5.12 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 1 submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (STREAMLINED) listing for the treatment of progressive familial intrahepatic cholestasis (PFIC).

1.2 Listing was requested on the basis of a cost-utility analysis versus standard of care (SOC) including partial external biliary diversion (PEBD) and liver transplantation (LT).

1.3 The key components of the submission are presented in Table 1.

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

Component	Description
Population	Patients with progressive familial intrahepatic cholestasis
Intervention	Odevixibat 40 mcg/kg orally administered once daily with dose escalation to 120 mcg/kg/day if adequate clinical response is not achieved at 3 months
Comparator	Standard of care including partial external biliary diversion and liver transplant.
Outcomes	Serum bile acid (sBA) response, pruritis response, sleep parameters, growth parameters, quality of life, safety.
Clinical claim	Superiority in terms of sBA response and pruritus response at 24 weeks Non-inferiority in terms of safety

Source: Table 1-1, p20 of the submission

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. The TGA Delegate's Overview was available at the time of PBAC consideration. The proposed TGA indication for odevixibat is for treatment of PFIC in patients aged six months or older.

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty packs	№.of Rpts	Effective DPMQ	Proprietary Name and Manufacturer
ODEVIXIBAT. 200 microgram capsules, 30 units	12	5	Public: $[redacted] Private: $[redacted]	Bylvay Ipsen Pty. Ltd
ODEVIXIBAT. 400 microgram capsules, 30 units	6	5	Public: $[redacted] Private: $[redacted]	Bylvay Ipsen Pty. Ltd
ODEVIXIBAT. 600 microgram capsules, 30 units	12	5	Public: $[redacted] Private: $[redacted]	Bylvay Ipsen Pty. Ltd
ODEVIXIBAT. 1200 microgram capsules, 30 units	6	5	Public: $[redacted] Private: $[redacted]	Bylvay Ipsen Pty. Ltd

Category/Program:	Section 100 – Highly Specialised Drugs Program
PBS indication:	Progressive familial intrahepatic cholestasis
Treatment phase:	**Initial**
Restriction:	☒Streamlined
Treatment criteria:	Must be treated by a prescriber who is either: (i) a gastroenterologist, (ii) a hepatologist; **OR** Must be treated by a medical practitioner who has consulted at least one of the above mentioned specialist types, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion. Patient must not have been previously treated with odevixibat.
Clinical criteria:	Patient must have elevated serum bile acids **AND/OR** Patient must be experiencing symptomatic pruritus
Population criteria:	Patient must be aged 6 months or older.
Treatment phase:	**Continuing**
Restriction:	☒Streamlined
Treatment criteria:	Must be treated by a prescriber who is either: (i) a gastroenterologist, (ii) a hepatologist; **OR** Must be treated by a medical practitioner who has consulted at least one of the above mentioned specialist types, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion. Patient must be previously treated with odevixibat.
Clinical criteria:	Patient must have elevated serum bile acids AND/OR Patient must be experiencing symptomatic pruritus
Population criteria:	Patient must be aged 6 months or older.

Source: Table 1-13 and 1-14, pp55-6 of the submission

3.1 The submission stated that the maximum quantities provided for one month supply at the recommended 40 mcg/kg/day dose and for patients who may require up-titration to 120 mcg/kg/day. This was informed by the dosing information from the draft product information (PI).

3.2 The proposed restriction did not specify any diagnostic criteria for PFIC. Genetic testing is the gold standard for PFIC diagnosis (Baker 2018) and the PEDFIC studies presented in the submission also required genetic confirmation of PFIC diagnosis. The proposed indication allows for treatment for all PFIC subtypes, though odevixibat was noted to lack efficacy in PFIC2 bile salt export pump (*BSEP*)-3 and possibly PFIC5 subtypes due to the complete absence of the BSEP protein (see paragraph 4.5).

Genetic testing would be required to identify these patients in whom odevixibat was not expected to be effective. However, genetic testing related to PFIC is not currently subsidised on the MBS and may present an equity issue for access to treatment. The evaluation considered a codependent submission may have been more appropriate to ensure equity in access and to minimise use in patients with subtypes of PFIC in which odevixibat would be ineffective. The Pre-Sub-Committee Response (PSCR) stated that the genetic testing is sometimes inconclusive, whereas all PFIC patients have elevated bile acid levels and intense pruritus and noted that NICE did not stipulate genetic testing for access to treatment. The ESC, noting that genetic confirmation of PFIC was a requirement of the clinical trial, considered that genetic testing would be appropriate for initial supply.

3.3 The proposed initial restriction lacked clarity as it did not define "elevated serum bile acid [sBA]" and "significant pruritus". The ESC considered that quantification of sBA levels and severity of pruritus at initial supply would be required.

3.4 Further, the requested continuing treatment restriction stated that patients must have an elevated sBA and significant pruritis and must have been previously treated with odevixibat. This was contradictory to the goals of treatment (i.e., to reduce sBA levels and pruritus symptoms) and in its current form would exclude patients who respond to treatment. Additionally, if there is to be a treatment discontinuation criterion that aligns with the draft PI, a definition of 'no treatment benefit' may be required. The ESC considered that adequate response criteria were essential. Further, the ESC advised that a discontinuation rule (e.g. due to lack of response or progression to surgical biliary diversion (SBD) or liver transplantation (LT)) should also be included in the continuing supply restriction to ensure that only patients who were receiving benefit from odevixibat continued treatment. The ESC noted it may sometimes be appropriate for some responding patients to discontinue treatment with odevixibat and be able to recommence if needed and the restriction criteria should allow this. DUSC also considered that there may be a need for inclusion of a retreatment criteria in the proposed restriction. The Pre-PBAC Response agreed that quantification of sBA and pruritis for initiation and continuation criteria would be appropriate and that the restriction should appropriately meet the goals of treatment.

3.5 There was no age cutoff with the restriction only requiring patients to be 6 months of age at initiation, although the clinical trial excluded patients who were over 18 years of age. The PSCR stated that this would exclude patients who presented as late onset in young adulthood, as is more common in patients who have the PFIC subtype of PFIC3. The ESC noted that the key trial, PEDFIC 1, only enrolled patients with the PFIC subtypes of PFIC1 and PFIC2. Although the extension study, PEDFIC 2, enrolled five patients with PFIC3, these data were noncomparative and the patients only received treatment at the 120 mcg/kg/day dose level, with no evidence provided at the 40 mcg/kg/day dose. Thus, the effectiveness and cost effectiveness of odevixibat in PFIC 3-6 and late onset patients is unknown.

3.6 Dose escalation protocols for odevixibat were not described in the restriction. The draft PI stated "(i)f an adequate clinical response has not been achieved after 3 months of continuous therapy, the dose may be increased … (and) alternative treatment should be considered in patients for whom no treatment benefit can be established following 6 months of continuous daily treatment with odevixibat". Further, a definition of an adequate response was not provided in the restriction. The basis for these assessment and discontinuation time points was not clear given that in the clinical evidence presented, patients escalated their dose after ~22 weeks at 40 mcg/kg/day in PEDFIC 1 (as opposed to the 3 months suggested in the draft PI) and this was independent of response.

3.7 The number of repeats in the initial supply restriction provides 6 months of treatment which does not align with the proposed timepoint of assessment of response (3 months). The financial estimates were aligned with the draft PI (3-month initial treatment period and 6-month discontinuation period given inadequate response). The PSCR stated that a maximum of 2 repeats (3 months of treatment) for the initial supply was reasonable as this aligned with the proposed assessment of clinical response and timing for possible dose escalation.

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

4 Population and disease

4.1 PFIC is a rare, heterogeneous group of genetic liver disorders of autosomal recessive inheritance that reduces or stops the transportation of bile acid out of the liver resulting in systemic accumulation. PFIC is estimated to affect between 1 per 50,000 and 1 per 100,000 live births globally. PFIC is characterised by an early onset of cholestasis (usually during infancy) with pruritus (itching) and malabsorption, which rapidly progresses to liver failure. PFIC is also associated with portal hypertension, liver failure, cirrhosis, hepatocellular carcinoma, and may also have extrahepatic manifestations. The ESC noted neonatal cholestasis affects 1 in 2,500 infants and ~13% of these infants have PFIC.[1]

4.2 There are six known PFIC subtypes, each caused by different underlying genetic mutations that affect bile secretion (Table 2).

[1] Liver disease basics, PFIC Advocacy & Resource Network, Inc. Available at: https://www.pfic.org/learn-about-pfic-disease/liver-disease/

Table 2: Genetic mutations and resultant abnormalities in PFIC subtypes

PFIC subtype	Genetic abnormality	Dysfunctional protein	Biochemical findings
PFIC1	*ATP8B1*	FIC1	Loss of canalicular membrane integrity causing decreased BSEP function with reduced bile acid transport from hepatocytes into canalicular spaces.
PFIC2	*ABCB11*	BSEP	Absent or dysfunctional BSEP protein and absent or decreased transport of bile acids from hepatocytes into canalicular spaces. PFIC2 can be categorised according to *BSEP1, BSEP2, and BSEP3* genotypes. BSEP protein functionality decreases from *BSEP1* to *BSEP3* genotypes. Patients with *BSEP1* and *BSEP2* genotype have residual BSEP protein functionality whereas patients with *BSEP3* genotype have non-functional or absent BSEP protein.[2, 3]
PFIC3	*ABCB4*	MDR3	Absence of phosphatidylcholine from the biliary canaliculi; increased free bile salts in canaliculi; cholangiocyte damage
PFIC4	*TJP2*	TJP2	Compromised tight junctions; bile salt leakage into the paracellular space resulting in hepatocyte and cholangiocyte damage, loss of hepatocyte polarity and diminished BSEP function
PFIC5	*NR1H4*	FXR	Undetectable expression of BSEP in the bile canaliculi
PFIC6	*MYO5B*	MYO5B	Disruption of hepatocyte polarity and the localisation of canalicular proteins; mislocalisation and loss of BSEP function

Source: Table 1-3, p25 of the submission
BSEP = bile salt export pump; FXR = Farnesoid X Receptor; MDR3 = Multidrug Resistance Class 3 glycoprotein; MYO5B = Myosin 5B; PFIC = progressive familial intrahepatic cholestasis; TJP2 = Tight Junction Protein 2
Note: odevixibat was noted to lack effectiveness in PFIC subtypes that have complete absence or lack of function of the BSEP protein, such as PFIC2 BSEP3 and PFIC5.

4.3 PFIC1, PFIC2, and PFIC3 are the main PFIC subtypes, whereas PFIC4, PFIC5, and PFIC6 subtypes are rarer. Five out of six PFIC subtypes (except for PFIC3) disrupt the ability of BSEP to transport bile acids from the hepatocytes into the canalicular spaces. PFIC2 is directly due to abnormalities in the BSEP protein that leads to reduced or absent BSEP function; within PFIC2 are the *BSEP1*, *BSEP2*, and *BSEP3* genotypes. In PFIC1, PFIC4, PFIC5, and PFIC6 the impact is indirect, either through decreased BSEP activity due to changes in the canalicular membrane or inability to localise BSEP to the canalicular membrane. In PFIC3 the impact is independent of the BSEP protein, where an excess of free bile acids results in cholangiocyte damage which eventually progresses to hepatocyte damage. All six types of PFIC result in elevated serum bile acids and pruritus.

4.4 The clinical evidence presented in the submission was primarily in patients with PFIC1 and PFIC2 subtypes. The PEDFIC 1 trial enrolled only PFIC1 and PFIC2 patients. The PEDFIC 2 study enrolled mostly PFIC1 and PFIC2 patients (5/69 patients had PFIC3 and 1/69 patients had PFIC6). There was no evidence presented for patients with PFIC4 and PFIC5 subtypes in the submission.

[2] Van Wessel DBE, et al. (2020). Genotype correlates with the natural history of severe bile salt export pump deficiency. J Hepatol 73(1): 84-93.
[3] Alam, S & Lal, BB (2022). Recent updates on progressive familial intrahepatic cholestasis types 1, 2 and 3: Outcome and therapeutic strategies. World J Hepatol. 14(1):98-118. doi: 10.4254/wjh.v14.i1.98. PMID: 35126842; PMCID: PMC8790387.

4.5 Patients with PFIC2 *BSEP3* are not expected to benefit from odevixibat due to the complete lack of function in the BSEP protein. Patients with PFIC5 may also not benefit from odevixibat based on a National Institute of Care Excellence (NICE) consideration.[4] However, PFIC5 is a very rare subtype with only nine patients identified worldwide in the literature. The submission excluded patients with PFIC2 *BSEP3* subtype in the financial estimates. However, the ESC noted that, without genetic testing, this subtype was not excluded by the restriction.

4.6 PFIC can lead to progressive liver disease, usually within the first decade of life and eventually liver failure. Intense pruritus is the most common and debilitating symptom of PFIC that has a negative impact on both patient and caregiver quality of life (QoL). Untreated PFIC can result in intractable itching so severe that bleeding often occurs, and the intense itch may lead to lack of sleep which negatively impacts other areas such as schooling. The submission claimed that pruritus severity is the leading factor in the decision to seek a LT. In PFIC1 and PFIC2, jaundice and severe pruritus usually occur in the first months of life. Patients with PFIC2 generally present earlier and with severe and rapidly progressing liver disease and have an elevated risk of developing hepatic cell carcinoma. PFIC3 can present through infancy into young adulthood and has a more heterogeneous presentation, while progression of liver disease and pruritus is often less severe compared to PFIC1 and PFIC2.

4.7 Off-label oral therapies such as ursodeoxycholic acid (UDCA) and rifampicin are first-line therapies for PFIC but have limited effectiveness.[5] Progressive liver disease and pruritus are the two main indications for SBD or LT, and without SBD or LT, the survival in PFIC patients is 50% at age 10 and almost 0% at age 20. SBD lowers serum bile acids (sBA) levels by diverting bile from the gallbladder, decreasing the influx of bile acid to the gut and reuptake of bile acid in the small intestine. The submission stated that reductions in sBA levels after undergoing SBD was associated with prolonged native liver survival (i.e., time to liver transplantation or death) in PFIC1 and PFIC2 patients.

4.8 Types of SBD include partial external biliary diversion (PEBD), partial internal biliary diversion (PIBD), and ileal exclusion (IE). PEBD is the most common and is recommended to delay or avoid LT. However, PEBD is an invasive procedure and is associated with complications related to the external stoma (e.g., surgical revision), post-operative cholangitis, and dehydration and hyponatraemia. Noncomparative data is suggestive that PIBD and IE may be associated with better outcomes than PEBD (see paragraph 5.4). Patients with advanced fibrosis, end-stage liver disease, or

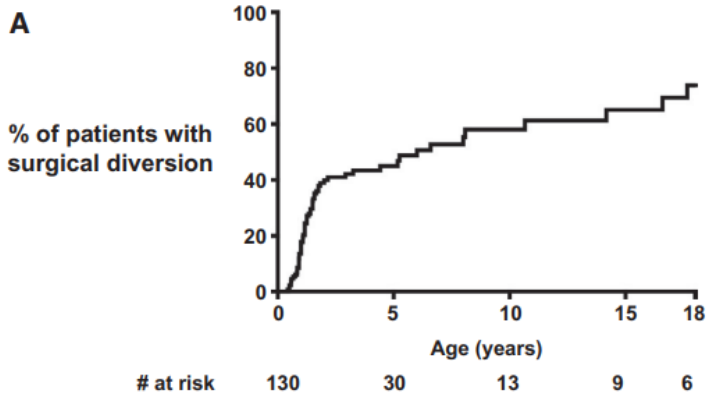
[4] Consideration of the evidence; Odevixibat for treating progressive familial intrahepatic cholestasis. Guidance, NICE

[5] McKiernan, P, et al. (2024) Opinion paper on the diagnosis and treatment of progressive familial intrahepatic cholestasis. JHEP Reports, Volume 6, Issue 1, DOI: https://doi.org/10.1016/j.jhepr.2023.100949

refractory pruritus despite SBD are indicated for LT.[6] The submission noted complications with LT such as immunosuppression, extrahepatic complications, and complications with surgery, although observed post-LT survival is high. The 5-year post-LT overall survival in patients with PFIC1 to PFIC4 was reported to be 98.5% over a median follow up of 80 months, according to a recent meta-analysis (Kavallar 2023[7]).

4.9 The natural history of PFIC patients (primarily PFIC1 and PFIC2) has been investigated in a large, multi-centre, retrospective database, referred to as NAPPED (Natural course and Prognosis of PFIC and Effect of biliary Diversion; N=590). From the NAPPED data, approximately 70% of PFIC1 and PFIC2 patients underwent SBD by age 18 years. Surgeries were most commonly performed at a younger age (see Figure 1 and Figure 2). A greater proportion of patients with the PFIC2 *BSEP1* subtype underwent SBD compared to *BSEP2* and *BSEP3*. This had implications on the submission's indirect treatment comparison (see paragraphs 6.14 and 6.15).

Figure 1: Surgical biliary diversion rates by age in PFIC1

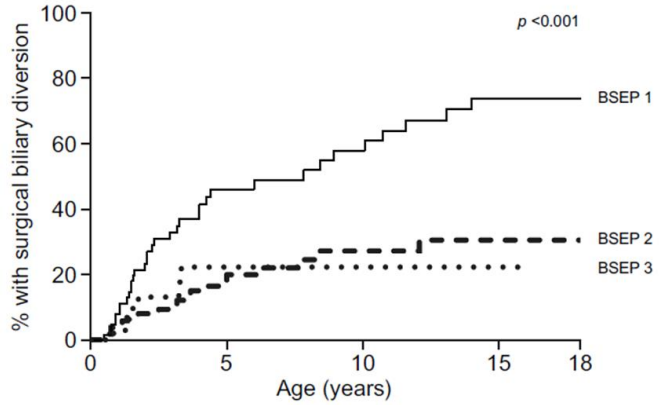


Source: Figure 2, p7 van Wessel 2021
PFIC = progressive familial intrahepatic cholestasis

[6] Alam, S & Lal, BB (2022). Recent updates on progressive familial intrahepatic cholestasis types 1, 2 and 3: Outcome and therapeutic strategies. World J Hepatol. 14(1):98-118. doi: 10.4254/wjh.v14.i1.98. PMID: 35126842; PMCID: PMC8790387.

[7] Kavallar, AM et al. (2023) Management and outcomes after liver transplantation for progressive familial intrahepatic cholestasis: A systematic review and meta-analysis. Hepatology Communications 7(10): e0286, October 2023. | DOI: 10.1097/HC9.0000000000000286

Figure 2: Surgical biliary diversion rates by age and BSEP subtype in PFIC2

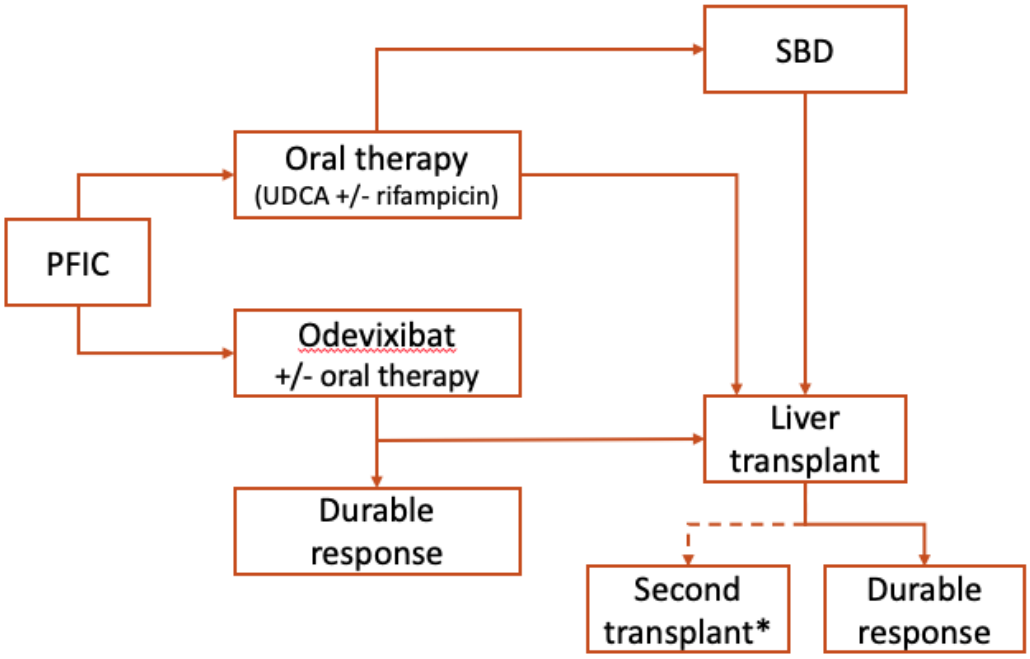


N° at risk					
BSEP 1	72	20	14	8	5
BSEP 2	136	43	22	16	11
BSEP 3	56	12	9	3	0

Source: Figure 3-9, section 3.4.2.1, p148 of the submission
BSEP = bile sale exporter pump; PFIC = progressive familial intrahepatic cholestasis

4.10 Odevixibat is an ileal bile acid transport (IBAT) inhibitor that binds to IBAT at the distal ileum and decreases reabsorption of bile acid from the small intestine to the liver, thereby reducing sBA levels. The submission claims that odevixibat will replace the need for PEBD and delay time to or avoid LT – see Figure 3.

Figure 3: Proposed clinical management algorithm



Source: Figure 1-6, p43 of the submission
SBD = surgical bile diversion; UDCA = ursodeoxycholic acid.
SBD is most commonly a partial external biliary diversion (PEBD)
* More frequent in PFIC1

4.11 The positioning of odevixibat as an alternative to SBD in the proposed clinical algorithm (and the economic model and financial estimates) did not align with the requested restriction. Although the clinical management algorithm proposed that odevixibat will replace the need for SBD and delay time to or avoid LT, the requested restriction did not limit odevixibat to any specific position, such that odevixibat could theoretically be used before or after other oral therapies and surgical interventions (SBD and LT). This was inconsistent with the economic model, which assumed patients would not undergo SBD after odevixibat; and the financial estimates which assumed patients who have previously had surgical intervention (SBD or LT) were ineligible for odevixibat despite this being allowed in PEDFIC 1 (provided the SBD was at least 6 months prior to commencement on the trial).

4.12 In the submission's economic model, it was assumed that patients treated with odevixibat who do not respond (or lose response) will not undergo PEBD. The submission justified that the mode of action of odevixibat and PEBD is similar, hence it was unlikely that a patient would benefit from PEBD if they did not respond to odevixibat. It was unclear whether this assumption was reasonable. Clinical experts from the NICE explained that PEBD is rarely used in UK clinical practice and is only an option in a limited group, for example, those who have no liver fibrosis and whose liver disease is not advanced. NICE concluded that sequential use of odevixibat and PEBD was unlikely in practice. Alam & Lal 2022 noted that SBD is not recommended in patients with advanced liver fibrosis.[8] Conversely, recommendations for the management of paediatric PFIC patients from six European clinical experts suggested that in patients who do not respond to odevixibat and oral therapies, SBD should be considered.[9] No Australian specific recommendations were presented in the submission nor apparent in the literature.

4.13 Moreover, the financial estimates assumed patients who have previously undergone SBD were not eligible for odevixibat and excluded these patients. This may present an equity issue for prevalent patients who have previously had SBD.

4.14 The ESC considered the appropriate clinical positioning of odevixibat was uncertain. The ESC noted it may be clinically appropriate to allow use anywhere in the treatment algorithm (as proposed in the restriction criteria) but this was not consistent with the economic or financial model (as discussed in paragraphs 4.11 and 4.12).

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

[8] Alam, S & Lal, BB (2022). Recent updates on progressive familial intrahepatic cholestasis types 1, 2 and 3: Outcome and therapeutic strategies. World J Hepatol. 14(1):98-118. doi: 10.4254/wjh.v14.i1.98. PMID: 35126842; PMCID: PMC8790387.

[9] McKiernan, P, et al. (2024) Opinion paper on the diagnosis and treatment of progressive familial intrahepatic cholestasis. JHEP Reports, Volume 6, Issue 1, DOI: https://doi.org/10.1016/j.jhepr.2023.100949

5 Comparator

5.1 The submission nominated standard of care (SOC), including PEBD and LT, as the comparator. The submission's clinical management algorithm proposed that odevixibat will be used as a first line treatment with or without oral therapies and will replace PEBD and delay time to, or avoid, LT.

5.2 The ESC considered that SOC was a reasonable comparator. The submission effectively proposed that odevixibat would replace PEBD (as per the proposed clinical management algorithm and the economic model). However, the ESC noted that the direct clinical evidence presented in the submission (PEDFIC 1) compared odevixibat to placebo only, primarily in patients who had not undergone prior SBD, and that there was no direct evidence comparing odevixibat with PEBD. The submission attempted to address this with an indirect comparison study comparing odevixibat with PEBD, OvEC Part B. However, there were a number of significant issues with this trial that limited its usefulness (see paragraphs 6.32 and 6.33).

5.3 SOC also included off-label oral therapies (i.e., UDCA and rifampicin); however, these are expected to be used alongside odevixibat, rather than be replaced. Moreover, the submission suggested that LT is effectively replaced by odevixibat in the proportion of patients who achieve and maintain a sBA and pruritus response while on treatment with odevixibat.

5.4 As discussed in paragraph 4.8, PEBD is the most common type of SBD. The submission assumed that PEBD will represent all SBDs in the economic model. Other types of SBDs were not considered which may not have been reasonable. A meta-analysis by Bolia 2022 (N=424, 25 studies) compared outcomes of PEBD (n=301), PIBD (n=93) and IE (n=30) in PFIC patients (mostly PFIC1 and 2).[10] Bolia 2022 reported that although statistically significant differences were not observed between different types of SBD, there were notable point estimate differences in the relative efficacy and post-surgery complications that may have implications on costs and benefits of biliary diversion surgeries, and it may not be reasonable to assume that PEBD was representative of all SBD. In addition, observational data from NAPPED suggested that more than 20% of PFIC patients underwent non-PEBD surgeries, including ileal exclusion, gallbladder colic diversion, and total biliary diversion surgery.[11, 12]

5.5 The ESC noted the submission nominated maralixibat, another IBAT inhibitor, as a near market comparator.

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[10] Bolia, R, et al. (2022) Biliary diversion in progressive familial intrahepatic cholestasis: a systematic review and meta-analysis, Expert Review of Gastroenterology & Hepatology, 16:2, 163-172, DOI:10.1080/17474124.2022.2032660

[11] Van Wessel DBE, et al. (2020). Genotype correlates with the natural history of severe bile salt export pump deficiency. J Hepatol 73(1): 84-93.

[12] Van Wessel DBE, et al. (2021) Impact of Genotype, Serum Bile Acids, and Surgical Biliary Diversion on Native Liver Survival in FIC1 Deficiency. Hepatology 74(2): 892-906

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease, including how treatment with odevixibat would be initiated, how response would be assessed, and how dosing would be escalated in clinical practice. In response to the Committee's questions, the clinician discussed the role of surgical biliary diversion (including PEBD) in patients who fail to adequately respond to odevixibat. The clinician stated that there are rare cases where patients who do not achieve a satisfactory response to odevixibat alone have undergone SBD and achieved additional relief of symptoms. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (35), health care professionals (4) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with odevixibat. Health care professionals emphasised the lack of alternative therapies, the potential for significantly improved quality of life for patients and caregivers with "life changing" reduction or resolution of both symptoms and complications of the disease, the relatively good safety profile (common adverse events include diarrhoea and abdominal pain), and a reduction in the need for hospitalisations and surgical interventions. Consumers commented on benefits including improved quality of life associated with reduced itch, reduced bleeding due to scratching, improved sleep, reduced anxiety, less growth delay, improved energy and appetite, and an increase in ability to attend school and work. Caregivers described that "everything changed for us since our kids are taking (odevixibat)" and that "life changed almost immediately", highlighting the positive impact of treatment on families. While many consumers commented on gastrointestinal side effects, tolerability of the treatment was emphasised. Consumers also commented that odevixibat would save time and money related to traveling to medical appointments associated with diversion surgery or transplant.

6.3 The PBAC noted the advice received from PFIC Network, PFIC and Related Disorders Australia, and Liver Foundation stating that PFIC often results in a "horrendous itch" that, in some cases may be incessant and lead to continuous scratching and bleeding, lack of sleep, anxiety, depression, post-traumatic stress disorder, and ultimately poor quality of life for patients, as well as their families. The advice stated that the itch associated with PFIC has led to job losses and children being unable to attend school. The organisations stated that the PBS listing of odevixibat may "potentially reduce the need for costly and risky surgeries", noting that, with respect to liver transplant, some patients must wait until they are "big enough or weigh enough to be able to handle

it", and that complications associated with surgery can lead to patients spending a substantial amount of time in hospital.

Clinical trials and studies

6.4 The submission was based on one direct randomised trial comparing odevixibat to placebo (PEDFIC 1, N=62). Supplementary evidence was provided by one ongoing single arm study (PEDFIC 2, N=69) and one indirect treatment comparison (ITC), OvEC, comparing odevixibat (based on patients from PEDFIC 1 and PEDFIC 2, n=69) to external controls (based on patients from NAPPED, n=80 [Part A] and n=24 [Part B]).

6.5 PEDFIC 1 recruited patients with genetically confirmed PFIC1 and PFIC2 aged between six months and 18-years old who had elevated sBA concentrations (≥ 100 µmol/L from an average of two samples at least seven days apart) and a history of significant pruritus. Patients with other subtypes (e.g. PFIC3) were excluded, which may affect the generalisability of the trial. Patients were randomised to receive one of odevixibat 40 mcg/kg/day, odevixibat 120 mcg/kg/day, or placebo for 24 weeks.

6.6 PEDFIC 2 recruited patients who rolled over from PEDFIC 1, both odevixibat-treated and placebo patients (Cohort 1, N=54), and new PFIC patients who were not considered eligible for PEDFIC 1 (Cohort 2, N=16). Patients could be considered as odevixibat-experienced (i.e., those from the 40 mcg/kg/day and 120 mcg/kg/day odevixibat arms of PEDFIC 1, n=34) and odevixibat-naïve (i.e., Cohort 2 and those from the placebo arm of PEDFIC 1, n=35). The ESC noted that Cohort 2 patients were older than those in Cohort 1 (7.9 years vs ~4.5 years) and that Cohort 2 included patients with the PFIC3 subtype (5/16, 31%). These differences suggested that patients in Cohort 2 may have had less severe disease than those who had previously been enrolled in PEDFIC 1.

6.7 All patients in PEDFIC 2 were treated with odevixibat 120 mcg/kg/day, irrespective of whether the patient had previously received or responded to odevixibat. The ESC noted that dose escalation in PEDFIC 2 was mandated irrespective of response and was not possible to assess if there was a benefit of increasing the dose from 40 mcg/kg/day to 120 mcg/kg/day. In the economic model, the submission claimed assumed that 25% of patients who did not respond to odevixibat 40 mcg/kg/day in PEDFIC 1 responded after they were enrolled in PEDFIC 2 and treated with odevixibat 120 mcg/kg/day. This could not be independently verified. The pre-PBAC Response stated that the transition to PEDFIC 2 demonstrated incremental benefit in patients who did not respond on 40 mcg/kg/day in PEDFIC 1 as dose escalation to odevixibat 120 mcg/kg/day in 9 non-responders (from the 40 mcg/kg/day dose on PEDFIC 1) resulted in 4 (44%) patients meeting pruritis response at 12 and 24 weeks of treatment. The pre-PBAC response also stated that transition from odevixibat 40 mcg/kg/day in PEDFIC 1 to odevixibat 120 mcg/kg/day in PEDFIC 2 resulted in a higher proportion of sBA responders.

6.8 OvEC was conducted in two parts. Part A compared odevixibat to controls who had not undergone SBD and Part B compared odevixibat to controls who had undergone

SBD. In OvEC, inverse probability of treatment weighting (IPTW), estimated by propensity scores, was used to balance important baseline covariates across cohorts (including age, sex, PFIC type and BSEP genotype, height and weight z-scores, hepatic parameters, and geographic region).

6.9 Details of the PEDFIC 1, PEDFIC 2, and OvEC studies presented in the submission are provided in the Table 3. Hansen 2023 reported on OvEC Part A only. There were no publications for OvEC Part B, and all data provided was from a conference presentation included in the submission. As such, results from OvEC Part B could not be verified during the evaluation.

Table 3: Trials, studies, and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
PEDFIC1 NCT03566238	PEDFIC 1 Clinical Study Report. Odevixibat treatment in progressive familial intrahepatic cholestasis: a randomised, placebo-controlled, phase 3 trial Thompson RJ, Arnell H, Artan R, Baumann U, Calvo PL, Czubkowski P, et al. Odevixibat treatment in progressive familial intrahepatic cholestasis: a randomised, placebo-controlled, phase 3 trial.	September 2022 Lancet Gastroenterol Hepatol. 2022 Sep. 7(9):830-842. doi: 10.1016/S2468-1253(22)00093-0. Epub 2022 Jul 1. PMID: 35780807
PEDFIC2 NCT03659916	PEDFIC 2 Clinical Study Report. An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of A4250 in Children With Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC 2) Thompson RJ, Artan R, Baumann U, Calvo PL, Czubkowski P, Dalgic B, et al. Interim results from an ongoing, open-label, single-arm trial of odevixibat in progressive familial intrahepatic cholestasis	Ongoing, last update March 2024 Interim analysis presented in the CSR was as of 15 July 2020 JHEP Reports, 5 (8): 100782. 29 April 2023 https://doi.org/10.1016/j.jhepr.2023.100782
OvEC	Hansen B, Valcheva V, Yu Q, van Wessel DBE, Thompson RJ, Gonzales E, et al. P1 Analysis of long-term treatment effects of odevixibat on clinical outcomes in children with progressive familial intrahepatic cholestasis in odevixibat clinical studies vs external controls from the NAPPED database.	Journal of Hepatology, 2023; 72: A13; 10.1136/gutjnl-2023-BASL.17.

Source: 'Large files' attachment to the submission

6.10 The key features of the included evidence are summarised in the Table 4 below.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s) [d]	Use in modelled evaluation
Odevixibat vs placebo						
PEDFIC 1 [a]	40 mcg/kg = 23 120 mcg/kg = 19 Placebo = 20	R, DB, MC 24 weeks	Low	PFIC1 and 2; ≥ 6 months and < 18 years; No SBD within < 6 months of enrolment	sBA response, pruritus response, safety	Not used
PEDFIC 2 [b]	Cohort 1 = 54 Cohort 2 = 16 All received 120 mcg/kg	SA, OL Ongoing	High	Cohort 1 = PEDFIC 1 Cohort 2 = PFIC any subtype and age	sBA levels and pruritus score	Used for discontinuation rates
ITC: Odevixibat (PEDFIC 1 and 2) vs External Controls (NAPPED)						
OvEC [c]	Odevixibat 'all doses' = 69 Control (Part A) = 80 Controls (Part B) = 24	ITC 22.6 months follow-up	High	PFIC1 and 2 ≥ 6 months and < 18 years Part A = no prior SBD Part B = prior SBD	EFS (primary) NLS, DFS, OS (secondary)	Base case

Source: Section 2 of the submission.

DB = double blind; DFS = diversion-free survival; EFS = event free survival; ITC = indirect treatment comparison; MC = multi-centre; NLS = native liver survival; OL = open label; OS = overall survival; PFIC = progressive familiar intrahepatic cholestasis; R = randomised; SA = single arm; sBA = serum bile acid; SBD = surgical biliary diversion

[a] PEDFIC 1 24-week study period was completed and patients could roll over to PEDFIC 2 (prior to or at completion of study).

[b] PEDFIC 2 interim analysis as of 15 July 2020 reporting on results at 24 weeks; 71 patients enrolled but 69 dosed; Cohort 1 comprised PEDFIC 1 patients (both odevixibat-treated and placebo); Cohort 2 comprised new PFIC patients

[c] Data extracted from PEDFIC 1 and PEDFIC 2 on 31 January 2022 and from the NAPPED database on 23 February 2020. Part A compared odevixibat to SOC in SBD-free patients. Part B compared odevixibat to patients who have had SBD.

[d] sBA response in PEDFIC 1 and PEDFIC 2 defined as ≥70% reduction in fasting sBA concentration from baseline or reaching a level ≤ 70 µmol/L. However, in NAPPED (used in the control arm of OvEC) sBA response was defined as ≥75% reduction in sBA from baseline or sBA levels ≤65 µmol/L.
Pruritus response defined as Observer reported outcome (ObsRO) score of ≤1 or at least a 1-point drop from baseline
EFS defined as time to first surgical biliary diversion, liver transplant, or death
NLS defined as time to first liver transplant or death
DFS defined as time to first biliary diversion surgery or death
OS define as time to death

6.11 The submission presented PEDFIC 2 interim results at 24 weeks (data cutoff on 15 July 2020, n=70). The ESC noted that a further interim analysis, with results at 72 weeks (data cutoff 31 July 2022), was presented in the TGA Clinical Evaluation Report. This included a total of 114 patients (63 patients had completed the 72-week treatment period, 25 patients were still on treatment and 26 had discontinued treatment prior to Week 72). The ESC noted that it appeared that an additional 44 patients were recruited into Cohort 2 of PEDFIC 2 between the July 2020 and the July 2022 data cutoffs. Noting that these later results were provided to the TGA, the ESC considered that the submission should have included this updated evidence.

6.12 Of the included evidence, only OvEC Part B provided any information regarding the comparative efficacy of odevixibat with the nominated comparator of SOC, i.e. included patients who had undergone PEBD. The only direct evidence was from PEDFIC 1, which compared odevixibat with placebo in patients who were mostly SBD-free (i.e., patients who had not received SBD within six months of enrolment were included in PEDFIC 1). OvEC Part A also compared odevixibat with patients who had not undergone a prior SBD.

6.13 PEDFIC 1 was considered to have a low risk of bias overall but, given the severity of itching associated with PFIC and the use of a placebo-control arm, there was potential for performance bias in relation to the subjectively reported patient reported outcomes (PROs) and observer reported outcomes (ObsRO) (e.g., pruritus scratching scores, sleep disturbances, QoL, and safety). PEDFIC 2 was a single arm, open-label study and was considered at high risk of bias.

6.14 In OvEC Part A, the control arm (from NAPPED) included patients who were younger (mean age 2.5 vs 4.1 years) and had greater proportion of patients with the PFIC2 *BSEP1* subtype (39% [31/80] vs 29% [15/69]) compared to odevixibat-treated patients (from PEDFIC 1 and PEDFIC 2). Therefore, the patients in the control arm of OvEC Part A potentially reflected a more severe phenotype. This was also suggested by lower mean height (-1.9 vs -1.6) and weight z-scores (-1.4 vs -1).

6.15 SBD was commonly performed by age three in PFIC1 patients and by age five in PFIC2 patients; and a greater proportion of PFIC2 *BSEP1* patients underwent SBD compared to patients with the *BSEP2* and *BSEP3* genotypes (see Figure 1 and Figure 2). Therefore, patients in the control arm of OvEC Part A inherently had a higher probability of undergoing SBD during the follow up period due to their younger age at baseline compared to the older odevixibat-treated patients (i.e., patients from NAPPED aged 2.5 years had a higher likelihood of SBD compared to odevixibat-treated patients aged 4.1 years whose probability of SBD plateaus after this age). As such, the event free survival (EFS), defined as time to first SBD, LT, or death, in OvEC was potentially biased in favour of odevixibat.

6.16 The ESC noted that no baseline characteristics for OvEC Part B were reported. As such, it was not possible to assess transitivity between treatment arms in OvEC Part B and the risk of bias should be considered high due to lack of information.

Comparative effectiveness

6.17 Results for the primary endpoint, sBA response (≥70% reduction in fasting sBA concentration from baseline to the end of treatment or reaching a level ≤ 70 µmol/L) and the key secondary endpoints; pruritus response (defined as a scratching score of ≤1 or at least a 1-point reduction from baseline on the PRUCISION ObsRO instrument [referred to as ObsRO from herein]) and pruritus response for ≥50% of the time from PEDFIC 1 are presented in Table 5.

Table 5: Proportion sBA response, pruritus response, and pruritus response for ≥50% of the time at 24 weeks– PEDFIC 1 (FAS)

	Placebo, n=20	40 mcg/kg, n=23	120 mcg/kg, n=19	All doses, n=42
Proportion of sBA response (primary)				
Responders, n (%)	0	10 (43.5)	4 (21.1)	14 (33.3)
95% CI	(0.00, 16.84)	(23.19, 65.51)	(6.05, 45.57)	(19.57, 49.55)
% Difference adjusted (95% CI) (Odevixibat vs Placebo)	-	**44.1 (23.61, 64.64)**	21.6 (-0.5, 43.8)	30.7 (12.6, 48.79)
1-sided unadjusted p-value	-	0.0003	0.0174	0.0015
1-sided adjusted p-value	-	**0.0015**	0.0174	-
Proportion of positive pruritus assessments (secondary)				
% mean (SE)	28.74 (5.21)	58.31 (6.21)	47.69 (8.11)	53.51 (5.01)
% LS Mean (SE)	30.10 (9.12)	58.34 (8.58)	51.81 (9.46)	55.08 (7.64)
% LS Mean Difference (SE) (Odevixibat vs Placebo)	-	28.23 (9.18)	21.71 (9.89)	24.97 (8.24)
95% CI	-	(9.83, 46.64)	(1.87, 41.54)	(8.45, 41.49)
1-sided unadjusted p-value	-	0.0016	0.0163	0.0019
Proportion of positive pruritus assessments for ≥50% of the time (secondary)				
Responders, n (%)	4 (20.0)	17 (73.9)	9 (47.4)	26 (61.9)
95% CI	(5.73, 43.66)	(51.59, 89.77)	(24.45, 71.14)	(45.64, 76.43)
Odds Ratio (95% CI) (Odevixibat vs Placebo)	-	16.22 (2.54, 106.32)	3.14 (0.72, 18.70)	6.21 (1.54, 27.43)
1-sided unadjusted p-value	-	0.0002	0.0391	0.0016

Source: Table 2-17, p82, Table 2-19, p86, and Table 2-20, p88 of the submission

CI = confidence interval; FAS = full analysis set; LS = least squares; sBA = serum bile acid; SE = standard error

Bold text indicates a statistically significant difference vs placebo. It was assumed that the overall Type 1 error of 0.025 was adjusted for the two comparisons of 40 mcg/kg/day vs placebo and 120 mcg/kg/day vs placebo (i.e., p<0.0125 for each).

6.18 Compared to patients treated with placebo at 24 weeks, there was a higher proportion of patients treated with 40 mcg/kg/day odevixibat who had:

- ≥70% reduction in fasting sBA from baseline or reaching a level ≤ 70 µmol/L (adjusted % difference = 44.1%, 95% CI: 23.61, 64.64, adjusted p=0.0015), and
- A scratching score of ≤1 or at least a 1-point drop from baseline on the ObsRO instrument (least squares [LS] mean difference = 28.2%, 95% CI: 9.83, 46.64, unadjusted p=0.0016).

6.19 For sBA, only adjusted p-values for the 40 mcg/kg/day versus placebo and 120 mcg/kg/day versus placebo arms were presented and only the 40 mcg/kg/day arm versus placebo demonstrated statistical significance. The adjusted difference in proportion of sBA response in the 120 mcg/kg/day arm (21.6%) was lower compared to the 40 mcg/kg/day arm (44.1%). The adjusted difference in the proportion of pruritus response was greater in the 40 mcg/kg/day arm compared to the 120 mcg/kg/day and placebo arms, although statistical significance was unclear as only unadjusted p-values were presented. Additionally, the ESC noted that approximately 30% of patients receiving placebo reported a pruritus response. Although maintaining pruritus response for more than 50% of the time (24 weeks) favoured the 40 mcg/kg/day odevixibat arm compared to the 120 mcg/kg/day and placebo arms, this was also uncertain as secondary endpoints in PEDFIC 1 were not adjusted for multiplicity.

6.20 The TGA Clinical Evaluation Report stated that "post-hoc analyses showed that both [40 mcg/kg/day and 120 mcg/kg/day] doses are equally effective in reducing sBAs and reducing pruritus (e.g. no statistically significant difference). A starting dose of 40 mcg/kg/day is considered most appropriate" (TGA Clinical Evaluation Report for odevixibat, March 2024).

6.21 Pruritus is an indicator for SBD or LT in children with PFIC and reduction in pruritus would be considered a clinically relevant outcome for patients. The submission relied on sBA response as a surrogate for pruritus response in the economic model. Reductions in sBA levels after SBD have shown to be associated with improved pruritus symptoms.[13] Although a strong correlation exists; it is possible that sBA response may not always result in pruritus response. For example, in PEDFIC1, 3/14 (21%) reported sBA response but not pruritus response and 7/28 (25%) reported no sBA response but had pruritus response. Given that pruritus response was measured directly as an outcome (via the ObsRO), it was unclear why a surrogate (via sBA) was necessary. Nonetheless, the TGA's Clinical Evaluation Report for odevixibat stated that, based on the PEDFIC studies, "the clinical relevance of reducing 70% in sBAs (change from baseline) and reduction of pruritus (change from baseline) has been sufficiently substantiated" (TGA Clinical Evaluation Report for odevixibat, March 2024).

6.22 However, the reliability of the ObsRO instrument, which was used in PEDFIC 1 to measure pruritus response, was uncertain. There was a paucity of information regarding the scoring of the ObsRO in the submission and the clinical significance of the definition of "a scratching score of ≤1 or at least a 1-point drop from baseline" was unclear. There was also uncertainty around the validity of the 9-item ObsRO used in PEDFIC 1 (the validation study for the ObsRO instrument by Gwaltney 2022[14] appears to have been based on an 8-item ObsRO), and it was unclear if it was reasonable to have used data from PEDFIC 1 to validate results from the very same trial. The PSCR indicated that the question regarding sleep and over the counter medications was not part of the validated ObsRO instrument and was included as the sponsor had an interest in this area. The PSCR stated that the 1 point change in scale being clinically meaningful applied only to the 5-point pruritus scale (0-4); and the pruritus score was based on the average of only 2 of the 9-items of the ObsRO which were scored from 0-4 (i.e., "How bad was your worst itching since you went to bed last night?" and "How bad was your worst itching since you woke up this morning?"). The ESC noted that the PSCR did not address the clinical significance of an improvement in scratching score of

[13] Verkade HJ, et al. (2020) Systematic Review and Meta-analysis: Partial External Biliary Diversion in Progressive Familial Intrahepatic Cholestasis. J Pediatr Gastroenterol Nutr;71(2):176-183. doi: 10.1097/MPG.0000000000002789. PMID: 32433433.

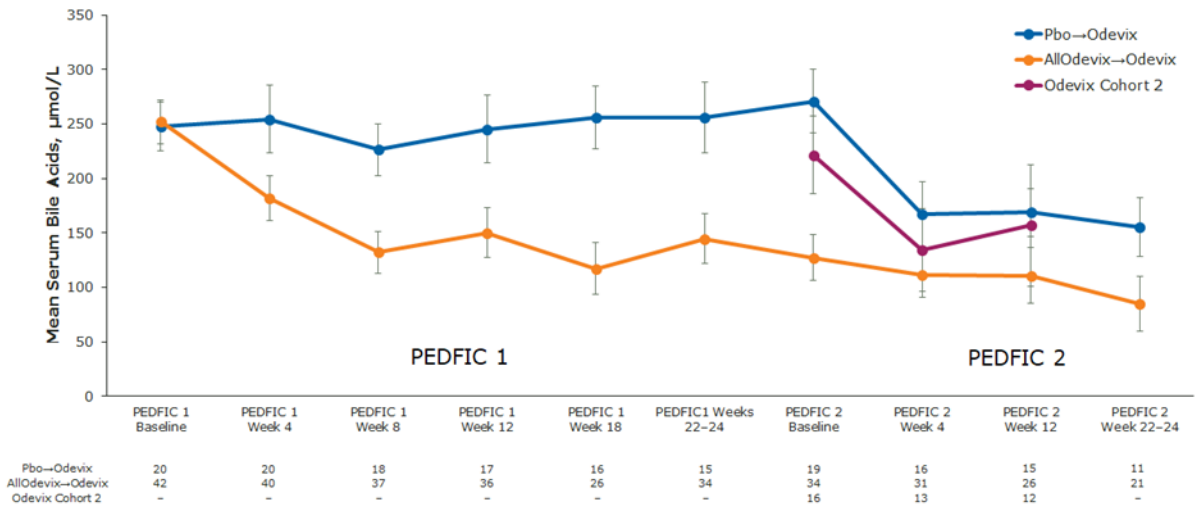
[14] Gwaltney, C., et al. (2022) Validation of the PRUCISION Instruments in Pediatric Patients with Progressive Familial Intrahepatic Cholestasis. Adv Ther 39, 5105–5125. https://doi.org/10.1007/s12325-022-02262-7

< 1 or at least a 1 point reduction from baseline. The ESC also expressed concern over the validity of the ObsRO instrument, noting that it was not appropriate that the data from PEDFIC 1 be used to validate results from the same trial with no independent validation. The PBAC also noted that the ObsRO instrument was applied by caregivers.

6.23 Other secondary endpoints in PEDFIC 1 included changes in growth, sleep, and hepatic parameters and changes in QoL as measured by the Paediatric Quality of Life Inventory (PedsQL; including the Family Impact Module), Global Impression of Symptoms (GIS) and Global Impression of Change (GIC) scores. For the secondary endpoints, the results tended to favour odevixibat over placebo; however, the results should be interpretated with caution given the small patient numbers (acknowledging that PFIC is a rare disease and that a number of enrolled patients appear not to have answered the questions) and as the secondary endpoints were not adjusted for multiplicity.

6.24 Change in sBA levels and pruritus response from PEDFIC 2 interim analysis at 24 weeks (data cutoff 15 July 2020) are presented in Figure 4 and Figure 5.

Figure 4: Mean (SE) change in sBA concentration (µmol/L) during PEDFIC 1 and 2 to Week 24 data cutoff 15 July 2020

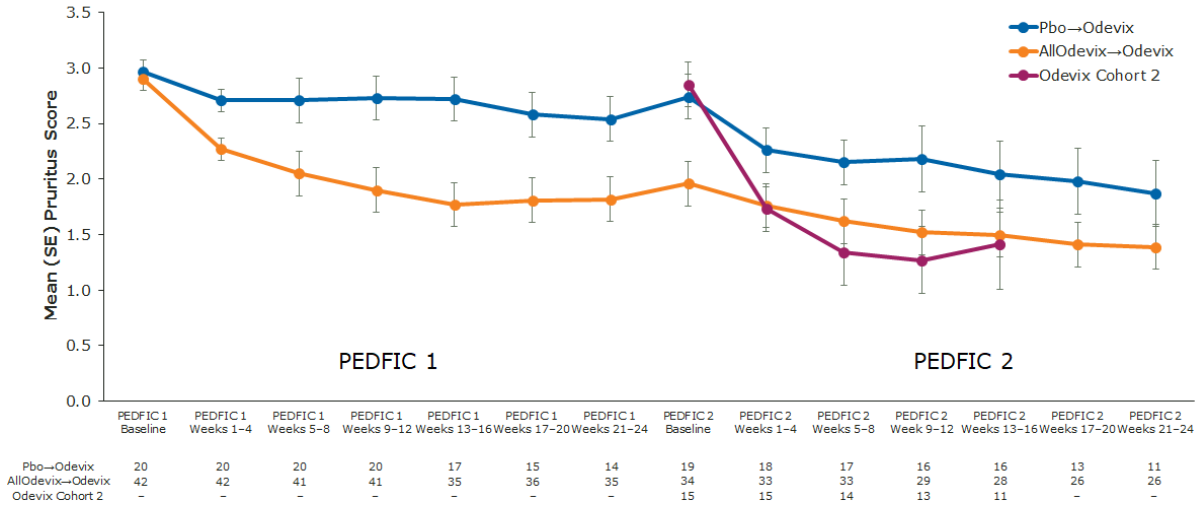


Source: Figure 2-11, p85 of the submission

Odevix = odevixibat; Pbo = placebo; sBA = serum bile acid; SE = standard error

Note: Cohort 2 + Placebo = Odevixibat-naïve patients i.e. those enrolled directly into Cohort 2 and those who were assigned to placebo during participation in PEDFIC 1. Baseline for PEDFIC 2/end of treatment for PEDFIC

Figure 5: Mean (SE) of the pruritus score by grouped weeks PEDFIC 1 and 2 data cutoff 15 July 2020



Source: Figure 2-21 p89 of the submission
Odevix = odevixibat; Pbo = placebo; SE = standard error
Note: Cohort 2 + Placebo = Odevixibat-naïve patients i.e. those enrolled directly into Cohort 2 and those who were assigned to placebo during participation in PEDFIC 1. Baseline for PEDFIC 2/end of treatment for PEDFIC

6.25 Two patients in PEDFIC 2 underwent surgery, both of whom were randomised to placebo in PEDFIC 1. One patient who underwent SBD at Week 37 did not see sBA reductions prior to SBD; and one patient underwent elective LT at Week 19 (PEDFIC 2 CSR).

6.26 As noted in paragraph 6.11, the TGA's Clinical Evaluation Report included results from the additional interim analysis of PEDFIC 2 at the later data cut on 31 July 2022. This interim analysis included more patients (up to 114, of whom 63 had completed at least 72 weeks of odevixibat treatment), presumably in Cohort 2.

6.27 Based on the interim analysis at the data cutoff on 31 July 2022, a trend of increasing sBA concentrations in the later periods of PEDFIC 2 (Weeks 46 to 72) in the odevixibat-experienced group was reported, but levels did not reach those at baseline in PEDFIC 1. This may suggest the durability of response wanes over time with ongoing treatment. Pruritus severity improved over the 72-week period in both Cohort 1 and 2. Fourteen patients underwent surgical intervention (three patients underwent SBD and 11 patients underwent LT). The three patients who underwent SBD after odevixibat is contrary to the submission's assumption applied in the economic model that no patients would undergo diversion surgery after odevixibat (see paragraph 6.51). Further, it is unknown what proportion of patients would have undergone SBD or LT without odevixibat given the absence of longer-term comparative evidence.

6.28 The submission also presented results from a *post-hoc* analysis of sBA responders and pruritus responders at six months and native liver survival (time to first LT or death)

up to three years based on pooled data from PEDFIC 1 and PEDFIC 2.[15] The *post-hoc* sBA responder analysis was from a conference abstract and the pruritus responder analysis could not be independently verified. The submission suggested that sBA response and pruritus response after six months of treatment with odevixibat was strongly associated with native liver survival for up to three years. Extended native liver survival was similarly observed in PFIC1 and PFIC2 patients who achieved an sBA response after SBD in the NAPPED studies. However, the incremental benefit on native liver survival of odevixibat compared to SOC (i.e., including SBD) was uncertain. Moreover, the TGA Delegate's Overview concluded that "(t)he data did not yet allow a conclusion that odevixibat could contribute to delays in requirement for surgical biliary diversion or liver transplantation… (a) long term follow up study is intended to address this question" (TGA Delegate's Overview, odevixibat, May 2024).

6.29 The event free survival (EFS), native liver survival, surgical biliary diversion-free survival (defined as time to first SBD or death), and overall survival (OS) results for OvEC Part A and Part B are presented in Table 6. Figure 6 below presents the Kaplan-Meier curves for EFS in odevixibat-treated and control patients from Part A.

Table 6: Survival outcomes in odevixibat-treated patients and external controls in OvEC – Part A and Part B

	Odevixibat-treated n = 69	Part A control n = 80	Part B control n = 24
Event-Free Survival [a]			
Events, n (%)	6 (9%)	44 (55%)	-
p value	-	**0.0016**	-
HR (95% CI)	-	**0.20 (0.09, 0.45)**	-
Native Liver Survival [b]			
Events, n (%)	4 (6%)	21 (26%)	6 (25%)
p value	-	0.0900	0.5069
HR (95% CI)	-	0.33 (0.11, 1.03)	0.66 (0.17, 2.57)
Diversion-Free Survival [c]			
Events, n (%)	2 (3%)	31 (39%)	-
p value	-	0.0023	-
HR (95% CI)	-	0.13 (0.04, 0.39)	-
Overall Survival [d]			
Events, n (%)	0 (0%)	4 (5%)	2 (8%)
p value	-	0.0845	0.0445
HR (95% CI)	-	0 (0, NE)	0 (0, NE)

Source: Table 2-29 and 2-30, pp120-21 of the submission

CI = confidence interval; HR = hazard ratio; NE = not estimable

Bold text indicates statistically significant difference ($p<0.05$). Sample sizes and events are unweighted. HRs and p values for odevixibat vs control cohorts are weighted. Secondary endpoints (native liver survival, diversion-free survival, and overall survival) were not adjusted for multiplicity.

[a] Event free survival defined as time to first surgical biliary diversion, liver transplant, or death

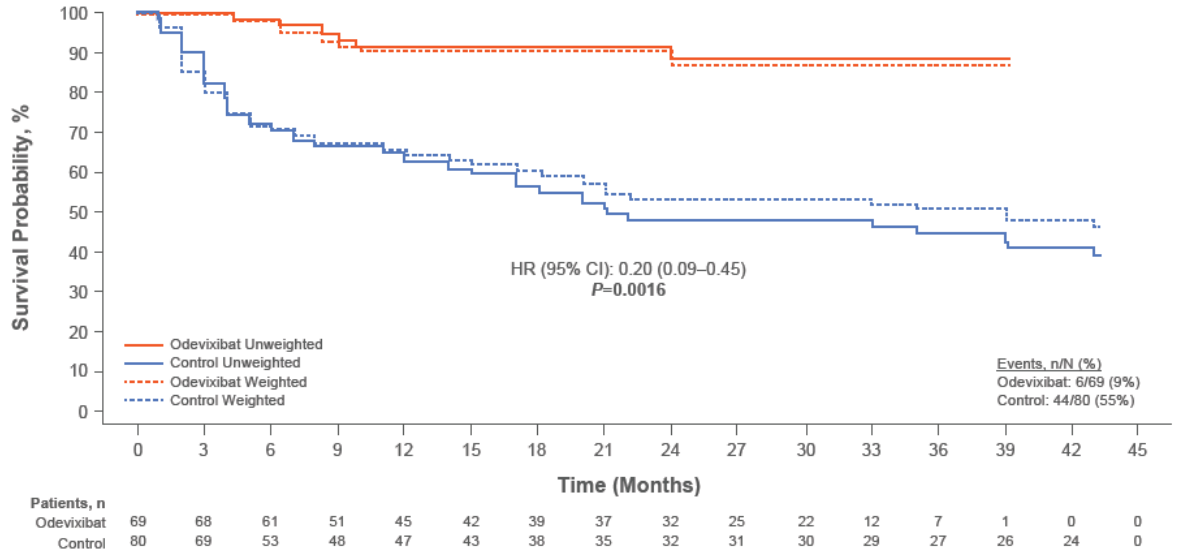
[b] Native liver survival defined as time to first liver transplant or death

[c] Diversion-free survival defined as time to first biliary diversion surgery or death

[d] Overall survival define as time to death

[15] Thompson R, et al. (2022) OC46 Native liver survival in odevixibat serum bile acid responders: data from PEDFIC studies in patients with progressive familial intrahepatic cholestasis. Frontline Gastroenterology 2023;14:A28-A29

Figure 6: Primary endpoint: EFS in odevixibat-treated patients and external controls (OvEC – Part A)



Sample sizes and events are unweighted; HRs and *P* values are weighted.
EFS, event-free survival; HR, hazard ratio; NAPPED, NAtural course and Prognosis of PFIC and Effect of biliary Diversion; PFIC, progressive familial intrahepatic cholestasis.

Source: Figure 2-32, p120 of the submission
EFS = event free survival; HR = hazard ratio; n = number of patients experiencing event; N = total patients

6.30 In OvEC Part A, odevixibat-treated patients showed significantly higher EFS than controls from NAPPED (weighted hazard ratio [HR] = 0.20, 95% CI: 0.09, 0.45, p=0.0016). Secondary endpoints (native liver survival, diversion-free survival, and OS) were not adjusted for multiplicity, hence concluding statistical significance is uncertain.

6.31 As discussed in paragraph 6.14 and 6.15, patients in the control group in Part A of OvEC were younger than the odevixibat group, with a higher proportion of patients with PFIC2 *BSEP1*. Noting the propensity for SBD was most frequent at younger ages and also more likely in PFIC 2 *BSEP 1* (see paragraph 4.9 and Figure 2), the difference in baseline age likely biased the EFS results in favour of odevixibat.

6.32 In OvEC Part B, a numerical improvement in native liver survival in the odevixibat arm (6% [4/69]) compared to the SBD arm (25% [6/24]) was observed over a median follow up of 22.6 months for the odevixibat arm (the duration of follow up in the SBD arm was unclear). There was also a numerical difference in OS favouring odevixibat (no deaths in the odevixibat arm and 2/24 [8%] in the SBD arm) over 42 weeks.

6.33 As discussed in paragraph 6.12, OvEC Part B was the most relevant comparison to the submission based on the proposed comparator of SOC consisting of PEBD. However, OvEC Part B provided limited value and information due to the potentially high risk of bias given no baseline characteristics were reported, the small sample size (only 24 patients in the control arm) and the lack of statistical power to detect differences. Further, secondary endpoints (i.e., native liver survival and OS) were not adjusted for multiplicity and therefore, no statistical conclusion could be drawn.

Comparative harms

6.34 A summary of the safety results from PEDFIC 1 are presented in Table 7 below. Given the small sample size and short follow up in PEDFIC 1, it was difficult to draw meaningful and accurate conclusions (including statistical inferences) regarding the comparative safety of odevixibat and placebo.

Table 7: Summary of safety results – PEDFIC 1 (SAS) - over 24 weeks of treatment

Summary	Placebo N=20, n (%)	Odevixibat		
		40 µg/kg N=23, n (%)	120 µg/kg N=19, n (%)	All doses N=42, n (%)
TEAE	17 (85.0)	19 (82.6)	16 (84.2)	35 (83.3)
Drug-related TEAE [a]	3 (15.0)	7 (30.4)	7 (36.8)	14 (33.3)
Severe TEAE [b]	2 (10.0)	1 (4.3)	2 (10.5)	3 (7.1)
Serious TEAE	5 (25.0)	0	3 (15.8)	3 (7.1)
Drug-related serious TEAE	0	0	0	0
TEAE leading to study treatment discontinuation	0	0	1 (5.3)	1 (2.4)
TEAE leading to death	0	0	0	0

Source: Table 2.22, p97 of the submission
TEAE = treatment emergent adverse event
[a] Patients reporting more than one event are counted only once at the highest relationship reported
[b] Patients reporting more than one event are counted only once at the maximum severity reported

6.35 The proportion of patients experiencing a TEAE was similar across all arms (82-85%). Diarrhoea was the most commonly reported TEAE in both odevixibat-treated (31%) and placebo (30%) patients.

6.36 Serious adverse events (SAEs) were more frequent in the placebo arm (25%; four due to infection and one due to urinary tract infection, p201 PEDFIC 1 CSR) compared to the odevixibat arms (7%) but were noted to be unrelated to study treatment. In the 120 mcg/kg arm 16% of patients experienced SAEs, and 5% experienced diarrhoea that led to discontinuation. There were no deaths.

6.37 A summary of safety results from PEDFIC 2 (data cutoff 15 July 2020) is presented in Table 8. The ESC noted that the TGA received safety results from the 31 July 2022 data cutoff, which are presented in Table 9.

Table 8: Summary of safety results – PEDFIC 2 data cutoff 15 July 2020 (FAS)[a]

Summary	Odevixibat 120 µg/kg						
	Cohort 1				Cohort 2, N=16	Cohort 2 + placebo N=35	Overall (N=69)
	40 µg/kg, N=19	120 µg/kg, N=15	All doses, N=34	Placebo N=19			
TEAE	16 (84.2)	12 (80.0)	28 (82.4)	14 (73.7)	8 (50.0)	22 (62.9)	50 (72.5)
Drug-related TEAE	6 (31.6)	4 (26.7)	10 (29.4)	5 (26.3)	5 (31.3)	10 (28.6)	20 (29)
Severe TEAE	0	1 (6.7)	1 (2.9)	1 (5.3)	3 (18.8)	4 (11.4)	5 (7.2)
Serious TEAE	0	0	0	3 (15.8)	1 (6.3)	4 (11.4)	4 (5.8)
Drug-related serious TEAE	0	0	0	0	0	0	0
TEAE leading to death	0	0	0	0	0	0	0
TEAE leading to treatment discontinuation	0	0	0	1 (5.3)	2 (12.5)	3 (8.6)	3 (4.3)

Source: Table 2-25, p101 of the submission and Table 32, p195 PEDFIC 2 CSR
FAS = full analysis set; TEAE = treatment emergent adverse event
[a] PEDFIC 2 removed the SAS and used the FAS

6.38 Odevixibat-experienced patients experienced more TEAEs (82.4%) compared to odevixibat-naïve (62.9%) patients. Drug related TEAEs were similar between odevixibat-experienced (29.4%) and odevixibat-naïve (28.6%) patients. Serious TEAEs (11.4%) and TEAEs leading to discontinuation (8.6%) were only reported in odevixibat-naïve patients (and included hyperbilirubinemia, stoma complication, cholestasis, and acute pancreatitis, PEDFIC 2 CSR). Reasons for discontinuation were due to cholestasis (one patient in placebo arm), acute pancreatitis (one patient in Cohort 2) and splenomegaly, hypophagia, weight decreased, and jaundice (one patient in Cohort 2; PEDFIC 2 CSR). No deaths occurred. Most TEAEs were described as mild to moderate and assessed as unrelated to study treatment.

6.39 The safety results at the interim analysis at 72 weeks (data cutoff 31 July 2022) for PEDFIC 2 from the TGA's Clinical Evaluation Report for odevixibat are presented in Table 9.

Table 9: PEDFIC 2 overall summary of TEAEs at Week 72 based on Interim results data cutoff 31 July 2022

Summary	Odevixibat 120 µg/kg						
	Cohort 1				Cohort 2, N=56	Cohort 2 + placebo N=75	Overall cohort (N=112)
	40 µg/kg, N=21	120 µg/kg, N=16	All doses, N=37	Placebo N=19			
TEAE	21 (100)	16 (100)	37 (100)	18 (94.7)	48 (85.7)	66 (88)	103 (92)
Drug-related TEAE	10 (47.6)	9 (56.3)	19 (51.4)	7 (36.8)	14 (25)	21 (28)	40 (35.7)
Severe TEAE	1 (4.8)	1 (6.3)	2 (5.4)	1 (5.3)	10 (17.9)	11 (14.7)	13 (11.6)
Serious TEAE	1 (4.8)	4 (25)	5 (13.5)	4 (21.1)	14 (25)	18 (24)	23 (20.5)
Drug-related serious TEAE	0	1 (6.3)	1 (2.7)	0	0	0	1 (0.9)
TEAE leading to death	0	0	0	0	0	0	0
TEAE leading to treatment discontinuation	1 (4.8)	0	1 (2.7)	2 (10.5)	4 (7.1)	6 (8)	7 (6.3)

Source: extracted from TGA Clinical Evaluation Report for odevixibat (p19)
TEAE = treatment emergent adverse event
Note: results excluded two patients with benign recurrent intrahepatic cholestasis

6.40 The TGA Clinical Evaluation Report stated that drug-related TEAEs occurred in 36% of the participants; the incidence of drug-related TEAEs was comparable between patients in Cohort 1, although numerically higher in those patients who received 120 mcg/kg/day in PEDFIC 1 (40 mcg/kg – 48% of patients, 120 mcg/kg – 56%, and placebo – 37%), and in Cohort 2 (25%). Laboratory investigations, gastrointestinal disorders, and hepatobiliary disorders were most common; one serious drug-related TEAE was reported in one patient (an episode of gastroenteritis); and no deaths were reported. The TGA Delegate's Overview stated that "(f)rom a safety perspective, at present there is little evidence that odevixibat is likely to have significant toxic effects" but "uncertainties remain around the long-term safety of odevixibat" (TGA Delegate's Overview, odevixibat, May 2024).

Benefits/harms

6.41 A summary of the comparative benefits for odevixibat versus placebo is presented in the Table 10 below. No statistically significant differences between odevixibat and placebo with respect to adverse events were observed.

Table 10: Summary of comparative benefits and harms for odevixibat (40 mcg/kg, 120 mcg/kg and all doses) and placebo in PEDFIC 1 after 24 weeks of treatment

PEDFIC1	Odevixibat, n/N			Placebo, n/N	Event rate/100 patients*				RD (95% CI)
	40 mcg/kg	120 mcg/kg	All doses		40 mcg/kg	120 mcg/kg	All doses	Placebo	
Benefits (adjusted RD 40 mcg/kg/day vs placebo)									
sBA response	10/23	4/19	14/42	0/20	43.5%	21.1%	33.3%	0%	44.1%[1] (23.61, 64.64)

Source: Table 2-17, p82, Table 2-19, p86, and Table 2-20, p88; Table 2.22, p97 of the submission
RD = risk difference; sBA = serum bile acid
1.RD for sBA response was the adjusted difference between the 40 mcg/kg and placebo as this was the only comparison demonstrating statistical significance (see Table 5).

6.42 On the basis of direct comparative evidence presented by the submission, for every 100 patients treated with odevixibat (40 mcg/kg/day) in comparison with placebo, after 24 weeks of treatment:

- Approximately 44 additional patients will achieve a sBA response (at least a 70% reduction in sBA concentrations from baseline or reaching ≤ 70 µmol).

Clinical claim

6.43 The submission described odevixibat as superior in terms of effectiveness compared to SOC. The ESC considered that this claim was likely supported and that odevixibat was likely effective at lowering sBA and causing a reduction in pruritus symptoms. The PBAC also felt that odevixibat potentially increased native liver survival, but that this was less likely. However, the magnitude of benefit was considered to be highly uncertain, and the incremental benefit compared to the nominated comparator of SOC (which includes SBD and LT) could not be determined as:

- The direct evidence from PEDFIC 1 suggested that odevixibat was effective at lowering sBA when compared to placebo in patients with PFIC1 and PFIC2 (except

for PFIC2 *BSEP3*). However, placebo was not the nominated comparator and the results of PEDFIC 1 may not be sufficient to support a clinical claim compared to SOC. Randomised trial evidence from PEDFIC 1 was also limited to 24 weeks. Further, there were applicability issues regarding the dosage of odevixibat used in PEDFIC 1 and PEDFIC 2, in which a dose increase from 40 mcg/kg/day to 120 mcg/kg/day was not a clinical decision that was dependent on response to the 40 mcg/kg/day dose and no clinical benefit of the higher dose was provided; and

- The evidence from the OvEC unanchored ITC Part B which compared odevixibat and SBD reported some numerical differences in native liver survival and deaths (see paragraph 6.32) that favoured odevixibat. However, these results were highly uncertain as:
    - No baseline characteristics were reported. As such, it was unclear whether there were transitivity issues or imbalances in characteristics which may have biased the results;
    - The number of patients in the control arm was small (n = 24),
    - The results were nonrandomised and
    - The primary outcome of OvEC was EFS. All other outcomes (e.g. native liver survival and OS) were considered exploratory only and not adjusted for multiplicity.

6.44 The PBAC considered that odevixibat was superior in terms of effectiveness compared to placebo in patients with PFIC1 and PFIC2 based on the results of the PEDFIC 1 trial. Compared to SOC, the PBAC considered that odevixibat was possibly superior in terms of effectiveness, based on the results of OvEC Part B, but that the magnitude of the benefit was highly uncertain.

6.45 The submission described odevixibat as non-inferior in terms of safety compared to SOC. The ESC considered that the claim was not adequately supported by the evidence presented, noting that the comparative data from PEDFIC 1 was against placebo and this comparative data was only for a maximum period of 24 weeks. Noting that discontinuation in PEDFIC 1 and PEDFIC 2 due to AEs was low, no deaths were reported during follow up and that no signals of serious toxicity were evident in the limited patient exposure to date, the ESC considered that odevixibat may have comparable safety compared to SOC.

6.46 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data due to the lack of comparative data presented versus SOC. The PBAC considered that a claim of comparable safety between odevixibat and SOC was reasonable.

Economic analysis

6.47 There were a large number of discrepancies between what the submission claimed was used in the base case of the economic model and what was actually used (both in terms of the values of inputs and the source of inputs). The base case model used data from OvEC despite the submission claiming to have used data from PEDFIC 1, PEDFIC 2, and NAPPED individually (see paragraph 6.55 and Table 12). Most of the data used from OvEC could not be verified during the evaluation. As such, there was considerable uncertainty associated with the model base case.

6.48 The submission presented a cost utility analysis (CUA). The key components of the economic evaluation are presented in Table 11.

Table 11: Summary of model structure, key inputs, and rationale

<table>
<tr><th>Component</th><th>Summary</th></tr>
<tr><td>Treatments</td><td>Odevixibat vs SOC</td></tr>
<tr><td>Time horizon</td><td>Lifetime time horizon up to 100 years vs 24-week trial period in PEDFIC 1. The ESC considered that a 100-year time horizon was too long, questioning whether the clinical effects of odevixibat observed in the 24-week PEDFIC 1 trial would be maintained for the model horizon.</td></tr>
<tr><td>Outcomes</td><td>QALYs and LYG</td></tr>
<tr><td>Methods used to generate results</td><td>Markov state transition model</td></tr>
<tr><td>Health states</td><td>Response to treatment was defined as ‘pruritus response with or without sBA response’.
7 heath states capture disease progression:
1. ‘No PEBD, response’ – response to odevixibat or SOC
2. ‘No PEBD, no response’ – loss of response or no response to odevixibat or SOC
3. ‘PEBD, response’ – achieving response after PEBD
4. ‘PEBD, no response' – loss of response or no response after PEBD
5. LT
6. Post-LT
7. Death</td></tr>
<tr><td>Cycle length</td><td>1 year</td></tr>
<tr><td>Transition probabilities</td><td>The model was primarily informed by OvEC despite the submission claiming to have used PEDFIC and NAPPED data. A comparison of what the submission claimed and what the model used is presented in Table 12. The transition probability inputs and sources below describe what the base case model used (OvEC).
<table>
<tr><th>No.</th><th>Transition</th><th>Source used in model</th></tr>
<tr><td>0</td><td>No PEBD, response</td><td>Odevixibat response based on OvEC ‘doses combined’ which was from internal data from the Sponsor (62.28%) [a]
SOC response was assumed to be 0%.</td></tr>
<tr><td>1</td><td>No PEBD, no response (or loss of response)</td><td>Odevixibat annual discontinuation was based on PEDFIC 2 (3.53%); SOC discontinuation was assumed to be 0%.</td></tr>
<tr><td>2</td><td>PEBD, response</td><td>PEBD response based on OvEC data (32.3%). Note that odevixibat patients cannot transition to either PEBD health state.</td></tr>
<tr><td>3</td><td>PEBD, no response</td><td>PEBD no response was the complement to no.2 (67.7%)</td></tr>
<tr><td>4</td><td>Loss of response to PEBD</td><td>PEBD loss of response assumed to be 5%</td></tr>
<tr><td>5</td><td>LT without PEBD</td><td>Based on OvEC (2.47%)</td></tr>
<tr><td>6</td><td>LT after PEBD response</td><td>Assumed to be 0%</td></tr>
<tr><td>7</td><td>LT after PEBD non-response</td><td>Based on NAPPED data for PFIC1 and PFIC2 then estimated a joint probability using PFIC1 and 2 proportions from PEDFIC 1 (27% PFIC1 and 73% PFIC2) (9.9%)</td></tr>
<tr><td>8</td><td>LT to post-LT</td><td>Complement of no.9 (re-transplant) and no.10 (acute post LT mortality) (78.8%)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Component</th><th>Summary</th></tr>
<tr><td></td><td>
<table>
<tr><td>9</td><td>Re-transplant</td><td>Based on Bull 2018 (a retrospective multi-centre study of 42 PFIC1 and 60 PFIC2 patients who had previously undergone LT over the median follow-up time of 3.6 years) and a weighted probability was estimated based on PFIC1 and PFIC2 proportions from PEDFIC1 (9.81%)</td></tr>
<tr><td>10</td><td>Mortality</td><td>Pre-LT mortality was based on OvEC (0.38%)
Acute (1 year) post-LT mortality from meta-analysis of Wanty 2004, Hori 2011, Aydogdu 2007, and Valamparampil 2019.
Long-term (2-5 year) post-LT mortality was based on pooled data from Hori 2011 and Wanty 2004 (1.91%)</td></tr>
</table>
Source: Table 3-15 from the submission (modified to reflect the base case)
[a] Included patients who up titrated to 120 mcg/kg and response (25% based on internal data). OvEC 'combined doses' response was 49.7%. Therefore, adjusted response was calculated as 49.7% + (100 – 49.7%) × 25%
</td></tr>
<tr><td>Extrapolation method</td><td>For transitions to PEBD and LT, exponential models were fitted to OvEC data.
For transitions to long-term post-LT mortality, an exponential model was fitted to pooled data from two studies (Hori 2011 and Wanty 2004) to informed transitions of long-term post-LT mortality and a weighted average of PFIC1 (27.4%) and PFIC2 (72.6%).</td></tr>
<tr><td>Health related quality of life</td><td>Utilities from PEDFIC 1 were not used. Utility values were informed from the literature. For all health states except for 'LT' (no. 5), PedsQL scores from respective studies were mapped to the EQ-5D using the mapping algorithm by Khan 2014. A short stature disutility multiplier (0.97) estimated from Al-Uzri 2013 was applied to 'no PEBD, no response' (no.2), and the 'PEBD, no response' (no.4) health states. A stoma bag disutility multiplier (0.722) estimated from Hornbrook 2011 was applied to 'PEBD, response' (no.3) and 'PEBD, no response' (no.4) health states. The utility values and sources are presented below.
<table>
<tr><th>Health state</th><th>Utility</th><th>Source</th></tr>
<tr><td>No PEBD, response</td><td>0.91</td><td>'Healthy children' from Kamath 2015</td></tr>
<tr><td>No PEBD, no response</td><td>0.83</td><td>'CIC children' from Kamath 2015; 'Short stature multiplier' from Al-Uzri 2013</td></tr>
<tr><td>PEBD, response</td><td>0.659</td><td>'Healthy children' from Kamath 2015; 'Stoma bag multiplier' from Hornbrook 2011</td></tr>
<tr><td>PEBD, no response</td><td>0.599</td><td>'CIC children' from Kamath 2015; 'Short stature multiplier' from Al-Uzri 2013; 'Stoma bag multiplier' from Hornbrook 2011</td></tr>
<tr><td>LT</td><td>0.71</td><td>'Severe pruritus patients' from Kini 2011</td></tr>
<tr><td>Post-LT</td><td>0.774[a]</td><td>'Post LT children' from Parma 2017,</td></tr>
</table>
[a] The submission reported post LT utility as 0.85 however, in the model base case this value was 0.774
</td></tr>
<tr><td>Healthcare resource use and costs</td><td>The submission included costs associated with:
<table>
<tr><th>Resource use or cost</th><th>Source used in model</th></tr>
<tr><td>Odevixibat drug acquisition costs</td><td>Based on the dose administered (40 or 120 mcg/kg/day); patient weight and weight distribution data (CDC growth charts and ABS); and corresponding capsule strengths (200, 400, 600, and 1200 mcg). Low dose patients initiate on either 200 or 400 mcg capsules dose escalations to either 600 mcg or 1200 mcg capsules based on patient weight. Odevixibat costs are only incurred in the 'no PEBD, response' state</td></tr>
<tr><td>Oral therapy drug acquisition cost (UDCA, cholestyramine, rifampicin, and naltrexone)</td><td>Proportion of use was informed by PEDFIC 1 (UDCA, rifampicin), a burden of illness study (HCD 2021*; cholestyramine), and the NICE (naltrexone). Both odevixibat and SOC arms receive oral therapies in the 'no PEBD, response' and 'no PEBD, no response' health states only.</td></tr>
<tr><td>LT costs (including surgery, immunosuppression, monitoring, and complications)</td><td>Pre-transplant costs were based on the McElroy 2017 and LT and organ retrieval costs were sourced from NHCDC. Post-LT costs were also based on McElroy 2017 and include outpatient visits, blood tests, imaging tests and inpatient admission</td></tr>
</table>
</td></tr>
</table>

Component	Summary	
	PEBD costs (including surgery, reoperations, complications, and monitoring)	The proportion of patients with complications (re-operations, infection or bowel prolapse) was informed by Bjornland 2021. The weighted average cost of PEBD and associated complications was applied once-off for new patients entering the PEBD health state. The unit costs, mean number of visits, and the proportion of patients who have clinical were informed by the HCD 2021* burden of illness study.
	AE	AE events included were based on PEDFIC 1.
	Societal costs including lost productivity (scenario analysis only)	Lost productivity was based on the proportion of work impairment recorded in the burden of illness study (HCD 2021*).
	* Note: The HCD 2021 burden of illness study was not provided, and no clear citations presented, hence could not be verified	

Source: Table 3-1, p128; and Table 3-15, pp147-8; Table 3-15; Table 3-13, p145; Table 3-32, p156 of the submission
ABS = Australian Bureau of Statistics; AEs = adverse events; CDC = Centre for Disease Control; EQ-5D = EuroQol-5 Dimension; LT = liver transplant; LYG = life years gained; NHCDC = National Hospital Cost Data Collection; NICE = National institute for Health Care and Excellence; PEBD = partial external biliary diversion; PedsQL = Paediatric Quality of Life Inventory; PFIC = progressive familial intrahepatic cholestasis; QALY = quality-adjusted life years; sBA = serum bile acid; SOC = standard of care; UDCA = Ursodeoxycholic acid

6.49 The submission considered pruritus response with or without sBA response as the clinically relevant outcome and that model progression was predicated on losing or not achieving response (i.e., worsening of pruritus symptoms due to elevated sBA).

6.50 Patients were assumed to be either treated with odevixibat or SOC and initially distributed to either the 'no PEBD, pruritus with/without sBA response' or 'no PEBD, no response' health states based on the sBA responder rate. OvEC informed sBA response for odevixibat and the submission assumed sBA response was 0% for SOC. At this point, all patients were assumed not to have undergone PEBD. Patients could lose response and progress to PEBD or LT, but the model assumed that only patients in the SOC arm could undergo PEBD, and these patients could respond or not respond to PEBD. Patients could progress to LT from the post-PEBD states or the initial PEBD-naïve state. From LT, patients enter the post-LT state and could also undergo a second transplant. All patients were assumed to be at risk of death, with additional mortality risks following LT.

6.51 A key driver of the model was the assumption that patients from the odevixibat arm will not undergo PEBD after losing response whereas those from the SOC arm were modelled to enter PEBD states. This assumption resulted in odevixibat patients remaining in the 'no PEBD, no response' health state for an extended period compared to the SOC arm. Additionally, the model may have been overly optimistic to assume that patients who lose response and experience pruritus symptoms and/or progressive liver disease would go without any intervention over this time or that there would not be any adjustment to transitions to LT or death.

6.52 As noted in paragraph 4.12, although the NICE considered that PEBD was unlikely to be offered after odevixibat, the ESC noted there was conflicting advice regarding the clinical utility of PEBD following odevixibat treatment. Although clinical experts from the NICE explained that surgery is only an option for a limited group who have no liver fibrosis and where their disease is not advanced, information from six European experts suggested that in patients who do not respond to odevixibat and oral

therapies, SBD should be considered. The pre-PBAC Response stated that local advice from clinicians experienced in treating PFIC conditions indicated that PEBD may be considered in only a very small number of cases following lack of response with an IBAT inhibitor, and that PEBD does not reflect a standard treatment pathway for all odevixibat non-responders.

6.53 The submission's assumption in regard to post-odevixibat PEBD did not align with the 72-week data for PEDFIC 2 (see paragraph 6.27) that reported that three patients had received PEBD following odevixibat. Nonetheless, the 'no PEBD, no response' health state had a higher utility (0.83) than the post-PEBD health states (0.659 for 'PEBD, response' and 0.599 for 'PEBD, no response'), which did not appear reasonable as transition into the post-PEBD health state is not a sign of disease progression but a conscious choice made by the patient (or their carer) to improve, rather than worsen, their quality of life. The 'no PEBD, no response' health state was also associated with decreased odevixibat costs, hence cost-effectiveness favoured odevixibat over the SOC arm (see Table 11 and paragraph 6.62). Including PEBD within the odevixibat arm increased the ICER by 36%.

6.54 The annual odevixibat discontinuation rate was informed by PEDFIC 2 (3.53% per year). This was highly uncertain and likely underestimated given it was based on 1/34 patients discontinuing over a 42.54-week period. Further, it was unclear if it was appropriate to apply the annual probability to Cycle 1 (cycle length = 1 year) of the model given patients would be on initiation treatment for 3-6 months (depending on whether there was dose escalation).

6.55 The submission claimed that PEDFIC 1 informed odevixibat response rates, and NAPPED informed PEBD response rates as well as transitions to PEBD and LT. However, OvEC data informed these inputs. The OvEC data were considered highly uncertain as they could not be independently verified. Table 12 compares the inputs and sources claimed by the submission with what was applied in the model. Using data from PEDFIC 1/2 and NAPPED (i.e., not using OvEC) to inform the model led to a 5% increase in the ICER.

Table 12: Comparison of inputs between OvEC and PEDFIC and NAPPED

Input	Base case input in model	Submission's claim
Response inputs		
'No PEBD, response' rate (odevixibat)	**62.28% (OvEC)**	**57.63% (PEDFIC)**
'No PEBD, response' rate (SOC)	0% (assumption)	0% (assumption)
'PEBD, response' rate	**32.3% (OvEC)**	**60.15% (NAPPED)**
Transition probabilities		
'No PEBD, no response' → 'PEBD, response' and 'PEBD, no response'	**5.52% [a] (OvEC)**	**8.43% (<3 years old) (NAPPED)** **4.75% (>3 years old) (NAPPED)**
'No PEBD, no response' → 'LT'	**2.47% [b] (OvEC)**	**6.85% (NAPPED)**
'PEBD, response' → 'LT'	0% (assumption)	0% (assumption)
'PEBD, no response' → 'LT'	9.9% (NAPPED)	9.9% (NAPPED)
'Retransplant'	9.81% (Bull 2018)	9.81% (Bull 2018)
Pre-LT mortality	**0.38% [c] (OvEC)**	**0.27% (NAPPED)**
Long-term post-LT mortality	1.91% (pooled estimates from Hori 2011 and Wanty 2004)	1.91% (pooled estimates from Hori 2011 and Wanty 2004)

Source: 'Clinical data – Efficacy' and 'OvEC data' worksheets from the economic model
LT = liver transplant; PEBD = partial external biliary diversion; SOC = standard of care
[a] 29/44 (65.9%) SBD events x 8.38% annual event probability
[b] 13/44 (29.5%) LT events x 8.38% annual event probability
[c] 2/44 (4.5%) death events x 8.38% annual event probability
Bold text indicates the inputs that differed between the model and the submission's claim

6.56 The 'no PEBD, response' rate applied in the model of 62.28% was derived from the sBA response rate from OvEC for 'combined doses' (49.7%) (see Table 11), adjusted to include patients who responded to the up-titrated 120 mcg/kg/day dose (25% based on internal data from the Sponsor). As the OvEC response comprised of PEDFIC 1 and PEDFIC 2 patients, it potentially included those who escalated from 40 to 120 mcg/kg/day doses. Since it was not clear what treatment period was reflected in OvEC, the response of dose escalators was potentially double counted. If the model was proposing that patients initiate at the 40 mcg/kg/day dose and then up-titrate to 120 mcg/kg/day if no response, then it would be more reasonable to inform the initial response using the 40 mcg/kg arm from PEDFIC 1 (43.5%) then adjust this by the proportion who responded after escalating to 120 mcg/kg/day (25%), rather than using 'all doses combined'. This approach would result in an sBA response of 57.63% for odevixibat, which was used in the financial estimates.

6.57 The submission claimed to have applied the 'PEBD, response' rate from NAPPED data (60.15%). However, 'PEBD, response' rate from OvEC (32.3%) was applied in the base case and, as only patients from the SOC arm occupied the PEBD states, the lower response rate applied favoured odevixibat. Assuming 0% response at the start of the model (i.e. 100% of patients in the SOC arm started in the 'no PEBD, no response' health state) also favoured odevixibat as in PEDFIC 1, 20% of placebo patients achieved and maintained pruritus response despite no sBA response (see Table 5).

6.58 For transitions to PEBD (5.52%), LT (2.47%), and death (0.38%) from the 'no PEBD, no response' state, event counts for SBD (29/44, 65.9%), LT (13/44, 29.5%), and death (2/44, 4.5%) were used and the annual event probability 8.38% based on the exponential model was applied. These event rates were not consistent with OvEC Part

A results from the submission or Hansen 2023 (see Table 6) and could not be independently verified.

6.59 A meta-analysis of four studies (Hori 2011, Wanty 2004, Aydogdu 2007, and Valamparampil 2019) informed the acute post-LT mortality. The analysis weighted studies by the number of death events, not sample size, which biased mortality towards studies with greater death events. Valamparampil 2019, a study of LT mortality in India, reported the highest mortality and had the highest weighting in the meta-analysis, but it was unclear if results from this study were applicable to the Australian setting. Long-term post-LT mortality was estimated by fitting an exponential model to the pooled data from Hori 2011 and Wanty 2004. For consistency, it may have been more reasonable to rely on the same studies (i.e., Hori 2011 and Wanty 2004 only) for both acute and long-term post-LT mortality. There were also errors in the meta-analysis of acute post-LT mortality which had previously been identified by NICE in 2022 and were uncorrected in the submission. Specifically, the submission reported 4/12 deaths in Aydogdu 2007 and 1/49 deaths in Wanty 2004; however, upon review, there were 3/12 deaths in Aydogdu 2008 and 1/38 deaths in Wanty 2004. Moreover, it appears that more studies were considered by NICE and it was unclear why these additional studies were excluded from the submission. The search strategies for literature on post LT mortality was not reported by the submission.

6.60 Re-transplant probability (9.81%) was obtained directly from Bull 2018. This was aligned with other evidence for re-transplantation.[16] The submission assumed that mortality after the second LT was the same as after the first LT which may not be reasonable.

6.61 The base case utility values were informed by various literature. The base case utility values were highly uncertain as none of the selected studies were in the PFIC population. Although the use of utilities from PEDFIC 1 would have been most representative of PFIC patients, PEDFIC 1 patient-reported values were considered implausible, for example, the 'no PEBD, no response' health state (0.769) was higher than the 'no PEBD, response' health state (0.737). Use of PEDFIC 1 parent-reported utility values (see Table 13) increased the ICER by 28%.

6.62 The base case utility values were likely biased towards health states that odevixibat patients occupied, particularly regarding the assumption that odevixibat patients do not undergo PEBD. The stoma bag disutility multiplier (0.722) applied to PEBD health states potentially underestimated QALYs associated with the health states which were occupied only by SOC patients and appeared to contribute to the lack of face validity in utility values. Notably, the 'no PEBD, no response' health state had higher utility

[16] Kavallar AM, et al. (2023) Management and outcomes after liver transplantation for progressive familial intrahepatic cholestasis: A systematic review and meta-analysis. Hepatol Commun. 7:e0286. https://doi.org/10.1097/HC9.0000000000000286

(0.83) than the 'PEBD, response' state (0.659). This favoured the odevixibat arm and also implied that patients preferred pruritus symptoms over achieving a response after PEBD, which may not be plausible. A sensitivity analysis in which the utility in the 'PEBD, response' state equalled that in the 'no PEBD, no response' state (i.e. 0.830) increased the ICER be 9%.

Table 13: Base case utility values and parent-reported values from PEDFIC 1

Mapped EQ-5D score	Base case	PEDFIC 1 Parent-reported
No PEBD, response	0.914	0.791
No PEBD, no response	0.830	0.664
PEBD, response	0.659	0.571
PEBD, no response	0.599	0.479
LT [a]	0.710	0.710
Post-LT [a]	0.774	0.774

Source: 'HRQoL data' worksheet from the economic model
EQ-5D = EuroQol-5 Dimension; LT = liver transplant; PEBD = partial biliary diversion
[a] LT and post-LT utilities did not change from the base case under these scenarios

6.63 Patients undergoing LT were expected to derive higher utility values in the year of transplant (0.71) compared to patients who achieved response with PEBD (0.659). This may not be plausible given LT is supposed to reflect the most severe health state and can be associated with complications (e.g., immunosuppression, recurrence). Noting that Kini 2011, the source of the LT utility, investigated adults with pruritus, it was not clear how applicable this value was to PFIC children. The submission stated that the post-LT utility value was 0.85; however, the model assumed a utility decrement of 0.076 to reflect patients who experienced recurrence of PFIC after LT. The derivation of the 0.076 decrement was not clear; however, the resulting utility value (0.774) was consistent with considerations from the ERG from NICE who stated that post-LT utility values ranged from 0.70-0.78 in the literature.

6.64 The submission presented a scenario analysis that included caregiver disutilities. A value of -0.1 was applied to 'PEBD, no response', and -0.05 was applied to 'no PEBD, response', 'PEBD response', and 'post-LT' states. This decreased the ICER by 16%.

6.65 Odevixibat treatment costs were a key driver of the model and contributed to over 95% of total costs. The cost of odevixibat varied substantially between patients receiving the low dose (40 mcg/kg/day) and those receiving the high dose (120 mcg/kg/day; see Table 14). The ESC considered that the assumption applied in the model that 25% of patients who did not respond to odevixibat 40 mcg/kg/day responded after they were treated with 120 mcg/kg/day was not supported by the evidence and appeared implausible. The ESC considered that there was no clinical justification to increase the dose in patients who did not respond to the 40 mcg/kg/day dose, noting that the submission did not supply data justifying the superiority of the 120 mcg/kg/day dose. Further, the ESC noted that the 120 mcg/kg/day dose was significantly more expensive than the 40 mcg/kg/day dose.

Table 14: Annual cost by weight band

Weight	Daily dose (mcg)		Capsules/day		Daily cost		Annual cost	
	Low dose	High dose	Sprinkle	Swallow	Low dose	High dose	Low dose	High dose
4 to < 7.5	200	600	1	-	$	$	$	$
7.5 to < 12.5	400	1200	2	-	$	$	$	$
12.5 to < 17.5	600	1800	3	-	$	$	$	$
17.5 to < 19.5	800	2400	4	-	$	$	$	$
19.5 to < 25.5	800	2400	-	2	$	$	$	$
25.5 to < 35.5	1200	3600	-	3	$	$	$	$
35.5 to < 45.5	1600	4800	-	4	$	$	$	$
45.5 to < 55.5	2000	6000	-	5	$	$	$	$
≥ 55.5	2400	7200	-	6	$	$	$	$

Source: Table 3-41, p161 of the submission

6.66 The submission informed the patient weight-for-age in the model using the Centre for Disease Control and Prevention growth charts (2022) for patients up to 18 years old and Australian Bureau of Statistics (2017-18) data for patients aged 18 and older. The model assumed that patients were in the 25th percentile of weight in the year they initiate treatment, then in the 33rd percentile in the second year, and then the 50th percentile each year thereafter. The submission calculated the weighted average weight of males and females (assuming 50% female). The resulting annual costs used in the model are shown in Table 15. The PBAC noted the average cost of odevixibat per patient per year was high and varied considerably from approximately $ to $, depending on a patient's weight and dose.

Table 15: Mean weight by age and the corresponding annual cost of odevixibat

Age (years)	Weight			Daily cost			Annual cost
	Male (kg)	Female (kg)	Average [a]	Low dose	High dose	Average [b]	
4	15.02	14.52	14.77	$	$	$	$
5	17.92	17.44	17.68	$	$	$	$
6	20.68	20.24	20.46	$	$	$	$
7	23.07	22.76	22.91	$	$	$	$
8	25.64	25.63	25.63	$	$	$	$
9	28.55	28.99	28.77	$	$	$	$
10	31.94	32.89	32.41	$	$	$	$
11	35.89	37.21	36.55	$	$	$	$
12	40.47	41.65	41.06	$	$	$	$
13	45.59	45.82	45.71	$	$	$	$
14	51.00	49.36	50.18	$	$	$	$
15	56.28	52.04	54.16	$	$	$	$
16	60.92	53.88	57.40	$	$	$	$
17	64.57	55.14	59.85	$	$	$	$
18	67.20	56.19	61.69	$	$	$	$
25	77.40	63.00	70.20	$	$	$	$
35	83.00	66.00	74.50	$	$	$	$
45	86.20	68.50	77.35	$	$	$	$
55	88.70	72.30	80.50	$	$	$	$
65	87.20	70.20	78.70	$	$	$	$
75	82.60	69.40	76.00	$	$	$	$

Source: 'General population' worksheet from the economic model

[a] Average weight based on 50% females

[b] Average dose based on the assumption that 30.15% of patients received high dose odevixibat

6.67 In the base case, the proportion of patients on high dose odevixibat (30.15%) was informed by the proportion of responders on 40 mcg/kg/day from PEDFIC 1 (43.5%) and the proportion of responders in OvEC (62.28%), after adjusting for the patients who responded after up-titrating to 120 mcg/kg/day given non-response to 40 mcg/kg/day (25%).[17] Using response inputs from PEDFIC 1 and PEDFIC 2 (57.63%) would have been more appropriate to avoid potential double counting. The proportion of patients on high dose odevixibat based solely on PEDFIC 1 and PEDFIC 2 was 24.5% and was also consistent with the inputs used for the financial estimates.[18] As the proportion of patients on high dose odevixibat was dependent on the response rate of up-titrators (which could not be verified), this estimate was highly uncertain. Assuming no patients underwent dose escalation led to a 47% reduction in the ICER.

6.68 The key drivers of the model are presented in Table 16.

[17] % high dose odevixibat (OvEC) = 1 – (43.5% / 62.28%) = 30.15%

[18] % high dose odevixibat (PEDFIC) = 1 – (43.5% / 57.63%) = 24.5%

Table 16: Key drivers of the model

Description	Method/Value	Impact Base case: $[1]/QALY
Assumption that patients in the odevixibat arm do not undergo PEBD	The model assumed that odevixibat patients do not undergo PEBD after losing response. Only the patients in the SOC arm transitioned to the PEBD states. As such, odevixibat patients occupied the 'no PEBD, no response' state for an extended period of time. The 'no PEBD, no response' state had a higher utility compared to the PEBD states. In addition, patients in the 'no PEBD, no response' state no longer accrued costs of ongoing treatment.	High, favoured odevixibat. Assuming patients in the odevixibat arm can undergo PEBD increased the ICER by 36% ($[1]/QALY). Assuming a 100% discontinuation rate for the odevixibat arm (i.e., null treatment effect) decreased the ICER by 95% ($[2]/QALY). Although this analysis was not plausible, it further highlights the bias of this assumption.
Odevixibat drug acquisition costs	The proportion of patients receiving high dose odevixibat (120 mcg/kg/day) had a high impact on total costs. The model assumed 30.15% of patients were receiving the high dose which was based on the response of patients who up-titrated to 120 mcg/kg/day.	High. Assuming patients only received the 40 mcg/kg/day dose (i.e., no dose escalation) decreased the ICER by 47% ($[3]/QALY) Assuming flat cost for odevixibat (i.e., cost of 120 mcg/kg/day equal to the 40 mcg/kg/day dose) decreased the ICER by 38% ($[4]/QALY)
Utilities values for 'no PEBD' and 'PEBD' health states	The utility values were potentially overestimated and biased toward health states that odevixibat patients would occupy. The utility values were more favourable in the 'no PEBD, response' and 'no PEBD, no response' state and less favourable in the 'PEBD, response' and 'PEBD, no response' states (Table 13).	Moderate, favoured odevixibat. Assuming the 'PEBD, response' utility equals that in the 'no PEBD, no response' increases the ICER by 9% ($[1]/QALY).

Source: various sensitivity analyses from the economic model

ICER = incremental cost-effectiveness ratio; PEBD = partial external biliary diversion; QALYs = quality adjusted life years; SOC = standard of care. The results of the economic evaluation are presented in Table 17. The disaggregated costs and outcomes are presented in Table 18.

The redacted values correspond to the following ranges:

[1] > $1,055,000

[2] $55,000 to < $75,000

[3] $655,000 to < $755,000[4] $755,000 to < $855,000

Table 17: Results of the economic evaluation (discounted)

Component	Odevixibat	SOC	Increment
Costs	$	$219,662	$
LYG	18.22	16.69	1.53
QALYs	15.14	12.41	2.73
Incremental cost/extra LY gained			$[1]
Incremental cost/extra QALY gained			**$[1]**

Source: Tables 3-55 and 3-56, p169 of the submission

LYG = life years gained; QALY = quality adjusted life year; SOC = standard of care.

The redacted values correspond to the following ranges:

[1] > $1,055,000

Table 18: Disaggregated costs, QALYs (discounted) and LYG (undiscounted) included in the economic evaluation

LYG (undiscounted)	SoC	Odevixibat	Incremental	Absolute increment	% Absolute increment
Years in no PEBD, response	0.00	16.15	16.15	16.15	30.0%
Years in no PEBD, no response	11.43	27.85	16.42	16.42	30.5%
Years in PEBD, response	4.04	0.00	-4.04	4.04	7.5%
Years in PEBD, no response	6.29	0.00	-6.29	6.29	11.7%
Years in LT	1.02	0.77	-0.25	0.25	0.5%
Years in post-LT	29.18	18.57	-10.61	10.61	19.7%
Total life-years	51.95	63.33	-	53.76	100.0%
QALYS (discounted)					
QALYs with no PEBD, response	0.00	6.57	6.57	6.57	56.6%
QALYs no PEBD, no response	6.04	6.65	0.60	0.60	5.2%
QALYs PEBD response	0.89	0.00	-0.89	0.89	7.7%
QALYs PEBD no response	1.40	0.00	-1.40	1.40	12.1%
QALYs LT	0.32	0.15	-0.17	0.17	1.4%
QALYs post-LT	3.75	1.77	-1.99	1.99	17.1%
QALY decrements	0.00	0.00	0.00	0.00	0.0%
Total QALYs	12.41	15.14	-	11.62	100.0%
Costs (discounted)					
Response	$0	$[redacted]	$[redacted]	$[redacted]	[redacted]%
Loss of response	$36,059	$92,061	$56,002	$56,002	[redacted]%
PEBD	$45,679	$0	-$45,679	$45,679	[redacted]%
LT	$116,666	$56,468	-$60,197	$60,197	[redacted]%
Post-LT	$5,823	$2,818	-$3,005	$3,005	[redacted]%
Immunosuppression	$15,435	$7,757	-$7,679	$7,679	[redacted]%
Adverse events	$0	$2,073	$2,073	$2,073	[redacted]%
Death	$0	$0	$0	$0	0.0%
Total	$219,662	$[redacted]	-	$[redacted]	100.0%

Source: Tables 3-58 and 3-59, p169 of the submission

LT = liver transplant; LYG = life years gained; PEBD = partial external biliary diversion; QALY = quality adjusted life year; SOC = standard of care.

The disaggregated results indicated that the primary driver of benefits was odevixibat patients occupying the 'no PEBD, response' health state (see Table 18 above). Due to discounting, while the incremental life-year gain (LYG) in the 'no PEBD, no response' health state was of a similar magnitude to the 'no PEBD, response' state (incremental 16.42 and 16.15 LYG, respectively), the discounted incremental QALYs in this health state (0.60) was substantially smaller than in the 'no PEBD, response's state (6.57). This was due to patients in the 'no PEBD, no response' state occupying this state over a longer and later portion of the time horizon.

6.69 The primary cost driver was the odevixibat drug acquisition costs (increment $[redacted]) which contributed to [redacted]% of total incremental costs compared to SOC. This was attributed to the additional time spent in the response health state and the substantial cost of odevixibat. In particular, the proportion of patients assumed to be treated with high dose (120 mcg/kg/day) odevixibat contributed over a third of total costs. Assuming a flat cost for odevixibat regardless of dose (i.e., assumed the cost of the 120 mcg/kg/day was equal to the 40 mcg/kg/day) led to a 36% reduction in total odevixibat costs and 38% reduction in the ICER. Assuming no dose escalation (i.e., patients only received the 40 mcg/kg/day dose) resulted in a 47% decrease in the ICER. The ESC noted that the differences in these changes to the ICER were due to differences in assumed clinical effectiveness.

6.70 The results of key univariate and multivariate sensitivity analyses are summarised in Table 19.

Table 19: Sensitivity analyses

Sensitivity analysis conducted by the submission	Inc cost	Inc QALY	ICER	% Δ
Base case	$[redacted]	**2.73**	$[redacted] [1]	**-**
Include option to receive PEBD in odevixibat arm (base = excluded PEBD in odevixibat arm)	$[redacted]	2.02	$[redacted] [1]	+[redacted]%
Utilities from PEDFIC 1 (parent-reported) (base = utilities informed from various literature sources)	$[redacted]	2.13	$[redacted] [1]	+[redacted]%
Utilities in 'PEBD, response' and 'no PEBD, no response' health states are equal, i.e. 0.830 (base = 0.659 in 'PEBD, response' and 0.830 in 'no PEBD, no response')	$[redacted]	2.50	$[redacted] [1]	+[redacted]%
Odevixibat 40 mcg/kg dose (PEDFIC 1 40 mcg/kg response + no dose escalation) (base = OvEC 'combine doses' + up-titration to 120 mcg/kg if no response)	$[redacted]	2.25	$[redacted] [2]	-[redacted]%
50-year time horizon (base case= 100 years)	$[redacted]	2.45	$[redacted] [1]	+[redacted]%
Discount cost and outcomes = 0% (base = 5% discount rate)	$[redacted]	12.07	$[redacted] [3]	-[redacted]%
Discount cost and outcomes = 3.5% (base = 5% discount rate)	$[redacted]	3.84	$[redacted] [1]	-[redacted]%
Loss of response to odevixibat 10% (base = 3.53%)	$[redacted]	2.07	$[redacted] [2]	-[redacted]%
Caregiver disutility applied (base = no caregiver disutility applied)	$[redacted]	3.25	$[redacted] [1]	-[redacted]%
Societal perspective adopted includes productivity losses (base = productivity losses excluded)	$[redacted]	3.25	$[redacted] [4]	-[redacted]%
Age at baseline: 6 months old (base = mean age of 4.25 years)	$[redacted]	2.73	$[redacted] [1]	-[redacted]%
Additional sensitivity and scenario analyses conducting during the evaluation				
A1: Worse-case scenario: 100% discontinuation odevixibat	$[redacted]	1.26	$[redacted] [5]	-[redacted]%
A2: Informing inputs using PEDFIC and NAPPED (i.e., do not use OvEC)	$[redacted]	2.25	$[redacted] [1]	+[redacted]%
A3: Assumed a flat cost for odevixibat (i.e., assumed the cost of the 120 mcg/kg/day dose was equal to the 40 mcg/kg/day dose)	$[redacted]	2.73	$[redacted] [3]	-[redacted]%

Source: Tables 3-60 and 3-61, p172; Table 3-63, p174 of the submission

ICER = incremental cost-effectiveness ratio; PEBD = partial external biliary diversion; QALY = quality adjusted life year.

A1: Set Cell D26 'Clinical data – Efficacy' worksheet to 100%

A2: unselect Cell B22 'Key results' worksheet (see Table 12 for comparison of inputs)

A3: Set Cells G12:G24 to equal F12:F24 in 'General population' worksheet

The redacted values correspond to the following ranges:

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

[2] *$655,000 to < $755,000*

[3] *$755,000 to < $855,000*

[4] *$955,000 to < $1,055,000*

[5] *$55,000 to < $75,000*

6.71 Overall, the base case ICER of > $1,055,000 per QALY gained was unreliable, likely underestimated and favoured odevixibat as:

- Patients in the odevixibat arm were assumed to not undergo PEBD whereas the patients in the SOC arm were modelled to enter PEBD states. This resulted in odevixibat patients remaining in the 'no PEBD, no response' state which had more favourable outcomes (greater utility and lesser cost) compared to the PEBD states that patients from the SOC arm were modelled to enter;
- The utility values lacked face validity and likely favoured the health states that patients in the odevixibat arm occupied compared to those in the SOC arm;
- sBA response rates, which were applied in the model, were more favourable towards odevixibat compared to pruritus response; and

- The base case was informed by the more favourable OvEC data (i.e., more favourable odevixibat response and less favourable PEBD response compared to PEDFIC and NAPPED, respectively). This was associated with high uncertainty as inputs could not be verified. OvEC response was likely overestimated as the response of patients who up-titrated from 40 mcg/kg/day to 120 mcg/kg/day was potentially double counted.

6.72 The PSCR also requested that the ICER for odevixibat be considered in the context of PFIC being an ultra-rare condition. The PSCR noted that the PBAC has considered higher than typical ICERs in the context of rare conditions, for example, when considering eculizumab in November 2021, the PBAC noted "that it has previously considered ICERs in the range of $100,000 to $300,000 per QALY acceptable for rare diseases".[19] In the consideration of nusinersen [for adults with spinal muscular atrophy diagnosed under 19 years of age] in March 2022, the PBAC considered the ICER of $855,000 to < $955,000 per QALY "was acceptable in the context of a very high clinical need, in a limited and diminishing population and where equity of access is an additional consideration".[20] Finally, the PSCR noted Berdud, Drummond and Towse (2020)[21], which considered higher ICERs for ultra-rare conditions take into account differences in patient populations and costs of research and development in order to sustain prices that generate rates of return from investments in developing orphan drugs that are no greater than the industry average.

[19] https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2021-11/files/eculizumab-psd-nov-2021.pdf

[20] https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2022-03/nusinersen-solution-for-injection-12-mg-in-5-ml-spinraza

[21] Berdud, Drummond & Towse (2020) Establishing a reasonable price for an orphan drug. *Cost Eff. Resour. Alloc.* 18, 1–18 (2020).

Drug cost/patient/year

Table 20: Drug cost per patient for proposed and comparator drugs based on PEDFIC 1

	Odevixibat [a]			SOC		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Proportion receiving high dose, i.e. 120 mcg/kg/day	43.23%	30.15%	24.5%	NA	NR	NR
Mean duration	40 mcg/kg: 21.65 weeks 120 mcg/kg: 21.74 weeks [b]	16.15 years	6 years	NA	11.43 years	6 years
Cost/patient/year	$ to $ [c]	$ [d]	$ [e]	NA	$5,754 [f]	$139 [g]

Source: calculated the trial-based cost using on the weight distribution data from the model and mean weight from PEDFIC 1; 'Base case results' worksheet from the economic model

LT = liver transplant; NA = not applicable; NR = not reported; PEBD = partial external biliary diversion; SOC = standard of care

[a] Weight dependent cost per patient for each odevixibat dose reported in Table 14

[b] Mean duration of exposure to 40 mcg/kg/day dose and to 120 mcg/kg/day in PEDFIC 1

[c] Cost per patient over the trial period (not year) presented as the cost range at the low dose and high dose. Based on the mean weight of 15.5 kg in the 40 mcg/kg/day arm (p105 PEDFIC 1 CSR) the corresponding daily cost from the model was $/day for the low dose and $/day for the high dose. Cost at the low dose = 21.65 weeks x 7 x $. Cost at the high dose = 21.74 weeks x 7 x $.

[d] Undiscounted cost of response state divided by time spent in response state for odevixibat arm = $ / 16.15 years

[e] Average cost of odevixibat over six-year financial period divided by the total number of prevalent and incident patients (< 500) = $0 to < $10 million /< 500. Lower than in economic model as patient's may not have reached full adult weight in the six years of financial estimates

[f] Undiscounted cost of non-response state divided by time spent in non-response state for SOC arm = $65,766 /11.43 years

[g] Average cost of oral therapies in SOC over six-year financial period divided by the total number of prevalent and incident patients (< 500) = $0 to < $10 million / < 500. Financial estimates did not include costs for PEBD or LT.

6.73 The cost per patient per year varied between the PEDFIC 1 trial, economic model, and the financial estimates. The cost per patient per year in the economic model and financial estimates differed due to differences in the proportion of patients who received high dose odevixibat (30.15% versus 24.5%), the treatment duration of odevixibat (16.15 versus 6 years), and the mean starting age of patients (4.25 years versus 4 [incident] and 12 years [prevalent]), respectively. The cost per patient per year in the financial estimates was notably lower compared to the economic model as the incident patients did not reach full adult weight over the six-year period in the financial estimates whereas the economic model was over a lifetime (100-year) time horizon.

Estimated PBS usage & financial implications

6.74 This submission was considered by DUSC. The submission adopted an epidemiological approach to estimating the financial impact of odevixibat.

6.75 The key inputs for the financial estimates are presented in Table 21.

Table 21: Key inputs for financial estimates

Parameter	Value applied and source	Comment
PFIC patients (incident and prevalent)	Prevalence rate = 0.07 per 10,000 persons (estimated from Baker 2019 a systematic review of studies of the epidemiology, natural history, and burden of PFIC in the European population) Applied the Australian population in Year 1 (27,562,195). Incidence rate = 1 per 50,000 children born (reported in Davit-Spraul 2009 without citation of source). Applied to the number of child births in Australian in 2022 (300,684) in Year 2 onward. **2024 2025 2026 2027 2028 2029** Prev [redacted]1 [redacted]1 [redacted]1 [redacted]1 [redacted]1 [redacted]1 Incident [redacted]1 [redacted]1 [redacted]1 [redacted]1 [redacted]1 [redacted]1 Source: Baker 2019; Davit-Spraul 2009; Australian Bureau of Statistics Only prevalent patients were counted for Year 1, and only incident patients were counted for Year 2 onwards to avoid double counting.	DUSC considered the estimates of prevalent and incident patients were likely overestimated. DUSC commented that the estimated prevalence rate of 0.05 to 0.07 per 10,000 people may be the best estimate based on available evidence. However, DUSC considered that applying this rate to the entire population may not have been appropriate. DUSC commented that this rate could be applied to the population aged 0-19 years old but suggested that the older population were more likely to have undergone a liver transplant or have died and considered that the utilisation in adults should be estimated separately. DUSC considered that the incidence rate may be overestimated. DUSC suggested that an alternative approach could be to apply 0.07 per 10,000 live births (1 per 142,857 live births) to the ABS projections of birth rates between 2025 and 2029. DUSC considered this estimate of 2-3 per year may be more reasonable than the estimated number of < 500 in the submission.
PFIC2 *BSEP3* subtype	The submission excluded patients with PFIC2 *BSEP3* subtype based on the draft PI. The estimation of PFIC2 BSEP3 was: • % PFIC patients that have PFIC2 subtype = 34.2% • % PFIC2 patients that have *BSEP3* genotype = 21% • % PFIC2 BSEP3 patients = 7.2% (34.2% × 21%) and applied to the prevalent patients. Alsohaibani 2023 was a retrospective study of patients diagnosed with PFIC in single-centre in Saudi Arabia (N=79) who reported 34.2% of PFIC patients had PFIC2. Van Wessel 2020 was a multicentre retrospective cohort study of PFIC2 patients including *BSEP1*, *2*, and *3* from the NAPPED database. The total PFIC cohort in the NAPPED database was 590, of which 264/590 (44.8%) patients had confirmed PFIC2 subtype, of whom 56/264 (21.2%) had the *BSEP3* subtype.	The proposed restriction criteria did not exclude patients according to PFIC subtype. If PFIC subtypes are excluded, then genetic testing is required to identify eligible patients. Genetic testing was not considered and likely underestimated the financial estimates (it is acknowledged that MBS items for PFIC genetic testing were not available). DUSC agreed that without genetic testing, patients with these subtypes were likely to initiate but not respond after three months of treatment. DUSC considered these estimates could instead inform continuation rates. Justification for informing PFIC2 subtype rates using Alsohaibani 2023 was not clear. Van Wessel 2020 provided a complete single source for estimating PFIC2 *BSEP3* patients. The NAPPED data was considered robust and representative of PFIC and estimated 9.5% PFIC2 *BSEP3* patients (44.8% × 21.2%). Overall, DUSC considered the approach underestimated eligible patients.
Prior PEBD and LT	The submission stated that odevixibat is not intended for patients who have already undergone PEBD or LT, therefore excluded these patients. Based on Sponsor assumption: • % who have undergone previous PEBD = 50% • % who have undergone previous LT = 80%	The proposed restriction did not exclude patients according to prior PEBD or LT. DUSC considered the submission's approach underestimated the number of patients who would be treated. Further, DUSC noted that patients who have already undergone PEBD

<table>
<tr><th>Parameter</th><th>Value applied and source</th><th>Comment</th></tr>
<tr><td></td><td>Applied to the prevalent patients.</td><td>were not excluded from the PEDFIC1 trial and considered it may not be reasonable to exclude these patients from the estimates.

DUSC agreed that it was reasonable to exclude LT patients, but considered the submission's estimate that 80% had undergone prior LT was likely an overestimate, particularly for the paediatric population. DUSC noted van Wessel 2020 stated 45.5% of patients had prior LT, and considered that an estimate of 45.5% should be applied to the proportion of patients under the age of 20 years having undergone prior LT.</td></tr>
<tr><td>Eligible patients</td><td>The submission stated patients are either in the initiating or continuing treatment phase:
The initiating phase reflected patients in their first three months of treatment at the low dose (40 mcg/kg) and
The continuing phase reflected patients who either (i) responded to the low dose and continued at 40 mcg/kg, or (ii) who escalated to the high dose (120 mcg/kg) due to non-response at the low dose, and then subsequently responded and continued at 120 mcg/kg.
Of [redacted][1] prevalent patients identified only [redacted][1] assumed to be eligible for treatment.</td><td>DUSC noted it was reasonable to assume that all eligible prevalent patients will be treated in the first year of listing, as patients are likely already managed by specialists. DUSC agreed that it was reasonable to only count prevalent patients in Year 1, and to only count incident patients for Year 2 onwards.</td></tr>
<tr><td>Dosing protocol</td><td>The submission follows the weight-based dosing regimen from the draft PI. Patients at the low dose (40 mcg/kg/day) receive 200 mcg or 400 mcg capsules. Patients at the high dose (120 mcg/kg/day) receive 600 mcg or 1200 mcg capsules. Patients who weigh <19.5 kg initiate on the 200 mcg capsules and then progress to 600 mcg capsules if they dose escalate. Patients ≥19.5 kg initiate on the 400 mcg capsules and then progress to 1200 mcg capsules if they dose escalate.</td><td>DUSC considered this was reasonable.</td></tr>
<tr><td>Responders and non-responders</td><td>The submission stated presented three potential treatment pathways for patients. These are summarised below.<table><tr><th>Pathway</th><th>Value</th><th>Source</th></tr><tr><td>1. Respond to low dose (40 mcg/kg) and continue</td><td>43.5%</td><td>Response rate in 40 mcg/kg arm in PEDFIC 1</td></tr><tr><td>2. No response to low dose at three months, but then respond to high dose at six months (120 mcg/kg) and continue</td><td>14.5%</td><td>Calculated as 24.5% x 58%

24.5% = % high dose (internal data and PEDFIC response)
58% = total responders</td></tr><tr><td>3. No response to low dose, and no response to high dose and discontinue</td><td>42%</td><td>Calculated as 100% - 57.63% (total responders).</td></tr></table></td><td>The dose escalation and discontinuation rules in the financials followed the draft PI; however, these were not specified in the proposed restriction. The basis for the three-month initial treatment period was unclear given that patients in PEDFIC 1 escalated dose after ~22 weeks.

PEDFIC 1 response rates to 40 mcg/kg/day dosage were reasonable. However, these inputs were not consistent with the economic model base case, which relied on OvEC inputs (49.4% response rate). There was uncertainty in the proportion of patients who received high dose odevixibat (24.5%) as the response of patients who up-titrated could not be verified.

DUSC noted that:</td></tr>
</table>

<table>
<tr><th>Parameter</th><th>Value applied and source</th><th>Comment</th></tr>
<tr><td></td><td></td><td>• patients with other subtypes with unknown response will be eligible to initiate treatment thus, 43.5% might be an overestimate
• the 3 month response rates were based on 22 week response rates from PEDFIC 1, in the 40 mcg group only (43.5%) – response rates might be lower at 12 weeks (3 months)
• patients initiated on 120 mcg/kg did not respond as well at 22 weeks (21.1%), and
• the response of patients who up-titrated could not be verified, which increases uncertainty.</td></tr>
<tr><td>Treatment duration</td><td>The following treatment durations for the three treatment scenarios were assumed:
1. Responders at low dose: initial treatment 3 months, then continue treatment for 72 months
2. Responders at high dose: continue treatment for 72 months
3. Non-responders at all doses: continue treatment for 6 months
The patients assumed to be receiving treatment are summarised below
<table>
<tr><th>Patients</th><th>2024</th><th>2025</th><th>2026</th><th>2027</th><th>2028</th><th>2029</th></tr>
<tr><td>Prevalent patients</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Prevalent initiating</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td></tr>
<tr><td>Prevalent continuing</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td></tr>
<tr><td>At low</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td></tr>
<tr><td>At high</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td></tr>
<tr><td>At high but NR</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td></tr>
<tr><td>Incident patients</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Incident initiating</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td></tr>
<tr><td>Incident continuing</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td></tr>
<tr><td>At low</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td></tr>
<tr><td>At high</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td></tr>
<tr><td>At high but NR</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td><td>[redacted]</td><td>1</td></tr>
</table>
Source: Table 4-7, p181 of the submission, sheet 2.d, submissions financial workbook
NR = no response
patients in each treatment category each year were extracted from the '2.d Patients - DTG' worksheet. The sum of patients within each treatment pathway for prevalent and incident patients were calculated.</td><td>Initial and continuing treatment durations were not specified in the proposed restriction and may not be reasonable.</td></tr>
<tr><td>Units dispensed</td><td>The weighted average number of units per strength was based on patient weight and weight distribution data. The submission assumed the mean age of prevalent patients was 12 years and for incident patients it was 4 years (assumed from the model). The submission then estimated the corresponding weight distributions for these mean ages from the model. The submission estimated that the proportion of patients initiating at a low and high strength based on the weight distribution around the mean age of 12 and 4 years. The submission then estimated the weighted average number of capsules for prevalent and incident patients who initiate</td><td>DUSC noted that the median age in PEDFIC 1 was 3.2 years. Additionally, it was unclear how the mean age of prevalent patients (12 years) was informed from the model. If the submission excluded patients who have had prior PEBD and LT, it is possible that the prevalent patients would be younger than 12 years of age. DUSC noted that in PEDFIC 2 Cohort 2 the mean age of patients was 7.8 years.

Given patients (especially incident patients, who will be at age 10 years at the end of 6 years of</td></tr>
</table>

<table>
<tr><th>Parameter</th><th>Value applied and source</th><th>Comment</th></tr>
<tr><td></td><td>at low (200 mcg) or high strengths (400 mcg) based on the weight distribution data and the recommended capsules at each weight category.

<table><tr><th></th><th colspan="2">% initiating at</th><th colspan="2">Average no. of capsules/day</th></tr><tr><th></th><th>Low</th><th>High</th><th>Low</th><th>High</th></tr><tr><td>Prevalent 12 years</td><td>0.13%</td><td>99.87%</td><td>3.45/day</td><td>4.96/day</td></tr><tr><td>Incident 4 years</td><td>38.60%</td><td>61.40%</td><td>3.36/day</td><td>2.44/day</td></tr></table>Source: ‘General population’ worksheet from the economic model, CDC growth charts; ABS
Read as, for example, the 99.87% of prevalent patients initiating at the high strength will have 4.96 x 400 mcg capsules per day.</td><td>treatment) may not have reached their full adult weight at the end of the financial estimates, the cost per patient per year of treatment was likely to continue to grow beyond the financial estimates.

DUSC noted that reducing the mean age of prevalent patients from 12 to 8 years would reduce the net cost by 22%. DUSC considered using a mean age of 12 years may overestimate utilisation.</td></tr>
<tr><td>Compliance and uptake</td><td>100% compliance and uptake rate assumed</td><td>Likely conservative but reasonable and consistent with the model. No wastage was considered in the submission.</td></tr>
<tr><td>Grandfathered patients</td><td>The submission included [redacted] [1] patients from a compassionate access program as part of the prevalent patients. The mean treatment duration for these patients was 3.2 months, hence it was assumed all these patients would enter via the continuing treatment stage.

When calculating the scripts of prevalent patients in the initiating phase, the proportion of patients initiating treatment was reduced to 33.1% (1 – 12/18). This was applied to the prevalent patients who respond to low dose (40 mcg/kg) odevixibat and continued.</td><td>The evaluation considered that grandfathered patients who have been treated for < 3 months may receive a higher dose after 3 months. This was not considered and would underestimate financial estimates.

DUSC considered it was reasonable to assume that grandfathered patients will all continue treatment and that some may increase their dose to 120 mcg/kg.</td></tr>
<tr><td>Script numbers</td><td>The estimated annual scripts for odevixibat are shown below.
<table><tr><th></th><th>2024</th><th>2025</th><th>2026</th><th>2027</th><th>2028</th><th>2029</th><th>% total</th></tr><tr><td>200 mcg</td><td>[redacted] 1</td><td>[redacted] 1</td><td>[redacted] 1</td><td>[redacted] 1</td><td>[redacted] 1</td><td>[redacted] 1</td><td>11%</td></tr><tr><td>400 mcg</td><td>[redacted] 1</td><td>[redacted] 2</td><td>[redacted] 2</td><td>[redacted] 2</td><td>[redacted] 2</td><td>[redacted] 2</td><td>59%</td></tr><tr><td>600 mcg</td><td>[redacted] 1</td><td>[redacted] 1</td><td>[redacted] 1</td><td>[redacted] 1</td><td>[redacted] 1</td><td>[redacted] 1</td><td>5%</td></tr><tr><td>1200 mcg</td><td>[redacted] 1</td><td>[redacted] 1</td><td>[redacted] 1</td><td>[redacted] 1</td><td>[redacted] 1</td><td>[redacted] 1</td><td>25%</td></tr><tr><td>Total</td><td>[redacted] 2</td><td>[redacted] 2</td><td>[redacted] 2</td><td>[redacted] 2</td><td>[redacted] 2</td><td>[redacted] 2</td><td>100%</td></tr></table>Source: Table 4-10, p184 of the submission</td><td>The 400 mcg and 1200 mcg capsules contributed ~85% of total scripts and reflects the proportion of prevalent patients initiating and continuing treatment and those who escalate dose to 120 mcg/kg.

DUSC considered that the estimated annual script volumes were impacted by the mean age estimates and may be overestimated.</td></tr>
<tr><td>Odevixibat</td><td>The published and effective prices of odevixibat are shown below.
<table><tr><th>Capsule Strength</th><th>AEMP</th><th colspan="2">DPMQ</th></tr><tr><th></th><th></th><th>Public</th><th>Private</th></tr><tr><td>Published</td><td></td><td></td><td></td></tr><tr><td>200 mcg</td><td>$[redacted]</td><td>$[redacted]</td><td>$[redacted]</td></tr><tr><td>400 mcg</td><td>$[redacted]</td><td>$[redacted]</td><td>$[redacted]</td></tr><tr><td>600 mcg</td><td>$[redacted]</td><td>$[redacted]</td><td>$[redacted]</td></tr><tr><td>1200 mcg</td><td>$[redacted]</td><td>$[redacted]</td><td>$[redacted]</td></tr><tr><td>Effective</td><td></td><td></td><td></td></tr><tr><td>200 mcg</td><td>$[redacted]</td><td>$[redacted]</td><td>$[redacted]</td></tr><tr><td>400 mcg</td><td>$[redacted]</td><td>$[redacted]</td><td>$[redacted]</td></tr><tr><td>600 mcg</td><td>$[redacted]</td><td>$[redacted]</td><td>$[redacted]</td></tr><tr><td>1200 mcg</td><td>$[redacted]</td><td>$[redacted]</td><td>$[redacted]</td></tr></table>Source: Table 4-11, p184 of the submission
AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity</td><td>The submission reported the DPMQ for the 200 mcg capsules and 600 mcg capsules as:
$[redacted] (public) and $[redacted] (private) for the 200 mcg at the published price
$[redacted] (public) and $[redacted] (private) for the 200 mcg at the effective price
$[redacted] (public) and $[redacted] (private) for the 600 mcg at the published price
$[redacted] (public) and $[redacted] (private) for 600 mcg at the effective price
However, these values appeared to reflect a maximum of four packs. This was not consistent with the maximum quantity of 12 packs as proposed by the submission (see the Requested Listing). The DPMQs were changed to reflect a maximum quantity of 12 packs.</td></tr>
</table>

<table>
<tr><th>Parameter</th><th>Value applied and source</th><th>Comment</th></tr>
<tr><td></td><td>The DPMQ for the 200 mcg and 600 mcg capsules were not consistent with the maximum quantity packs (12) reported by the submission. Italicised text indicates the DPMQ for the 200 mcg and 600 mcg strengths that aligns with a maximum of 12 packs (italicised text)

The submission did not present the impact on the RPBS. Based on a proxy measure, (amifampridine; an orphan drug that is accessible for a paediatric population) the effect of odevixibat to the RPBS was expected to be insignificant.</td><td>DUSC noted that patients who were initiated on the higher dose of 120 mcg/kg did not respond as well at 22 weeks as those who initiated on 40 mc/kg (21.1% compared to 43.5%) and considered it may not be reasonable for the higher dose to have a higher price.</td></tr>
<tr><td>SOC</td><td>The submission considered the impact on PBS-listed oral therapies and are presented below.
<table><tr><th>Therapy</th><th>Item Code</th><th>Cost</th></tr><tr><td>UDCA 250mg</td><td>8448P</td><td>$113.65</td></tr><tr><td>Cholestyramine (paediatric) 4000mg</td><td>2967E-9249T</td><td>$41.21</td></tr><tr><td>Rifampicin (paediatric) 150 mg</td><td>12190N-1982H</td><td>$194.72</td></tr><tr><td>Naltrexone 50 mg</td><td>8370M</td><td>$104.96</td></tr></table>Source: Table 4-14, p186 of the submission

The submission considered that odevixibat aims to delay LT by approximately 22 years (appears to be based on difference between mean time spent before LT in the economic model, see Table 18), which was beyond the 6-year financial period, therefore was not included.</td><td>The changes in use of oral therapies were inconsistent with the clinical algorithm and economic model which assumed that oral therapies would be use alongside odevixibat. The submission's approach would overestimate the cost offsets compared to the economic model and therefore financial impact was underestimated. However, SOC costs were small relative to odevixibat costs.</td></tr>
<tr><td>MBS items</td><td>The submission stated that there were no expected changes to MBS items for the listing of odevixibat and that LT and PEBD procedures do not have any relevant MBS item codes and therefore were not include in the financial estimates.</td><td>The submission did not consider relevant genetic testing to diagnose PFIC, particularly when the financial estimates excluded PFIC2 BSEP3 patients. DUSC considered it was reasonable to not include costs of genetic testing based on the proposed PBS restriction, but noted these would need to be included if the requested restriction was altered to require genetic testing.

The evaluation noted that the submission did not consider changes in testing or monitoring associated with a reduction in PEBD due to odevixibat, which was not consistent with the economic model.</td></tr>
</table>

Source: Section 4.2.1 of the submission

ABS = Australian Bureau of Statistics; Avg = average; BSEP = bile salt exporter pump; DUSC = Drug Utilisation Sub-Committee; LT = liver transplant; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PEBD = partial external biliary diversion; PFIC = progressive familiar intrahepatic cholestasis; PI = Product Information; RPBS = Repatriation Pharmaceutical Benefits Scheme; UDCA = Ursodeoxycholic acid; SOC = standard of care.

The redacted values correspond to the following ranges:

[1] < 500

[2] 500 to < 5000

6.76 The estimated use of odevixibat is presented in Table 22.

Table 22: Estimated use of odevixibat

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Prevalent PFIC patients	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Incident PFIC patients	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Exclude PFIC2 BSEP3 (7%) and previous PEBD (50%) and LT (80%) [a]						
Prevalent PFIC patients	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Incident PFIC patients	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Patients initiating and continuing						
Prevalent – initiating	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Prevalent – continuing [b]	[redacted] c 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
At low dose	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
At high dose	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
At high dose but did not respond at 6 months	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Incident – initiating	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Incident – continuing [d]	[redacted] 1	[redacted] e 1	[redacted] e 1	[redacted] e 1	[redacted] e 1	[redacted] e 1
At low dose	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
At high dose	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
At high dose but did not respond at 6 months	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Scripts (100% compliance and uptake) [b,						
200 mcg capsules	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
400 mcg capsules	[redacted] 1	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 2
600 mcg capsules	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
1200 mcg capsules	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Total scripts	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 2

Source: Section 4.2.1 of the submission; '2a. Patients – Incident', '2b. Patients – Prevalent', '3a. Scripts – proposed' worksheets from budget impact model.

BSEP = bile salt export pump; LT = liver transplantation; PEBD = partial external biliary diversion; PFIC = progressive familial intrahepatic cholestasis

[a] Prevalent patients excluded PFIC2 *BSEP3* and patients with prior PEBD or LT (0.93 × 0.50 × 0.20); Incident patients excluded PFIC2 *BSEP3* patients (0.93)

[b] The submission did not report continuation patients as cumulative and did not consider discontinuation after the initial 3 months.

[c] Sum of continuing patients = < 500+< 500+< 500 = < 500 patients

[d] Sum of incident patients = < 500+< 500+< 500 = < 500 patients

[e] scripts were based the proportion of prevalent and incident patients who receive low (0.13% and 38.6%, respectively) and high strength capsules (99.87% and 61.4%, respectively); the average number of low and high strength capsules for prevalent and incident patients (see Scripts – proposed' worksheet from the financial model); and assuming 3-month initiation period and 72-month continuation for responders; and 6-month continuation for non-responders.

The redacted values correspond to the following ranges:

[1] < 500

[2] 500 to < 5,000

6.77 The net financial cost of odevixibat is presented in Table 23.

Table 23: Estimated net cost of odevixibat to the PBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Effective prices (SPA)						
PBS cost	$[redacted] 1	$[redacted] 2	$[redacted] 2	$[redacted] 2	$[redacted] 2	$[redacted] 1
Patient copayment	-$[redacted] 3	-$[redacted] 3	-$[redacted] 3	-$[redacted] 3	-$[redacted] 3	-$[redacted] 3
Changed listing [a]	-$[redacted] 3	-$[redacted] 3	-$[redacted] 3	-$[redacted] 3	-$[redacted] 3	-$[redacted] 3
Net cost to PBS	$[redacted] 1	$[redacted] 2	$[redacted] 2	$[redacted] 2	$[redacted] 2	$[redacted] 1

Source: Table 4-12 and 4-13, p185; Table 4-15, p186 of the submission

PBS = Pharmaceutical Benefits Scheme; SPA = special pricing arrangement

[a] Change in oral therapies from standard of care arm

The redacted values correspond to the following ranges:

[1] $10 million to < $20 million

[2] $0 to < $10 million

[3] net cost saving

6.78 The net cost to the PBS of odevixibat was estimated to be $10 million to < $20 million in Year 6 and a total of $50 million to < $60 million over the first 6 years. The change in SOC oral therapies had a minimal impact on financial estimates.

6.79 The financial risk of underestimating prevalent patient numbers was substantial as the cost per patient per year for each prevalent patient may be as much as $0 to < $10 million (≥ 55.5 kg treated at 120 mcg/kg/day), or $0 to < $10 million over six years.

6.80 DUSC considered that overall, the submission's estimates of the number of incident and prevalent patients likely to receive treatment with odevixibat under the proposed restriction was reasonable. While DUSC considered that the submission had likely overestimated the number of prevalent and incident patients (see Table 21), the submission's approach to excluding patients by PFIC subtype may have reduced the estimates to reasonable level. However, DUSC noted that under the proposed PBS restriction, patients with a PFIC subtype excluded by the model would not be identified and would be likely to initiate and then not respond to odevixibat. Further, DUSC considered that the submission had overestimated the average age of prevalent patients at initiation of treatment.

Options to present additional relevant information

6.81 The submission requested that the PBAC consider the Rule of Rescue for odevixibat or, alternatively, be considered for the Life Saving Drugs Program if PBAC does not recommend odevixibat on the grounds of cost effectiveness. It was unclear whether odevixibat clearly met the Rule of Rescue consideration as:

- Although the evidence presented suggests odevixibat is effective in reducing sBA levels and improving pruritus at 24 weeks compared to placebo, direct evidence against the nominated comparator, SOC, was lacking, and the ITC presented was inadequate to support the comparison;
- The risk of imminent death was uncertain as in the model pre-LT mortality was 0.27% and long-term post-LT mortality was 1.91%. The life years gained in the SOC arm was 51.95 years compared to 63.33 years in the odevixibat arm. The literature also reported 5-year post-LT survival to be over 98%; and
- While PFIC is a rare condition, the eligible population who would likely benefit from treatment were likely underestimated in the financial estimates.

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 progressive familial intrahepatic cholestasis (PFIC). Although the PBAC recognised that there was a high clinical need for treatments for this rare condition, the PBAC noted that there were significant uncertainties regarding the proposed restriction, the clinical evidence

presented, the economic model and the utilisation estimates. The PBAC advised a facilitated resolution pathway would be appropriate given the potentially high added therapeutic value and complex nature of the outstanding issues.

7.2 The PBAC considered the primary reason for this outcome was due to the economic evaluation provided.

7.3 The PBAC noted and welcomed the substantial consumer comments provided in support of this submission. The comments described the significant burden PFIC has on the quality of life of patients, carers and their families. The PBAC considered there was a high and urgent need for effective therapies for patients with PFIC. The PBAC noted the comments received indicated that treatment with odevixibat reduced severe itch leading to improved quality of life, reduced bleeding due to scratching, reduced anxiety, and improved sleep, appetite, growth and energy.

7.4 In regard to the proposed restriction criteria, the PBAC noted the following:

- the requested Authority Required (Streamlined) listing was not reasonable and an Authority Required (in writing only via post or HPOS upload) would be more appropriate.
- no criteria for dose escalation was provided.
- the initial restriction did not include genetic testing for diagnosis despite some patients with PFIC (including those with PFIC2 *BSEP3* genotype and PFIC5) being unlikely to respond to odevixibat. The PBAC noted that absence of confirmatory genetic testing was contrary to the clinical trial, is likely to expose some patients to potential toxicity without clinical benefit, and reduce the net effectiveness and cost-effectiveness of odevixibat. The PBAC also noted that confirmatory genetic testing was not required in the proposed TGA indication.
- the initial restriction did not specify diagnostic criteria, lacking both the severity of symptomatic pruritis and a minimum level of serum bile acid (sBA), for patients to be eligible for treatment. The PBAC noted that the Canadian Agency for Drugs and Technologies in Health reimbursement recommendations for odevixibat included diagnostic criteria that were consistent with the clinical trial and implementable in clinical practice.
- no data was provided for patients initiating treatment at an age of > 18 years. The PBAC considered it appropriate for the restriction to require initiation at age < 18 years.
- the initial restriction did not exclude patients who had previously received surgical biliary diversion (SBD) or liver transplant (LT).
- the continuing restriction did not include a response criteria or discontinuation rule if patients, for example, progress to SBD.

- the restriction criteria did not allow for patients to stop and restart treatment, with the clinical criteria specifying that the patient must be experiencing symptomatic pruritus, which would not necessarily be the case for responders.
- the restriction allowed for patients to escalate from a dose of 40 mcg/kg/day to 120 mcg/kg/day if there was an inadequate response at 3 months, however dose escalation was not supported by the clinical data in the submission.
- the restriction should require prescription by a specialist experienced in the management of PFIC.

7.5 The PBAC considered the nomination of standard of care (SOC), including off-label use of medicines such as ursodeoxycholic acid and rifampicin, as well as partial external biliary diversion (PEBD) surgery, as a proxy for all SBDs, and LT, as the main comparator was reasonable. However, the PBAC noted the submission appeared to position odevixibat largely as an alternative to PEBD in the proposed clinical management algorithm and the economic model.

7.6 The PBAC noted the submission was based on the results from a randomised trial that compared odevixibat with placebo (PEDFIC 1), a single arm "extension" study (PEDFIC 2) and the results of an unanchored indirect treatment comparison (ITC) (OvEC). The OvEC study compared odevixibat (patients from PEDFIC 1 and PEDFIC 2) to external controls (patients from a natural history study of PFIC (NAPPED)). The PBAC noted that PEDFIC 1 included patients with PFIC1 and PFIC2 subtypes only (informed by genetic testing), whereas PEDFIC 2 included some patients with PFIC3 and PFIC6. The submission provided no comparative evidence for patients with PFIC3 or PFIC6 and no evidence for patients with PFIC4 and PFIC5 subtypes.

7.7 The PBAC noted that PEDFIC 1 compared the efficacy and safety of 42 patients aged between 6 months and 18 years of age who had elevated sBA concentrations (≥ 100 µmol/L) and who were treated with orally administered odevixibat compared to 20 patients treated with placebo over 24 weeks. The PBAC noted that 33.3% of patients treated with odevixibat achieved a sBA response[22], compared to 0% in the placebo arm (adjusted risk difference (RD): 30.7, 95% confidence interval (CI): 12.6, 48.8). The PBAC noted the RD for the comparison with placebo for the 40 mcg/kg/day dose was 44.1% (95% CI: 23.6, 64.6) and for the 120 mcg/kg/day dose was 21.6% (95% CI: -0.5, 43.8). The PBAC noted that 55.1% of patients treated with odevixibat achieved a positive pruritus assessment[23], compared to 30.1% in the placebo arm (RD: 25.0%, 95% CI: 8.5, 41.5). The PBAC noted the high placebo response for the positive pruritis assessment and considered this may not be observed in clinical practice. Additionally, the PBAC noted that placebo does not represent the nominated comparator of SOC,

[22] Defined as a ≥70% reduction in fasting sBA concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L

[23] Defined as a scratching score of ≤1 or at least a 1-point drop from baseline on the PRUCISION ObsRO instrument

as defined in paragraph 7.5.

7.8 The PBAC noted the reliability of the ObsRO instrument, which was used in PEDFIC 1 to measure pruritus response, was uncertain given the limited information regarding the scoring of the instrument, the unclear clinical significance of the definition of a positive pruritus assessment and it not being independently validated in a study distinct from PEDFIC 1.

7.9 The PBAC noted PEDFIC1 provided some comparative safety versus placebo and noted the proportion of patients experiencing a TEAE was similar across all arms (82-85%), with diarrhoea the most commonly reported TEAE in both odevixibat-treated (31%) and placebo (30%) patients.

7.10 The PBAC noted that PEDFIC 2 was a noncomparative study that enrolled mostly PFIC1 and PFIC2 patients (5/69 patients had PFIC3 and 1/69 patients had PFIC6), with all patients receiving a dose of 120 mcg/kg/day regardless of previous exposure or response to odevixibat in PEDFIC 1. The submission included data from the July 2020 data cut-off, however the PBAC noted that data with additional follow-up (July 2022 data cut-off) were available and provided to the TGA. The PBAC noted that, based on the July 2020 data cut-off, sBA and pruritis scores reduced over time (see Figure 4 and Figure 5).

7.11 The PBAC noted the submission presented an indirect treatment comparison (OvEC), comparing odevixibat (based on patients from PEDFIC 1 and PEDFIC 2, n=69) to external controls (based on patients from NAPPED, n=80 [Part A] and n=24 [Part B]). OvEC Part A compared odevixibat to controls who had not undergone SBD and OvEC Part B compared odevixibat to controls who had undergone SBD. The PBAC noted there were substantial transitivity issues with OvEC Part A (see paragraph 6.14) and limited details were provided for OvEC Part B (see paragraph 6.16). The PBAC noted OvEC Part B was more relevant as it compared odevixibat to SBD. The PBAC noted OvEC Part B reported a numerical improvement in native liver survival in the odevixibat arm (6% [4/69]) compared to the SBD arm (25% [6/24]) over a median follow up of 22.6 months for the odevixibat arm (the duration of follow up in the SBD arm was unclear).

7.12 The PBAC considered that odevixibat was superior in terms of effectiveness compared to placebo for patients with PFIC1 and PFIC2 (based on the results from PEDFIC 1) but noted that the patient numbers were small and the trial was of a short duration, only providing 24 weeks of comparative data.

7.13 The PBAC considered that the claim of superior effectiveness against SOC was uncertain, but possibly supported based on the results from OvEC Part B. The magnitude of benefit versus SOC was highly uncertain given the small patient numbers, limited comparative data, and likely transitivity issues.

7.14 The PBAC considered the clinical claim that odevixibat is non-inferior in terms of safety to SOC to be inadequately supported, given the lack of comparative data.

7.15 The PBAC noted the submission presented a cost-utility analysis in the form of a Markov state transition model with a 100-year time horizon. The Committee considered the time horizon to be too long, given the short-term duration of the comparative trial data from PEDFIC 1 (24 weeks) and the natural history of the disease. The PBAC noted the base case ICER presented in the submission was > $1,055,000 per quality adjusted life year (QALY).

7.16 The PBAC noted that although the model defined response to treatment as 'pruritis response with or without sBA response', the economic model used sBA as a surrogate for pruritis response. The PBAC considered that use of sBA as a surrogate was reasonable, noting there were a number of issues with the pruritis tool used in PEDFIC 1, the PRUCISION ObsRO instrument (see paragraph 6.21 and paragraph 7.8).

7.17 The PBAC noted that the transition probabilities were primarily informed by data from OvEC which favoured odevixibat (see paragraph 6.71) and, based on the information presented in the submission, the OvEC data could not be independently verified.

7.18 The PBAC noted that the submission assumed that odevixibat treated patients would not undergo PEBD after losing response and remained in the 'no PEBD, no response, health state for an extended period of time compared to SOC (28 years in odevixibat arm vs 11 years in SOC arm, see Table 18). The PBAC noted the 'no PEBD, no response' health state had a higher utility compared to the PEBD states (see paragraph 7.19) and did not accrue costs of ongoing treatment. The PBAC considered this favoured odevixibat and was not likely to reflect clinical practice given that three patients in PEDFIC 2 received PEBD following odevixibat and that the advice from the sponsor hearing was that some patients may also undergo PEBD in addition to remaining on treatment with odevixibat, should resolution of symptoms with odevixibat be suboptimal, or after losing response.

7.19 In terms of the utility values, the PBAC noted that although the utilities from PEDFIC 1 would have been the most representative of PFIC patients, results were reported for only 50% of the trial population and some of the results were considered implausible. The PBAC considered that some of the literature-based values applied in the model were highly uncertain as none of the selected studies were in the PFIC population. Notably, the 'no PEBD, no response' health state had higher utility (0.83) than the 'PEBD, response' state (0.659). This favoured the odevixibat arm and implied that patients preferred pruritus symptoms above achieving a response after PEBD, which was not plausible.

7.20 The PBAC noted the model assumed 30.15% of patients would be treated with odevixibat 120 mcg/ kg/ day and this was a key driver of the model (see Table 16). The PBAC noted that a higher price was proposed for the 120 mcg/kg/day dose, despite significant uncertainty regarding the benefit of dose escalation. The PBAC noted assuming patients are only treated with the 40 mcg/kg/day dose (i.e., no dose escalation) decreased the ICER by 47% and assuming flat treatment cost (i.e., cost of

120 mcg/kg/day dose the same as the 40 mcg/kg/day dose) decreased the ICER by 38%.

7.21 Overall, the PBAC considered that the economic model was biased in favour of odevixibat, that the incremental cost-effectiveness ratio (ICER) was extremely high and that odevixibat would not be cost-effective without a substantial price reduction.

7.22 The PBAC noted that the base case ICER was reduced when carer disutilities were included as a sensitivity analysis. Noting the consumer comments received, the PBAC considered that it would be likely that odevixibat would result in benefits for others beyond the patient.

7.23 The PBAC considered the utilisation of odevixibat would depend on the average age at initiation of treatment and the response rate, both of which may have been overestimated in the submission. The Committee also considered the number of patients who would undergo dose escalation was uncertain. The PBAC considered that revisions would be required to the financial estimates model, based on a revised restriction, and incorporating revisions to the epidemiological approach taken to define the prevalent and incident patient population in line with that recommended by DUSC (paragraph 6.80 and Table 21). The Committee considered that an RSA would be required, given the level of uncertainty in the estimates, including uncertainty in the duration of use and uptake. The PBAC considered that if the restriction does not require confirmatory genetic testing then the RSA should account for odevixibat being ineffective in patients with the non-responsive genotype.

7.24 The PBAC considered that the Rule of Rescue was insufficiently supported for odevixibat, given non-pharmacological therapies (i.e. SBD and LT) are available and that there is no imminent risk of death.

7.25 The PBAC considered odevixibat addresses a high and urgent unmet clinical need and is expected to provide a substantial and clinically relevant improvement in reducing elevated sBA and severe pruritis, over standard of care. The PBAC noted that a significant price reduction is required for odevixibat to be cost-effective (as outlined in paragraph 7.21), but if the sponsor is able to proceed on this basis then a facilitated resolution pathway may be acceptable for a resubmission (as defined in the Procedure Guidance for listing medicines on the Pharmaceutical Benefits Scheme). As part of this pathway, prior to a resubmission for odevixibat being made, the PBAC would like to offer the sponsor a solution-focussed workshop with one or more members of the PBAC, to explore feasible options to address the following issues:

- The restriction issues, as outlined in paragraph 7.4, including the feasibility of requiring confirmatory genetic testing as per the clinical trial;
- The economic modelling issues, as outlined in paragraphs 7.15 to 7.22, including a higher price for the 120 mcg/kg/day dose versus the 40 mcg/kg/day dose not being supported by the clinical evidence; and

- The utilisation of odevixibat, and appropriate RSA structure, as outlined in paragraph 7.23, including accounting for the proportion of patients unlikely to respond due to a non-responsive genotype.

The workshop agenda would be based on the issues for resolution outlined above. It should be noted that any advice provided by members of the PBAC, the sponsor or the department in a workshop is in no way binding on the PBAC, the department, sponsor, evaluation groups or sub-committees of the PBAC. If this option is not acceptable to the sponsor, a standard re-entry pathway is available.

7.26 The PBAC advised that any resubmission should be based on most recent clinical data (i.e., latest follow up) and provide adequate details for validation (i.e., OvEC Part A and Part B).

7.27 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.