the first 30 days.

6.63 The progression from non-responder to LT was based on a rate of 47% at 4 years, informed from Quiros-Tejeira 1999 (retrospective review of 43 children identified with cholestasis and ALGS from 1976–1997 at the University of California, Los Angeles, and from 1980–1997 at the University of California, San Francisco). Twenty patients (47%) underwent LT at a median age of 4 years (range, 1.3-15.4 years). The PBAC considered that use of the median age of LT as a proxy for the risk of LT over a four year time period was highly uncertain, and data from nearly 50 years ago was unlikely to be relevant to current practice. The GALA study (N=1433) reported the cumulative incidence of LT at 5, 10, and 18-years was 27.1%, 37.8% and 50.4% respectively; which was lower than the 47% at four years applied in the base case.

6.64 Utility values derived from ASSERT PedsQL data were mapped on to (EuroQol 5-Dimension 5-Level) EQ-5D utilities using the algorithm by Khan 2014 (UK based algorithm), which was also previously used in the 2024 odevixibat PFIC submission (Table 11, odevixibat PSD, July 2024 PBAC Meeting). Utilities were age-adjusted relative to the general population utility, based on the age and sex-matched general Australian population, to account for the change in baseline utility value with age.

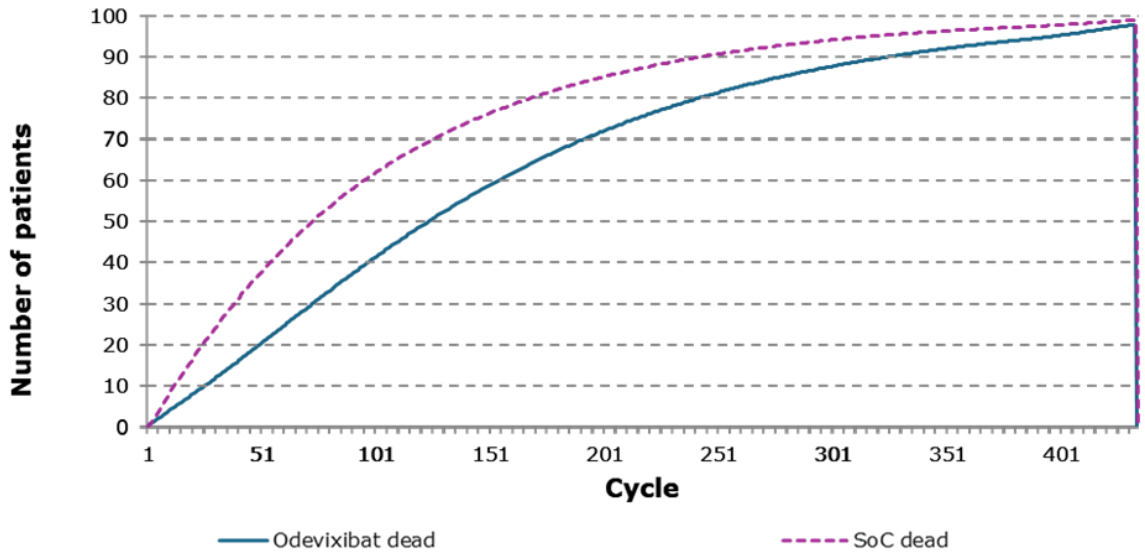
6.65 For the July 2024 PFIC PBAC resubmission, the utility values for the responder and non-responder health states were 0.91 and 0.83 respectively, derived from Kamath 2015 (Table 11, odevixibat PSD, July 2024 PBAC Meeting). The incremental utility benefit between the responder and non-responder was therefore 0.08 (0.91 – 0.83), which was noted to be smaller than the incremental utility in the ALGS model base case (0.147 = 0.881 – 0.734). The evaluation and the ESC considered there was no clinical justification proposed for why patients with ALGS would achieve approximately 1.8 times greater incremental utility than PFIC patients from odevixibat treatment, given that in both patient populations cholestatic pruritus is being managed.

6.66 The utilities for the LT and post LT health state were informed by published literature (Kini 2011 and NICE 2024, respectively). The LT health state utility (0.710) was consistent with the odevixibat PFIC economic model, however the post LT utility was greater in the submission compared the PFIC model (0.820 versus 0.774, respectively) (Table 13, odevixibat PSD, July 2024 PBAC Meeting). The post LT utility was reportedly consistent with the maralixibat NICE submission, however as these values were redacted in the NICE committee papers this could not be verified. The evaluation considered it was unclear whether it was reasonable for the post-LT health state to have lower utility than the responder health state (0.820 versus 0.881, respectively) given that, according to clinical experts consulted by NICE, some patients may achieve near-normal life expectancies post LT.

6.67 The base case did not apply SoC treatment costs to the odevixibat arm, which was inconsistent with the proposed clinical algorithm and clinical evidence from ASSERT that showed odevixibat patients continued to receive concomitant medications including UDCA and rifampicin, among others. The exclusion of SoC costs likely underestimated incremental costs and biased the model in favour of odevixibat.

6.68 Mortality traces from the base case model is shown in Figure 3.

Figure 3: Mortality traces for the odevixibat and SoC arms



Source: Figure 3-6, p132 of the submission
Abbreviations: SoC = standard of care

6.69 The mortality traces show the model assumes an early and sustained survival benefit with odevixibat. Median survival occurs at Year 28 (cycle 124) for odevixibat versus Year 16 (cycle 72) for SoC, representing a 12-year extension in median survival. The evaluation and the ESC considered that the modelled survival benefit, which the model trace shows occurring near immediately after commencing odevixibat and being sustained over the 50-year time horizon (cycle 217) was not supported by the presented clinical evidence.

6.70 A comparison of modelled survival with the GALA study (Vandriel 2022) is presented in Table 14.

Table 14: Modelled mortality compared with the GALA study (Vandriel 2022)

Age (yrs)	Survival		
	Vandriel 2022 (N=1433) [a]	Model	
		Odevixibat	SoC
5	92.8%	90%	79%
10	91.2%	81%	64%
18	88.1%	66%	45%

Source: Constructed during evaluation from Vandriel 2022 and the submissions economic model 'Markov Trace' worksheets
[a] Vandriel 2022 (i.e. GALA study) included a cohort of 1433 (57% male) clinically and/or genetically confirmed children with ALGS, with a median follow-up of 6.0 years (IQR 2.6 – 12.0).

6.71 Modelled survival in the SoC arm was substantially lower than overall patient survival reported in Vandriel 2022, and the modelled odevixibat arm survival was also lower. Overall, the PBAC considered that the modelled survival outcomes demonstrated poor external validation, and therefore the reliability and generalisability to the PBS ALGS population was highly uncertain.

6.72 The key drivers of the economic model are summarised in Table 15.

Table 15: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY
Assumption of a 0% SoC response rate	The model assumed a 0% pruritus response in the SoC arm. This was inconsistent with the 40% response rate reported in the Sponsor's post-hoc pooled analysis.	High, favoured odevixibat. Assuming a 40% SoC response rate per the Sponsor's pooled analysis increased the ICER by [redacted]% ($[redacted][1]/QALY).
SoC treatment costs	The model assumed that odevixibat treatment would replace SoC. I.e. no SoC treatment costs (UDCA, rifampicin etc.) were accrued in the odevixibat arm. This was inconsistent with the proposed clinical algorithm and clinical trial data from ASSERT which showed odevixibat treated patients continued to receive these concomitant medications.	High, favoured odevixibat. Including SoC treatment costs in the odevixibat arm increased the ICER by 115% ($[redacted][1]/QALY).
LT related mortality	The model assumed a once-off risk of death of 25.17% with LT surgery, in addition to an increased risk of death following LT compared to the responder and non-responder health states. In addition, the post-LT survival (80% at five years in the SOC arm) was lower than that reported by Vandriel 2022 and the Aus/NZ transplant registry (91% at 10 yrs)	High, favoured odevixibat. Removal of the once-off 25% risk of death with LT increased the ICER by [redacted]% ($[redacted][1]/QALY). Use of Vandriel 2022 post LT survival ([redacted]% at 10 years) increased the ICER by [redacted]% ($[redacted][1]/QALY).
Baseline age	The model assumed all patients commenced odevixibat treatment at six months of age. Due to the weight-based dosing of odevixibat, this meant that patients commenced treatment at the lowest possible dose.	High, favoured odevixibat. Increasing the baseline age to 6.29 years (ASSERT mean baseline) increased the ICER by [redacted]% ($[redacted][1]/QALY).
Rate of LT in non-responders	The progression from non-responder to LT was 47% at 4 years, informed from Quiros-Tejeira 1999 (N=43). This was higher than what was observed in the GALA study, reported the cumulative incidence of LT at 5, 10, and 18-years was 27.1%, 37.8% and 50.4% respectively.	Moderate, favoured odevixibat. Reducing the rate of LT to 50.4% at 18 years increased the ICER by [redacted]% ($[redacted][1]/QALY).

Source: Various sensitivity analyses from the economic model
Abbreviations: ICER = incremental cost effectiveness ratio; QALY = quality adjusted life years; SoC = standard of care; UDCA = ursodeoxycholic acid
The redacted values correspond to the following ranges:
[1] > $1,055,000

6.73 Results of the economic evaluation (Base Case 2; carer disutility excluded) are presented in Table 16. The submission did not present a stepped economic evaluation.

Table 16: Results of the economic evaluation (Base Case 2)

Component	SoC	Odevixibat	Incremental
Discounted			
Costs	$301,438	$[redacted]	$[redacted]
QALYs	8.733	11.608	2.88
LYs	*11.31*	*14.01*	*2.70*
Incremental cost/extra QALY gained			$[redacted][1]
Undiscounted			
Costs	$473,460	$[redacted]	$[redacted]
QALYs	16.480	23.718	7.238
LYs	21.111	28.999	7.888
Incremental cost/extra QALY gained			$[redacted][2]

Source: Table 3-30, p136 of the submission, submission's economic model

The redacted values correspond to the following ranges:

[1] *> $1,055,000*

[2] *$855,000 to < $955,000*

6.74 The submission's economic model estimated incremental discounted QALYs and LYGs of 2.88 and 2.70, respectively. The model estimated an incremental life year gain (LYG) of 7.9 years (undiscounted) from odevixibat treatment, largely resulting from the increased mortality associated with higher rates of LT in the SoC arm. In the July 2025 PFIC resubmission, the estimated incremental discounted QALY and LYG for patients treated with odevixibat were 1.21 and 0.57, respectively (Table 14, odevixibat PSD, March 2025 PBAC Meeting with Addendum July 2025). The ESC noted that the QALY gain in the PFIC population was much lower than stated for ALGS, potentially due to the baseline age for the PFIC base case of 4.26 years, compared to 6 months for the current submission for AGLS. The evaluation considered that there was no clinical justification proposed to explain why patients with ALGS would achieve substantially greater incremental benefit from odevixibat than patients with PFIC. The ESC considered that it may not be reasonable for LYGs to be modelled, given that the clinical data from ASSERT and ASSERT-EXT did not capture OS as an outcome.

6.75 The results of key univariate and scenario sensitivity analyses are summarised in Table 17.

Table 17: Key sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	Δ%
Base case 2	**$[redacted]**	**2.88**	**$[redacted][1]**	**-**
Carer disutility included (base case excluded)	$[redacted]	5.58	$[redacted][2]	-[redacted]%
Discount rate (base case 5% costs and outcomes)				
• 0% costs and outcomes	$[redacted]	7.24	$[redacted][3]	-[redacted]%
• 3.5% costs and outcomes	$[redacted]	3.63	$[redacted][4]	-[redacted]%
Time horizon (base case 50 years)				
• 20 years	$[redacted]	1.97	$[redacted][1]	[redacted]%
• 10 years	$[redacted]	1.11	$[redacted][1]	[redacted]%

Analyses	Incremental cost	Incremental QALY	ICER	Δ%
Baseline age (base case 6 months)				
• 6.29 yrs (ASSERT mean baseline)	$[redacted]	2.86	$[redacted]	[redacted]%
• 4.4 yrs (Australian EAP mean)	$[redacted]	2.87	$[redacted]	[redacted]%
Odevixibat response rate (base case 82.4%, Sponsor pooled analysis)				
• 80% (ASSERT 24 weeks)	$[redacted]	2.79	$[redacted]	[redacted]%
SoC response rate (base case 0% assumed)				
• 35.3% (ASSERT 24 weeks) [a]	$[redacted]	1.64	$[redacted]	[redacted]%
• 40% (Sponsor pooled analysis) [a]	$[redacted]	1.48	$[redacted]	[redacted]%
Median time on treatment (base case 7.6 yrs; post hoc analysis[b] of 5/50 patients at 92.6 weeks)				
• 5.3 yrs (6/50 patients at 72 weeks; ASSERT-EXT) [b]	$[redacted]	2.28	$[redacted]	-[redacted]%
• 10 yrs	$[redacted]	3.35	$[redacted]	[redacted]%
Rate from non-responder to LT (base case 2.7% per cycle; derived from 47% at 4 yrs; Quiros-Tejeira 1999)				
• 1.2% (Vandriel 2022; 27.1% at 5 yrs)	$[redacted]	2.58	$[redacted]	[redacted]%
• 0.9% (Vandriel 2022; 37.8% at 10 yrs)	$[redacted]	2.45	$[redacted]	[redacted]%
• 0.6% (Vandriel 2022; 50.4% at 18 yrs)	$[redacted]	2.36	$[redacted]	[redacted]%
Mortality at time of LT surgery (base case 25.17%)				
• Once-off risk removed (0%)	$[redacted]	2.23	$[redacted]	[redacted]%
Mortality post LT surgery (base case 0.92% per cycle; derived from 20% at 5 yrs; Hou 2021)				
• 0.21% (Vandriel 2022 and Aus/NZ transplant registry; 9% at 10 yrs)	$[redacted]	2.01	$[redacted]	[redacted]%
• 0.14% (Vandriel 2022; 12% at 20 yrs)	$[redacted]	1.89	$[redacted]	[redacted]%
Post LT health state utility (base case 0.82 versus 0.881 in responder)				
• Equal to responder (0.881)	$[redacted]	2.74	$[redacted]	[redacted]%
Scenario analyses				
Utility values (base case: responder =0.88; non-responder/cirrhosis/PHT/ascites =0.73; LT = 0.71; post-LT=0.82				
• Kamath utilities [c] (responder =0.80; non-responder =0.76)	$[redacted]	2.22	$[redacted]	[redacted]%
Submission's alternative mortality inputs [d]	$[redacted]	0.97	$[redacted]	[redacted]%
Odevixibat arm including concomitant treatments (base case assumes no SoC treatments)				
• SoC treatment costs included [e]	$[redacted]	2.88	$[redacted]	[redacted]%

Source: Table 3-33, p142 of the submission, additional sensitivity analyses conducted during evaluation.
Aus = Australian; EAP = early access program; LT = liver transplant; NZ = New Zealand; SoC = standard of care; yrs = years
[a] The SoC response rate was changed by editing Cell P153 and Q153 in the 'Data Store' worksheet from 0% and 100%, to the selected response rate and its complement (i.e. 1 –response rate), respectively.
[b] The flow of participants table in the submission reported 6/50 patients did not complete the 72-Week treatment period, which was inconsistent with the post-hoc analysis presented in the submission (5/50 patients at 92.6 weeks).
[c] The submission's "Kamath utilities" reduce the Responder utility from 0.88 to 0.80 and increase the Non-responder utility from 0.73 to 0.76. Lowering the Responder utility to 0.80 results in the Post-LT health state having higher utility than the Responder health state (0.82 versus 0.80, respectively).
[d] The submission included an alternative set of mortality transition probabilities which applied a per cycle mortality risk for the responder, non-responder and cirrhosis health state of 0.28% derived from (Vandriel 2022; mortality prior to LT of 6.10% at 5 years). This scenario also reduced the post-LT mortality from 0.92% per cycle to 0.37% per cycle and reduced the risk of death at time of LT from 25.17% to 2.75%.
[e] The treatment cost formula in columns BK:BN of 'Markov Trace (SoC)' were copied to the respective columns in 'Markov Trace (Odevixibat)'. For the responder health state, the treatment cost calculation in column BJ of 'Markov Trace (SoC) was added to the odevixibat

treatment cost calculation in BJ 'Markov Trace (Odevixibat)". Cholestyramine use was excluded in this analysis (usage set to 0%) to align with the ASSERT trial as odevixibat patients were not permitted to receive cholestyramine.
The redacted values correspond to the following ranges:
[1] *> $1,055,000*
[2] *$455,000 to < $555,000*
[3] *$855,000 to < $955,000*
[4] *$955,000 to < $1,055,000*

6.76 Overall, the evaluation and the ESC considered that the base case ICER of > $1,055,000 per QALY gained to be unreliable, underestimated, and favoured odevixibat, as:

- A time horizon of 50 years was applied, versus 24 weeks of comparative clinical evidence. It was highly uncertain whether the clinical benefit from odevixibat treatment observed in the 24-week treatment period would be maintained for the model horizon (see paragraph 6.55).
- Patients in the odevixibat arm were assumed to not be at risk of liver complications or disease progression, including cirrhosis, ascites, PHT or requiring LT (see paragraph 6.57).
- The base case extrapolated survival curves for the responder and non-responder health states lacked face validity, as median survival was not reached with the selected log-logistic curve, with 66.1% of patients alive at 100 years, which was not plausible (see paragraph 6.60).
- The modelled early and sustained overall survival benefit with odevixibat treatment was not supported by any clinical evidence (see paragraph 6.57 and Table 14).
- The QALY gain was much higher in the ALGS model than the PFIC model (see paragraph 6.74)
- There were zero SoC treatment costs accrued in the odevixibat arm, which was inconsistent with the clinical evidence from ASSERT and the proposed clinical algorithm (see paragraph 6.67).
- The baseline patient age of six months was younger than the ASSERT trial cohort (mean 6.29 years) or the Australian EAP (mean 4.4 years), which meant that patients were assumed to commence treatment on the lowest possible dose (see paragraph 6.58).
- The base case assumed a SoC response rate of 0%, which was not supported by the clinical evidence (see paragraph 6.56).
- The applied once-off risk of death at the time of LT of 25.17% lacked face validity and was notably higher than the one-year survival rate reported by ANZLITR for patients with ALGS post LT (91%) (see paragraph 6.62).

- The per cycle mortality risk for patients post LT was derived from a five-year survival of 80% (Hou 2021), which was lower than the GALA study and ANZLITR which both report a post-LT survival of 91% at five years (see paragraph 6.61).

6.77 The ESC noted the PBAC had previously considered odevixibat would be cost effective (for PFIC) with a cost per patient per year in the order of $[redacted] (paragraph 13.3, odevixibat PSD, July 2025 PBAC meeting). However, the ESC considered it remained highly uncertain if a similar cost per patient per year would be cost-effective for ALGS.

Drug cost/patient/year

Table 18: Drug cost per patient for proposed drug (AEMP)

	Trial (ASSERT)	Model	Financial estimates	July 2025 PFIC proposal	ALGS aligned with July 2025 PFIC patient weight
Mean dose	120 µg/kg/day	120 µg/kg/day	120 µg/kg/day	40 µg/kg/day	120 µg/kg/day
Patient age	6.29 years	Starting age 6 months	4.4 years (EAP)	Mean age 13 years	-
Patient weight	18.6kg	Starting weight 3.95kg	19.7kg (EAP)	45.1 kg	45.1kg
Daily dose [a]	2,232 µg	600 → 7200 (increasing with age)	2,358 µg	1,804 µg [c]	5,412 µg
Tablet strength	1200 µg	600 → 1200	1200 µg	400 µg	1200 µg
Tablets per day	1.86	-	1.97	4.51	4.51
AEMP/pack (30 units)	$[redacted]	$[redacted] → $[redacted]	$[redacted]	$[redacted]	$[redacted]
Per tablet cost	$[redacted]	-	$[redacted]	$[redacted]	$[redacted]
Per day cost	$[redacted]	-	$[redacted]	$[redacted]	$[redacted]
Cost per year	$[redacted]	$[redacted] [b]	$[redacted]	$[redacted]	$[redacted]

Source: Compiled from information in Table 24 March 2025 PBAC Meeting; ASSERT mean patient weight from Table 2-9, p54 of the submission; Undiscounted costs from Economic model 'Results' worksheet; Financial workbook '3c. Impact – proposed (eff)'.
Abbreviations: AEMP = approved ex-manufacturer price; EAP = early access program; NR = not reported; PFIC = progressive familial intrahepatic cholestasis
[a] Daily dose calculated by multiplying patient weight and mean dose. For example, 120 µg x 18.6kg = 2,232 µg
[b] Undiscounted odevixibat drug costs per patient $[redacted] (Cell E67 'Results') divided by modelled mean treatment duration (i.e. $[redacted] / 12.63 years = $[redacted] per year).
[c] 400 µg x 4.51

6.78 The cost per patient per year varied between the ASSERT trial, economic model, and financial estimates due to the use of different patient weights. In practice, the number of tablets per day would be rounded, i.e. the cost per year between a patient weighing 18.7kg and 19.7kg would likely be equivalent as both patients fall within the 17.5 to <25.5kg weight category for dosing.

6.79 The economic model cost per patient per year was notably higher than the trial based and financial estimates. This was due to the model assuming a substantial proportion of patients remain on treatment for more than 10 years. For instance, the responder population in the odevixibat arm remains at 43% at Year 10, declining to 23% at Year 20 and 4% by Year 50. Patients over 55.5kg (≈14–15 years and older per the submission's weight assumptions) require the maximum dosing according to the

product information of 6 x 1,200 µg tablets (7,200 µg per day; daily cost of $[redacted]; annual cost of $[redacted]) and therefore accrue a higher average treatment cost. The annual treatment cost increases significantly with patient weight.

6.80 The submission claimed that the annual drug cost based on the average age of a patient in the Australian early access program ($[redacted]) closely aligned to the annual cost of $[redacted] per patient accepted for the PFIC July-2025 submission. The evaluation considered that this comparison may not be reasonable as different patient ages were used to estimate each annual cost. A much younger patient population was assumed for the ALGS population compared to the July 2025 PFIC proposal (4.4 years versus 13 years, respectively). All else being equal, a dosage of 120 µg/kg/day will be three times that of 40 µg/kg/day at an AEMP of $[redacted] / mcg. The PSCR claimed that ALGS patients are notably younger than those with PFIC, commonly diagnosed within the first few months of life. However, the ESC noted patients with PFIC1 and PFIC2 (the most common subtypes) also frequently show clinical indications of cholestasis in the first few months of infancy. In addition, the mean age of the PEDFIC 1 (N=62) PFIC cohort was younger than the ASSERT (N=52) cohort (4.25 years and 6.29 years, respectively) and differed to the baseline age of 0.5 years used in the economic model. The PBAC considered comparing the cost per patient per year across patients with different weights was not appropriate.

Estimated PBS usage & financial implications

6.81 This submission was not considered by DUSC.

6.82 The submission used an epidemiological approach to estimate the use and financial implications of listing odevixibat for ALGS patients with cholestatic pruritus. The key data sources and primary assumptions used in the submission's utilisation and cost model are presented in Table 19.

Table 19: Key inputs for financial estimates

Data	Value / Source	Comment
Eligible population		
Incident patients	Applied 1 in 30,000 live births. Yr 1 (2026): 0 Yr 2: 10 Yr 3: 10 Yr 4: 11 Yr 5: 11 Yr 6: 11 Source: Leonard 2014 and Powell 2003 reported an incidence of 1 in 30,000 live births. Leonard 2014 estimated an incidence of 1 in 30,000–50,000 live births, however the author does not provide details for how this estimate was calculated. Incidence rate was applied to ABS birth projections 2025-26.	Uncertain, and likely over-estimated. A large study from Victoria, Australia (Danks 1977) of 790,385 children reported an incidence at birth of 1 in 70,000. The ALGS Alliance reports the current estimated incidence of ALGS is between 1 in 30,000–70,000. For context, the July 2025 odevixibat PFIC resubmission, which was based on an incident rate of 1 in 50,000, adopted an incidence of 4 patients per year (Table 27, odevixibat PSD, March 2025 PBAC Meeting with Addendum July 2025).

Data	Value / Source	Comment
Prevalent patient pool	Applied 1 in 100,000 prevalence rate to the ABS 2025 population. Yr 1 (2026): 280 Yr 2: 0 Yr 3: 0 Yr 4: 0 Yr 5: 0 Yr 6: 0 Source: Diaz-Frias 2022 reported an estimated prevalence from 1 in 30,000 to 1 in 100,000.	Uncertain and likely overestimated. The proportion of prevalent patients with prior LT was not considered in the submission. In consideration of odevixibat for PFIC, DUSC noted that prevalence should not apply to the entire population, but to the population aged 0-19 years and adult patients estimated separately (para 6.56, odevixibat PSD, March 2025 PBAC Meeting with July 2025 Addendum). The same approach may be appropriate for ALGS given the older population are more likely to have died or undergone LT. For context, the July 2025 odevixibat PFIC resubmission applied 0.07 per 10,000 to people aged 0-19 years (n=48) in addition to n=10 adult patients with PFIC (Table 26, odevixibat PSD, March 2025 PBAC Meeting with Addendum July 2025).
Grandfathered patients	N=[redacted][1] Source: [redacted][1] patients currently receive an iBAT inhibitor therapy via Sponsor EAPs. Of these patients, 13/[redacted][1] are receiving odevixibat and 17/[redacted][1] are receiving maralixibat. The submission stated advisory board feedback indicated hepatologists will transition all ALGS patients currently on iBAT inhibitors to odevixibat once listed on the PBS.	Reasonable.
Cholestasis prevalence	92.1% Source: Kamath 2018b. ALGS patient data from of 4 studies was combined. There were 255 of 277 (92.1%) pooled patients with cholestasis.	Reasonable. Vandriel 2022 (i.e. the GALA study) reported liver involvement at any age was reported in 95% (n=1321/1387) of children
Moderate – severe pruritus	46.2% Source: Abetz-Webb 2014. Abetz-Webb 2014 was a qualitative study with 24 interviews of caregivers for ALGS patients. The criteria for each level of pruritus severity was not described and therefore highly uncertain.	The evaluation noted Vandriel 2022 (i.e. the GALA study) reported pruritus in 74% (n=761/1028) of children with ALGS. In addition, given that there is likely overlap between patients with cholestasis and patients with pruritus, the use of both eligibility conditions (0.921 x 0.462 = 0.425) may underestimate the number of eligible patients owing to double counting.
Treatment utilisation		
Uptake rate – incident patients	Initiating: [redacted]% Source: Assumption.	The submission claimed this would be typical for new therapies in rare diseases that involve specialist care, and due to the heavy symptom burden and potential to delay LT.
Uptake rate – prevalent patients	Yr 1: [redacted]%; Yr 2: [redacted]%; Yr 3: [redacted]% (Total 100%) Source: Advisory board input.	The PBAC considered uptake in Year 1 in the prevalent population may be higher than proposed.
Continuation/ response rate	87.4% (88.5% - 1.1%) Source: 88.5%: Sponsor post-hoc pooled analysis of pruritus responder (≥1.0 point pruritus reduction in the	The proportion of patients with ≥1.0 point pruritus reduction in AM scores was a secondary endpoint of ASSERT and ASSERT-EXT and therefore uncertain.

<table>
<tr><th>Data</th><th>Value / Source</th><th>Comment</th></tr>
<tr><td></td><td>AM scores) patients at 48 weeks in ASSERT and ASSERT-EXT

Source: 1.1%: Sponsor post-hoc pooled analysis of discontinuation of odevixibat at 92.6 weeks due to TEAE in pooled ASSERT and ASSERT-EXT (1/50 patients) converted to annual rate.</td><td>The response rate of 87.4% was also inconsistent with the economic model response rate (82.4%), and the 24-week response rate in ASSERT (80%)

It was not reasonable to deduct discontinuation from the response rate, given these patients would still commence odevixibat.</td></tr>
<tr><td>Compliance</td><td>95.5%
Source: Mean compliance rate from ASSERT (n=35) at 24 weeks (95.51%, SD 8.17)</td><td>Reasonable.</td></tr>
<tr><td>Dosage</td><td>Patient weight: 19.7kg (average age of 4.4 years)
Dose: 120 µg/kg/day
Applied daily dose: 2,358 µg
Source: The mean weight of patients in the Australian EAP (N=6) was 19.7kg (range 5.8 – 41.3kg).</td><td>The use of a constant patient weight across the incident and prevalent population would not be reasonable given that incident and prevalent patients are expected to differ significantly in age and weight.</td></tr>
<tr><td>Scripts</td><td><table><tr><th>Strength</th><th>Capsules / month [a]</th><th>Scripts / year [b]</th><th>Population split %</th></tr><tr><td>200 µg</td><td>358.9</td><td>11.4</td><td>5.0%</td></tr><tr><td>400 µg</td><td>179.4</td><td>11.4</td><td>5.0%</td></tr><tr><td>600 µg</td><td>119.6</td><td>3.8</td><td>30.0%</td></tr><tr><td>1200 µg</td><td>59.8</td><td>3.8</td><td>60.0%</td></tr></table>[a] (2,358 µg daily dose / strength) x (365.25/12)
[b] 12.00 / (max units / capsules per month) * compliance

Source: Population split assumed by submission</td><td>The inclusion of 200 µg and 400 µg capsule strengths was inconsistent with the applied 120 µg/kg/day dosage and resulted in an inflated number of scripts (near 1 script per month) at these strengths which lacked face validity.

The inflated 200 µg and 400 µg script numbers resulted in overestimated co-payments, dispensing and administration fees.</td></tr>
<tr><td>Duration of treatment</td><td>Initiating: 6 months; Continuing: 66 months
(Total 72 months / 6 years)
The submission claimed patients are expected remain on odevixibat treatment for 72 months as supported by the ASSERT-EXT trial duration. However, the ASSERT-EXT trial duration was 72-weeks.</td><td>Highly uncertain. The submission's economic model calculated a median and mean treatment duration of 7.59 and 12.63 years, respectively. In ASSERT-EXT, 12.00% (6/50) of patients did not complete the 72-week treatment period. The March 2025 PFIC estimates applied an initial treatment duration of 3 months and a continuing treatment duration of 72 months (Table 19, odevixibat PSD, March 2025 PBAC Meeting with Addendum July 2025).</td></tr>
</table>

Source: Constructed during evaluation from Table 4-1, Table 4-2, Table 4-3, Table 4-4, Table 4-5, Table 4-6 of the submission and submission's utilisation and cost model.

Abbreviations: ABS = Australian Bureau of Statistics; ALGS = Alagille syndrome; CSR = clinical study report; iBAT = ileal bile acid transporter; LT = liver transplant; PBS = Pharmaceutical Benefits Scheme; PI = product information; RPBS = Repatriation Pharmaceutical Benefits Scheme: SD = standard deviation; UDCA = ursodeoxycholic acid; Yr = year

The redacted values correspond to the following ranges:

[1] *< 500*

6.83 The estimated use and financial impacts of listing odevixibat is presented in Table 20.

6.84 The submission assumed that uptake in the prevalent population would be split between the first three years of listing (Year 1: [redacted]%; Year 2: [redacted]%; Year 3: [redacted]%). However, the evaluation noted that grandfathered patients were only subtracted from the Year 1 prevalent patient pool, resulting in likely double counting of prevalent patients.

6.85 The submission claimed that as odevixibat is expected to be used as adjunctive therapy to SoC pharmacotherapy in patients with ALGS, no PBS-listed medicine is likely

to be replaced by odevixibat. This was inconsistent with the submission's base case economic model, which assumed that odevixibat would replace SoC therapies.

Table 20: Estimation usage and net financial impact of the propose listing at effective price

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Prevalent and incident patients						
Prevalent patients	280	280	280	0	0	0
Incident patients	0 [a]	10	10	11	11	11
Number of patients eligible						
Prevalent patients	89 [b]	119	119	0	0	0
Incident patients	0	4	4	5	5	5
Number of initiating patients						
Prevalent patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Scripts (95.5% compliance)						
Total scripts [b]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net cost to PBS/RPBS						
Net impact	$[redacted][3]	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]

Source: Constructed from Table 4-5 and Table 4-6 of the submission, and Sheets 2a. and 2b. of the submission's cost model.
[a] Year 1 incident patients were assumed to be included in the prevalent pool.
[b] Excluding n=< 500 grandfathered patients
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *500 to < 5,000*
[3] *$10 million to < $20 million*
[4] *$20 million to < $30 million*
[5] *$30 million to < $40 million*

6.86 The net cost to the PBS/RPBS of listing odevixibat was estimated to be $10 million to < $20 million in Year 1, increasing to $30 million to < $40 million in Year 6, totalling $100 million to < $200 million over the first 6 years of listing.

6.87 The evaluation and the ESC considered that the incident and prevalent patient pool was likely overestimated, as:

- The applied incidence rate of 1 in 30,000 live births (10–11 patients per year) was the highest rate identified in the literature, which range from 1 in 30,000 to 1 in 70,000 live births.
- The prevalence rate of 1 in 100,000 was applied to the entire population which may not be appropriate given the older ALGS population are more likely to have undergone LT or died. Previous DUSC advice in consideration of odevixibat for PFIC noted that prevalence should be estimated separately in adult patients (para 6.56, odevixibat PSD, March 2025 PBAC Meeting with Addendum July 2025).
- Grandfathered patients were not subtracted when estimating the Year 2 and Year 3 prevalent patient pool, resulting in likely double counting.

6.88 The evaluation and the ESCs considered that proportion of eligible patients may be underestimated as the applied proportion of ALGS patients with moderate to severe pruritus (46.2%; Abetz-Webb 2014) was lower than reported in the GALA study (74%; n=761/1028). In addition, the evaluation and the ESC considered it may not be

reasonable to apply independent pruritus and cholestasis eligibility filters (46.2% and 92.1%, respectively) as these criteria are likely to substantially overlap.

6.89 The evaluation and the ESCs considered the applied continuation/response rate (87.4%) was uncertain as it was based on a Sponsor conducted post-hoc pooled analysis of pruritus responders (≥1.0 point pruritus reduction in the AM scores) at 48 weeks and was inconsistent with the economic model response rate (82.4%). In addition, the assumed duration of treatment of 6 years was uncertain.

6.90 Dosage was based on the mean weight of patients in the Australian EAP (19.7kg, N=6). The use of a constant weight across the incident and prevalent population was uncertain given these patients are expected to differ in age and weight (see also paragraph 6.78).

6.91 The estimates assumed that no patients would discontinue odevixibat over the financial estimates. The evaluation considered that this may not be reasonable as in ASSERT-EXT, 12% (6/50) of patients did not complete the 72-week treatment period.

6.92 Overall, the evaluation and the ESC considered that it was unclear whether the net impact to the PBS/RPBS of listing odevixibat was overestimated or underestimated, as whilst the number of incident and prevalent patients was likely overestimated, the proportion of eligible patients may be underestimated. In the Pre-PBAC Response the sponsor acknowledged the uncertainties highlighted by the ESC and indicated it "is willing to revisit the epidemiological framework of the financial estimates, including reviewing both incidence and prevalence assumptions and exploring modelling prevalent paediatric and adult ALGS populations separately to provide a more accurate reflection of real-world utilisation."

Quality Use of Medicines

6.93 The submission stated that the Sponsor will provide educational materials to specialist prescribers upon PBS listing, available to all relevant prescribers and hospitals, including diagnostic criteria for ALGS, instructions for using the ObsRO instrument, guidance on treatment initiation, dose reduction, and monitoring, and Information on when to consider treatment discontinuation.

6.94 The submission proposed that The Department of Health should monitor PBS claims data utilisation patterns against epidemiological projections, investigating any sustained deviation exceeding forecast; and that establishment of an Australian ALGS patient registry would improve epidemiological data and facilitate detection of usage beyond the restriction.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend odevixibat for the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged six months and older. The PBAC considered that there is high unmet clinical need for this rare genetic condition, which has severe impacts on quality of life, including sleep, comfort, and wellbeing. The PBAC considered that there is evidence that odevixibat can reduce itching more than current standard of care (SoC) treatments for some patients with ALGS. However, the PBAC noted that odevixibat is not disease-modifying, and no evidence was presented to support survival benefit. Additionally, the long-term benefits remain uncertain. The PBAC considered the economic model to be unreliable due to unsupported and optimistic structural assumptions and inputs. The PBAC considered that odevixibat would be cost-effective for ALGS at a cost per patient per year no higher than for PFIC. The PBAC considered the financial estimates need to be revised. The PBAC considered that a risk sharing arrangement (RSA) would be required.

7.2 The PBAC acknowledged the input from consumers, healthcare professionals and organisations describing the substantial burden of cholestatic pruritus in ALGS in this vulnerable population. The PBAC noted that that persistent and severe pruritus may significantly impair sleep, schooling, development, family functioning and mental health, and that intractable pruritus in children can be a reason for liver transplantation in the absence of liver failure. The PBAC noted that current treatments for this condition are not PBS listed, and are non-specific, with limited effectiveness. Therefore, the PBAC considered that there is a high unmet clinical need in this rare genetic condition.

7.3 The PBAC considered that odevixibat would be used primarily for the symptomatic management of cholestatic pruritus in ALGS, noting that odevixibat is not considered to be disease-modifying in ALGS and its impact on underlying liver disease progression or long-term outcomes is unclear. The PBAC also noted that evidence demonstrating improvements in quality-of-life outcomes with odevixibat was limited and uncertain.

7.4 The PBAC considered that the proposed comparator, SoC, including medicines used off-label (UDCA, rifampicin and cholestyramine) and surgical procedures (biliary diversion surgery [SBD] and liver transplant [LT]), was reasonable.

7.5 The PBAC noted that the proposed restrictions were broadly consistent with the listing for PFIC. While noting that the restrictions set a relatively low threshold for continuation of therapy in ALGS, the PBAC considered that, given this alignment, the following would be appropriate:

- Age agnostic.
- No requirement for genetic testing for initiation of therapy.
- Written authority for initial and grandfather prescriptions, and telephone authority for continuing prescriptions.

- Continuing restriction to include requirement for improvement in pruritis score and initial restriction to require demonstration of response by 3 (rather than 6) cumulative months of treatment.
- 2 repeats for initial treatment listing to allow for 3 months' initial treatment, as per PFIC. 5 repeats for continuing.
- Dose reductions should be allowed in initial and continuing restrictions and patients should be allowed to continue on the lower dose providing they demonstrate and maintain an adequate clinical response (via the ObSRO score).
- No stopping rule is required providing patients continue to maintain a positive response. Assessment of response should occur for each continuing prescription.
- Restrictions to specify where recommencement of treatment can occur (i.e., initial criteria if less than 3 months of treatment received or continuing criteria) if treatment is ceased for reasons other than lack of response.

7.6 The PBAC noted that the submission relied on a single small randomised controlled trial (RCT, ASSERT n=52) of odevixibat vs placebo, supplemented by a 72 week single-arm open-label extension (ASSERT-EXT). The PBAC noted that there was minimal long-term comparative efficacy data (24 weeks), and limited long-term safety data, which limited assessment of long-term outcomes, particularly as a response was observed in the placebo arm. Further, the PBAC noted that clinical outcomes associated with disease progression (including native liver survival) and overall survival (OS) were not assessed, and that efficacy data were limited to a 120 mcg/kg dose, with no data for the 40 µg/kg/day dose available. Additionally, the PBAC noted placebo in the trial did not fully represent the comparator (SOC) as the comparative clinical evidence did not include treatment with SBD or LT (previous or planned), or cholestyramine (see paragraph 5.1). The PBAC acknowledged the inherent challenges of evidence generation in rare diseases.

7.7 The PBAC considered that the claim of superior comparative effectiveness of odevixibat compared to placebo (as a proxy for SOC) was reasonable, based on statistically significant improvements in pruritus as measured by the observer-reported (ObsRO) pruritus scratching score (least square [LS] mean difference 24 weeks = -0.88 [95% confidence interval (CI): -1.44, -0.33]). The PBAC noted that there was a statistically significant difference in the proportion of patients with a ≥1.5-point ObsRO scratching score reduction from baseline (exceeding the proposed Minimal Clinically Important Difference (MCID) of 1.0 to 1.5 score reduction) for odevixibat treated patients compared with placebo at Weeks 21–24 (difference 36.7%, odds ratio 5.15 [95% CI: 1.17, 34.16]). Although improvements in some sleep parameters were noted (see paragraph 6.46), no evidence of improvement in quality of life (QoL, i.e. PedsQL) was reported. The lack of demonstrated QoL or survival

benefit and short comparative data (paragraph 7.6) limited confidence in the clinical relevance and duration of the observed treatment effects beyond the trial setting.

7.8 The PBAC considered that the claim of non-inferior comparative safety was reasonable, while noting that the available evidence was limited by small patient numbers and the short duration of comparative follow-up. The PBAC noted the increase of gastrointestinal adverse events, especially diarrhoea, were more frequently reported with odevixibat compared with placebo; however, these events were mostly mild to moderate in severity, manageable, and rarely led to treatment discontinuation. Overall, odevixibat was considered to be well tolerated, with no statistically significant differences observed between treatment groups for serious adverse events or treatment-emergent adverse events leading to discontinuation.

7.9 The PBAC agreed with the ESC that, as with the similar model submitted for PFIC, the economic model for ALGS was not reliable for decision-making because of both implausible structural assumptions and uncertain and highly optimistic data inputs (see paragraph 6.76, and paragraphs 6.63 and 13.3, odevixibat PSD, July 2025 PBAC meeeting). The PBAC recalled that it had previously considered odevixibat would be cost effective (for PFIC) with a cost per patient per year in the order of $[redacted] (paragraph 13.3, odevixibat PSD, July 2025 PBAC meeting).The PBAC agreed with the ESC that it remained highly uncertain if a similar cost per patient per year would be cost-effective for ALGS (see paragraph 6.77), noting the lack of clinical data on long term outcomes. However, the PBAC considered that in the context of the small and vulnerable population with a high clinical need for effective treatments, odevixibat may be cost effective for ALGS with a cost per patient per year no higher than for PFIC (assuming the same patient weight).

7.10 In terms of the estimated number of eligible patients, the PBAC agreed with the ESC that the estimated incident and prevalent patient pool was overestimated and noted that the financials were informed by the upper range of the epidemiological estimates, and considered that more conservative assumptions, including reductions to the estimated incidence and prevalence, may be appropriate. The PBAC advised it would be appropriate to estimate prevalence separately in paediatric and adult patients (see paragraph 6.56 odevixibat PSD, March 2025 PBAC Meeting with Addendum July 2025). The PBAC also noted that the price would need to be updated, as per paragraph 7.9.

7.11 The PBAC considered that a risk sharing arrangement (RSA) would be necessary to mitigate any outstanding uncertainty regarding the eligible number of patients and utilisation.

7.12 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for odevixibat using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.

- Provide revised restriction criteria, as per paragraph 7.5.
- Propose a cost per patient per year no higher than recommended for PFIC assuming a dose of 120 mcg/day and the same patient weight, as per paragraph 7.9.

- Financial estimates should be updated to use more conservative, lower-end utilisation estimates, separated into paediatric and adult patients, and the updated cost-effective price, as per paragraph 7.10.
- Propose an RSA, as per paragraph 7.11.

The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.