SMC2843

odevixibat hard capsules (Bylvay®)

Ipsen Ltd

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The Scottish Medicines Consortium (SMC) has completed its reassessment of the evidence for the above product using the ultra-orphan framework:

Advice: following a reassessment through the ultra-orphan framework

odevixibat (Bylvay®) is accepted for use within NHSScotland.

Indication under review: for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.

In a phase III study, odevixibat significantly improved serum bile acid response and reduced pruritus symptoms at 24 weeks compared with placebo in paediatric patients with PFIC.

Reductions in serum bile acid concentration and pruritus symptoms were maintained for at least 72 weeks in an open-label extension study.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical context

1.1. Background

Odevixibat is a reversible, potent, selective inhibitor of the ileal bile acid transporter (IBAT), which acts locally in the gut and is minimally absorbed. IBAT inhibition reduces the reuptake of bile acids into the liver, increasing the clearance of bile acids through the colon and lowering hepatic bile acid load and serum bile acids.[1, 2] The mechanism of action requires that the enterohepatic circulation of bile acids and bile salt transport into biliary canaliculi is preserved.

The recommended dose of odevixibat is 40 micrograms/kg administered orally once daily in the morning. Improvement in pruritus and reduction of serum bile acid levels may occur gradually in some patients after initiating odevixibat therapy. If an adequate clinical response has not been achieved after 3 months of continuous therapy, the dose may be increased to 120 micrograms/kg/day (up to a maximum of 7,200 micrograms once daily). Alternative treatment should be considered in patients for whom no treatment benefit can be established following 6 months of continuous daily treatment with odevixibat.

1.2. Nature of condition

Progressive familial intrahepatic cholestasis (PFIC) is a rare life-threatening heterogeneous group of genetic diseases that are characterised by intrahepatic cholestasis with impaired bile acid secretion and transport. There are three main subtypes: PFIC1, PFIC2 and PFIC3, each based on a different mutation, although other rarer subtypes have been identified. The condition is chronically debilitating, and patients typically present in infancy and early childhood; the median age of onset is approximately 3 months. PFIC2 is considered the most severe form of the disease with rapid progression to end-stage liver disease in early childhood (neonatal onset).[1]

Each PFIC subtype leads to the accumulation of bile acid at hepatotoxic concentrations. When excreted into systemic circulation this can cause jaundice and in particular, severe pruritus which is common in children with PFIC. This has a substantial impact on quality of life, can lead to cutaneous mutilation, sleep deprivation, irritability, poor attention and impaired school performance. Other extrahepatic features of the disease include fat malabsorption, which affects growth and weight, and can lead to fat-soluble vitamin deficiency. The prognosis in patients with PFIC is poor and hepatic damage ultimately leads to portal hypertension, liver failure, cirrhosis and hepatocellular carcinoma. Survival in patients with PFIC not undergoing surgical biliary diversion or liver transplant is 50% at 10 years of age and <10% at 20 years of age.[1, 3]

Prior to the initial ultra-orphan assessment of odevixibat (SMC2411), there were no pharmacological therapies licensed for PFIC available in Scotland. Non-specific treatments aim to manage disease symptoms such as pruritus, provide nutritional support and prevent vitamin deficiencies. Off-label ursodeoxycholic acid, colestyramine, rifampicin, ondansetron, naltrexone and antihistamines can be used to treat pruritus. However, the efficacy of these

treatments is limited and often transient. As the disease progresses, surgical intervention with biliary diversion surgery (most commonly with partial external biliary diversion [PEBD]) may be required to manage symptoms such as treatment-resistant pruritus and prolong native liver survival. However, many patients eventually require a liver transplant because of refractory pruritus or end-stage liver disease.[1]

Clinical experts consulted by SMC considered that odevixibat fills an unmet need in this therapeutic area for the treatment of PFIC due to limited effective non-surgical treatment options.

The relevant comparator for this reassessment is standard of care which can include PEBD surgery and oral pruritus therapies.

1.3. Category for decision-making process

Eligibility for a PACE meeting:

Odevixibat meets SMC ultra-orphan criteria.

2. Impact of new technology

Comparative efficacy

Evidence to support the efficacy and safety of odevixibat comes from the PEDFIC1 study as detailed in Table 2.1.

Table 2.1 Overview of relevant study[1, 4]

Criteria	PEDFIC1
Study design	Multicentre, randomised, double-blind, phase III study.
Eligible patients	• Patients aged ≥6 months to ≤18 years with body weight >5 kg. • Genetically confirmed clinical diagnosis of PFIC1 or PFIC2. • Elevated serum bile acid concentration (≥100 micromol/L). • A history of significant pruritus as determined by the investigator and an average caregiver-reported observed scratching score of ≥2 (0 to 4 scale) in an electronic diary in the 2 weeks prior to randomisation. • Patients with biliary diversion surgery within 6 months of the screening period and patients with a previous or planned liver transplant within 6 months of randomisation were excluded.
Treatments	Oral odevixibat 40 micrograms/kg/day or 120 micrograms/kg/day, or placebo once daily for 24 weeks. Concomitant treatment with ursodeoxycholic acid, rifampicin and/or antihistamines were permitted provided the patient was on a stable dose ≥4 weeks before enrolment and during the study period. Any topical treatments were allowed.
Randomisation	Randomisation was equal and stratified according to PFIC subtype (PFIC1 or PFIC2) and age (6 months to 5 years, 6 to 12 years and 13 to ≤18 years).
Primary outcome	The proportion of patients with a serum bile acid response, defined as ≥70% reduction in fasting serum bile acids concentration from baseline or ≤70 micromol / L at week 24.

Selected secondary outcomes	• The proportion of positive pruritus assessments at patient level defined as a scratching score of ≤1 or ≥1-point reduction from baseline on the Albireo ObsRO instrument over 24 weeks. • The proportion of patients achieving positive pruritus assessment for more than 50% of the time during the 24-week treatment period on the Albireo ObsRO instrument. • Changes from baseline to week 24 in growth parameters and ALT.
Statistical analysis	A hierarchical statistical testing strategy was applied to the primary outcome which tested the odevixibat groups versus placebo in the following order: the pooled odevixibat group, the low dose odevixibat group and the high dose odevixibat group. There was no formal testing of outcomes after the first non-significant outcome in the hierarchy. Analyses of secondary outcomes were not controlled for multiplicity and therefore the results reported for these outcomes are descriptive only and not inferential (no p-values reported). The primary efficacy analysis was conducted in the full analysis set which included all randomised patients that received at least one dose of study treatment.

Abbreviations**:** ALT = alanine aminotransferase; ObsRO = observed reported outcome; PFIC = progressive familial intrahepatic cholestasis; PFIC1 = progressive familial intrahepatic cholestasis subtype 1; PFIC2 = progressive familial intrahepatic cholestasis subtype 2

The results from the PEDFIC1 study showed that a statistically significant higher proportion of patients in the odevixibat groups (both doses and the pooled group) had a serum bile acid response after 24 weeks of treatment, compared with placebo. The primary and selected secondary outcome results have been detailed in Table 2.2.[1, 4]

Table 2.2. Primary and selected secondary outcomes from PEDFIC1 in the full analysis set[1, 4]

	Odevixibat			Placebo n=20
	40 micrograms /kg/day n=23	120 micrograms /kg/day n=19	Pooled group n=42	
Primary outcome: Proportion of patients with a serum bile acid response at week 24				
Responders, %	44%	21%	33%	0
Proportion difference odevixibat versus placebo, 95% CI, p-value[a]	0.44 (0.24 to 0.65) p=0.0015[b]	0.22 (-0.01 to 0.44) p=0.0174[b]	0.31 (0.13 to 0.49), p=0.0015[e]	
Secondary outcomes				
Proportion of positive pruritus assessments at the patient level over the 24-week treatment period – Albireo ObsRO Instrument[d]				
Mean	58%	48%	54%	29%
LS mean difference odevixibat versus placebo, 95% CI[c]	28% (9.8 to 47)	22% (1.9 to 42)	25% (8.5 to 41)	
Proportion of patients with a positive pruritus assessment for >50% of the time during the 24-week treatment period – Albireo ObsRO Instrument[d]				
Responders, %	74%	47%	62%	20%
Proportion difference odevixibat versus placebo, 95% CI[a]	0.47 (0.23 to 0.70)	0.29 (0.03 to 0.54)	0.32 (0.11 to 0.53)	

Change from baseline to week 24 in growth parameters				
Height (z-score) LS mean difference versus placebo, 95% CI	-	-	0.24 (-0.05 to 0.53)	
Weight (z-score) LS mean difference versus placebo, 95% CI	-	-	0.18 (-0.08 to 0.44)	
Change from baseline to week 24 in ALT (units/L)				
LS mean difference versus placebo, 95% CI	-	-	-14.8 (-45.1 to 15.4)	

Abbreviations: ALT = alanine aminotransferase; CI = confidence interval; LS = least squares; ObsRO = observer reported outcome. [a]Miettinen-Nurminen (score) CI is reported adjusting for stratification factors. [b]1-sided adjusted p-value. [c] Non-parametric ANCOVA. [d]Positive pruritus assessment was defined as a scratching score of ≤1 or ≥1-point drop from baseline on an observer reported instrument.[e]1-sided unadjusted p-value.

Health-related quality of life was measured using the Paediatric Quality of Life Inventory (PedsQL) and Global Impression Score (GIS). The favourable results were consistent with the primary and secondary outcomes and indicated improvements in quality of life.[1]

PEDFIC2 was an ongoing open-label extension study (n=69) with limited data at the initial ultra-orphan assessment (data cut: 15 July 2020). Final results have now been presented as additional evidence for this reassessment.[1, 5]

The retrospective study, NAtural course and Prognosis of PFIC and Effect of Biliary Diversion consortium (NAPPED) aimed to characterise the natural disease pathway of PFIC1 (n=130) and PFIC2 (n=264) and assess the impact of surgical bile diversion on native liver survival. After approximately 4 years of follow-up, 48% and 23% of patients with PFIC1 and PFIC2 had biliary diversion surgery, and 29% and 45% with PFIC1 and PFIC2 had a liver transplant. A postsurgical biliary diversion serum bile acids concentration of <65 micromol/L for PFIC1 and <102 micromol/L for PFIC2 was associated with longer native liver survival. Survival analysis showed that at 18 years of age, 44% and 32% of patients with PFIC1 and 2 respectively were alive with a native liver. [6, 7]

Additional evidence on reassessment

Following an initial assessment in July 2022 (SMC2411), odevixibat has been available for patients with PFIC within the ultra-orphan pathway. During this time, the submitting company has had the opportunity to collect additional data to support its submission for reassessment. This included further evidence from the PEDFIC2 extension study, two real-world studies and an indirect comparison of odevixibat versus a matched external control.

The submitting company presented final results from the PEDFIC2 study (data cut: February 2024) after all patients had discontinued or completed the 72-week or 96-week (for patients who received odevixibat in PEDFIC1) treatment period. There was an optional extension period where patients could continue odevixibat until it was locally available. Since the initial submission, a protocol amendment was introduced which changed the starting dose from 120

micrograms/kg/day to 40 micrograms/kg/day. The study enrolled 116 patients (n=37 from the odevixibat group in PEDFIC1, n=19 from the placebo group in PEDFIC1 and n=60 treatment-naive patients who initiated odevixibat in PEDFIC2 [including 15 patients with PFIC3, PFIC4, PFIC6 or episodic PFIC]). The results showed rapid reductions in serum bile acids and improved pruritus symptoms that were sustained over the different treatment periods. In each group respectively, the mean change in serum bile acid concentration from baseline to 96 or 72 weeks was -104.00, -57.97 and -139.84 micromol/L and proportion of positive pruritus assessments after 72 weeks was 55%, 77% and 39% in patients with available measurements. Height and weight growth catch-up was also observed over the treatment periods and there were improvements in quality of life outcomes. A liver transplant was required by 13% (15/116) of patients, 2.6% (3/116) required biliary diversion surgery and one patient required both. The estimated rate of surgery-free survival was ≥76% and native liver survival was ≥77% at 4 years from the first dose of odevixibat.[8, 9]

Further evidence was also provided from two small real-world case studies (n=24 and n=9) which reported meaningful reductions in serum bile acids and improved pruritus scores for most patients after 6 and 11 months of treatment with odevixibat.[10, 11]

As part of the ultra-orphan reassessment, the submitting company also presented indirect evidence from the Odevixibat versus External Control (OvEC) study, which compared clinical outcomes from patients treated with odevixibat (PEDFIC1 and PEDFIC2) with control patients from a retrospective natural history study (NAPPED).[12] Further details are presented in Table 2.3.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Adjusted indirect comparison
Population	Paediatric patients (aged ≥6 months to ≤18 years) with PFIC1 or PFIC2.
Comparators	Odevixibat or matched external control Part A: odevixibat without prior surgical biliary diversion (SBD) versus external controls without prior SBD Part B: odevixibat without prior SBD versus external controls receiving SBD
Studies included	PEDFIC1, PEDFIC2 and NAPPED, as reported in the OvEC study[12]
Outcomes	• Event-free survival, defined as time to first occurrence of SBD (part A only), liver transplant or death. • SBD-free survival, defined as time to first occurrence of SBD or death. • Native liver survival, defined as the time to first occurrence of liver transplant or death. • Overall survival, defined as time to death. • Serum bile acid response, defined as either ≥70% reduction in serum bile acids or ≤102 micromol / L .
Results	The results from part A suggest that, after a median duration of 22.6 months' follow-up, treatment with odevixibat was superior to the external control for event-free survival and SBD-free survival. There appeared to be a numerical improvement in native liver survival for odevixibat compared with the external control cohort. The number of deaths was low.

Table 2.3.1. Selected outcomes from part A of the OvEC study.

	Odevixibat (n=69)	Control (n=80)
Event-free survival		
Events, n (%)	6 (9%)	80 (55%)
Weighted HR (95% CI)	0.20 (0.09 to 0.45)	
Surgical biliary diversion-free survival		
Events, n (%)	2 (3%)	31 (39%)
Weighted HR (95% CI)	0.13 (0.04 to 0.39)	
Native liver survival		
Events, n (%)	4 (6%)	21 (26%)
Weighted HR (95% CI)	0.33 (0.11 to 1.03)	
Overall survival		
Events, n (%)	0	4 (5%)
Weighted HR (95% CI)	0 (0 to NE)	

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

The proportion of patients that achieved a serum bile acid response was also numerically higher in the odevixibat group compared with the control group.

Table 2.3.2. sBA response rates at 48 weeks in patients from part A and part B.

	Part A		Part B	
	Odevixibat (weighted)	**Control (weighted)**	**Odevixibat (weighted)**	**Control (weighted)**
n	68	49	CIC	CIC
≥70% reduction in sBA or sBA ≤102 micromol/L	50%	40%	CIC	CIC

Abbreviations: sBA = serum bile acid; CIC = commercial in confidence

Company conclusion	The company concluded that the comparison of odevixibat-treated patients from the PEDFIC studies and aligned control patients from the NAPPED database suggested odevixibat treatment is associated with long-term clinical benefits in patients with PFIC, including improved event-free survival and surgical biliary diversion-free survival.

*Other data were also assessed but remain confidential.**

Comparative safety

In the PEDFIC1 study, the median duration of treatment in both odevixibat groups was 23.9 weeks and in the placebo group was 23.7 weeks. Any treatment-emergent adverse events (AE) were reported by 83% (35/42) of patients in the odevixibat groups and 85% (17/20) in the placebo group and these were considered treatment-related in 33% and 15% respectively. In the odevixibat and placebo groups respectively, patients with a reported serious AE were 7.1% versus 25%, the proportion of AEs that led to treatment interruptions were 21% versus 5.0% and patients discontinuing therapy due to an AE was 2.4% versus 0. The most frequently reported treatment-related AEs of any grade with an incidence >5% in the odevixibat group versus the placebo group were increased blood bilirubin (9.5% versus 5.0%), increased alanine

aminotransferase (9.5% versus 5.0%), increased aspartate aminotransferase (7.1% versus 5.0%) and diarrhoea (9.5% versus 0).[1]

On reassessment, the submitting company presented updated safety data from the PEDFIC2 study. At this final analysis (data cut: February 2024), 72% (83/116) of patients had completed 72 weeks and 53% (61/116) had completed 96 weeks of treatment with odevixibat; the median duration of treatment was approximately 2 years. Treatment-related AEs were reported by 39% and these were considered serious in 1.7%. The most commonly reported treatment-related AEs with an incidence of >5% included diarrhoea (12%), increased blood bilirubin (10%) and increased alanine aminotransferase (6.0%). The Summary of Product Characteristics (SPC) recommends assessment of liver function tests, fat-soluble vitamins and international normalised ratio (INR) before treatment with monitoring per standard clinical practice.[2, 8, 9]

Overall, the regulator concluded that odevixibat was well tolerated for at least 96 weeks of treatment and that most AEs were mild to moderate in severity.[8]

Clinical effectiveness issues

The key strengths and uncertainties of the clinical case are summarised below.

Key strengths:

- In PEDFIC1 after 24 weeks, 33% of patients treated with odevixibat achieved at least a 70% reduction in serum bile acids concentration from baseline or reached a level of ≤70 micromol/L compared with no patients in the placebo group. The reduction in serum bile acids was considered clinically relevant and similar to those observed with biliary diversion surgery by the regulator. The effect on secondary outcomes was favourable with a clinically relevant reduction in pruritus and an improvement in growth over time.[1, 4]
- On reassessment, final results from the PEDFIC2 open-label extension study suggest that the reduction in serum bile acids and improvement in symptoms of pruritus are maintained with at least 72 or 96 weeks of treatment. Growth catch-up was also observed and there were improvements in quality of life outcomes.[8, 9]
- At the initial ultra-orphan assessment, clinical experts consulted by SMC considered that odevixibat is a therapeutic advancement for the treatment of PFIC due to the promising results from the PEDFIC studies in reducing serum bile acids and improving itch and that its place in therapy is likely to be first-line or early in the treatment pathway. They noted that there is a lack of effective medical therapies and that odevixibat has a novel mechanism of action and is the first treatment licensed for PFIC. The once daily oral administration may be convenient for patients and caregivers. Most experts contacted by SMC at reassessment had no clinical experience of patients prescribed odevixibat since it was made available through the ultra-orphan pathway. Those who did considered it to be a therapeutic advancement in controlling pruritus with the potential to delay surgical intervention.

Key uncertainties:

- On reassessment, the submitting company provided longer-term data for the efficacy and safety of odevixibat from the PEDFIC2 study.[8, 9] However, these data are non-comparative and could introduce potential bias for subjective outcomes because of the single-arm, open-label design.
- In the absence of direct evidence that odevixibat delays biliary diversion surgery or liver transplant, indirect data from an external cohort comparison (OvEC) was presented for this reassessment. The comparison was associated with some limitations including the small sample size, short follow-up and low number of events for some outcomes. There were methodological differences in study design which may bias results due to variation in patient care and treatment between the clinical study and real-world settings. There were also differences in prior treatment that were not adjusted for. Despite these limitations, the company's conclusion that odevixibat improved event-free and biliary diversion-free outcomes seems reasonable, but the point estimates are uncertain. The native liver survival, overall survival and serum bile acid results remain uncertain.
- Efficacy and safety data for the use of odevixibat in PFIC subtypes other than 1 and 2 is limited which may be expected as these are less prevalent within the context of rare disease setting. Patients with the BSEP3 subtype of PFIC2 will not respond to odevixibat due to a complete absence or lack of function of the bile salt export pump.[2, 8, 10, 13]
- There is limited evidence in adults as PEDFIC1 excluded patients aged >18 years. Results from a subgroup of adult patients (n=7) in PEDFIC2 and case reports indicated a reduction in serum bile acids and pruritus scores, however these should be interpreted with caution because of the small sample size.[14-16]
- Patients with severe hepatic impairment were excluded from the PEDFIC studies. This may affect the generalisability of results to patients with more progressive disease and additional monitoring for adverse reactions is advised.[2]
- The exact place of odevixibat in the treatment pathway is uncertain. Clinical experts consulted by SMC indicated that for most patients, it would be used ahead of surgical intervention as a treatment option for refractory itch.

3. Impact beyond direct health benefits and on specialist services

Improvement in serum bile acids levels and pruritus could have a significant impact on the quality of lives of patients and caregivers. Patients may be able to lead a more normal life before surgical intervention is required, there may be improvements in sleep, mood and school attendance. Better symptom control may reduce the caregiver burden and may improve family functioning.

Clinical experts indicated that the impact on specialist services is likely to be minimal.

4. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **odevixibat**, as an **ultra-orphan** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Progressive Familial Intrahepatic Cholestasis (PFIC) is a very severe, rare, life-threatening condition. The most debilitating symptom, cholestatic pruritus, is relentless, uncontrollable and is not relieved by scratching. This leads to profound sleep deprivation, pain, severe skin damage and psychological distress. Prognosis in patients with PFIC is poor, and hepatic damage ultimately leads to portal hypertension, liver failure, cirrhosis and hepatocellular carcinoma.
- Existing off-label oral treatments are often ineffective and historically, liver transplantation has been the only option to control refractory symptoms, despite its major risks. Therefore, a substantial unmet need remains for an effective oral treatment option for patients with PFIC.
- Odevixibat directly reduces circulating bile acids, thereby reducing, and in some cases eliminating, debilitating itch. Odevixibat has been available in NHSScotland via the ultra-orphan pathway, and PACE participants described that it has transformed daily life for patients and families currently receiving treatment by improving sleep, reducing pain and skin damage. It improves daytime functioning, and the ability for children to attend school or nursery, participate in normal childhood activities, and reach important developmental milestones. Odevixibat offers an effective non-surgical option for the management of pruritus, potentially delaying the need for liver transplantation which has substantial risks and resource costs.
- Odevixibat delivers considerable benefits for families and carers. Improvements in sleep and reduction in constant care needs allow parents and carers to regain a normal daily routine, return to work where possible, and better support siblings, resulting in meaningful improvements in overall family quality of life.
- Odevixibat is generally well tolerated, with a low side-effect profile. Odevixibat can be delivered within existing paediatric liver services without additional burden on patients, carers, or healthcare resources.
- PACE participants considered that odevixibat would be used as a treatment for PFIC after failure of standard off-label antipruritic therapies. Use should be initiated and monitored under the supervision of tertiary liver units.

Additional Patient and Carer Involvement

We received a patient group submission from the British Liver Trust, which is a registered charity. British Liver Trust has received 12% pharmaceutical company funding in the past two

years, including from the submitting company. A representative from British Liver Trust participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

5. Value for money

An economic case was presented and is summarised in Table 5.1

Table 5.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	A lifetime time horizon of 96 years was used
Population	The economic analysis considered the use of odevixibat in patients aged 6 months or older with PFIC.
Comparators	The comparator in the model was standard of care (SoC), which included a combination of oral drugs (UDCA, cholestyramine, rifampicin and naltrexone) and surgery in the form of partial external biliary diversion (PEBD). It should be noted that only a small proportion of patients (8% of children aged up to 3 years and 5% of patients aged 3 and above) in the SoC arm receive PEBD.
Model description	A Markov model was developed with the following health states: no PEBD (response or no response), PEBD (response or no response), liver transplant (LTx), post LTx and deathPatients in the odevixibat arm enter the model in the 'No PEBD, response' health state, and patients in the SoC arm enter in the 'No PEBD, no response' state. Patients in the odevixibat arm do not receive PEBD in the base case and therefore do not enter the PEBD health states. As the condition is progressive, patients could remain in the same health state or progress to subsequent states in the model.
Clinical data	The response rate for odevixibat was sourced from OvEC Part A (where data were collected at 48 weeks) and used to approximate 24-week response in the model.[12] The annual loss of response for odevixibat was sourced from PEDFIC1.[1, 4] The response rate for SoC therapies was assumed to be 0%, based on company clinical opinion. The response rate for PEBD was sourced from OvEC Part B SoC arm data, which was collected at 48 weeks.[12] The probabilities of 'LTx after no response to PEBD' and 'LTx without prior PEBD' were sourced from NAPPED data.[6, 7] Treatment-related adverse events were taken from PEDFIC1.[1, 4]
Extrapolation	Health state transitions relied on transition probabilities derived from PEDFIC1, NAPPED and OvEC data.[1, 4] Long-term event-free survival was sourced from OvEC Part A, which compared odevixibat results from PEDFIC1 and SoC results from NAPPED data.[12] A Kaplan-Meier curve was generated, against which, the company generated a selection of parametric curves, choosing the exponential curve in the base case. From these extrapolations, total annual event probability was generated, which was then used to calculate the probability of PEBD, probability of LTx and probability of pre-LTx mortality according to their relative frequencies. The probability of death in the first year of LTx and post-LTx mortality were meta-analysed from different sources from the literature.[17-21]
Quality of life	Health state utilities in the model were derived from the literature, as the company viewed EQ-5D data mapped from PEDFIC1 to be inappropriate due to small patient numbers and low statistical power.[1, 4] There were no available sources for PFIC, so these were taken from adult populations for similar health conditions or disease areas. These included the following values: • No PEBD, response: 0.910

	• No PEBD, no response: 0.830 • PEBD, response: 0.659 • PEBD, no response: 0.599 • LTx: 0.710 • Post LTx: 0.850
Costs and resource use	Costs included in the model were medicine acquisition for odevixibat and SoC, resource use and complications costs related to PEBD and LTx and post-LTx monitoring costs.
PAS/contract price	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount of was offered on the list price.

5.1. Results

SMC would wish to present the with-PAS cost-effectiveness results that were used for decision-making. However, SMC is unable to publish these results due to commercial in confidence concerns regarding the PAS.

5.2. Sensitivity analyses

A range of sensitivity and scenario analyses were considered, and descriptions of these key scenarios are provided in Table 5.2.

Table 5.2.

	Parameter	Base case	Scenario
1	PEBD in odevixibat arm	Exclude	Include
2a	Loss of response to odevixibat	3.53%	5%
2b		3.53%	10%
3a	Odevixibat dose	40 micrograms/kg titrating up	40 micrograms/kg
3b		40 micrograms/kg titrating up	120 micrograms/kg
4	Response to SoC	0%	10%
5	Response to odevixibat	sBA and pruritus response	Pruritus response
6	LTx mortality source	Meta-analysis	NHS report
7a	Time horizon (years)	96	20
7b		96	30
7c		96	50
8a	Utility source	Literature	PEDFIC1
8b		Literature	ScHARR PEDFIC1
9	Extrapolation EFS curves (OvEC data)	Exponential	Weibull
10	Odevixibat response rate source	OvEC	PEDFIC1
11	OvEC data	Include	Exclude

12	Perspective	NHS	Societal
13	Carer disutilities	Exclude	Include
C1a	Key economic uncertainties combined (conservative)	Base case	Scenarios 1, 4, 6, 8a and NHS perspective
C1b			Scenarios 1, 4, 6, 8a and societal perspective
C2a	Key economic uncertainties combined (based on company comments)	Base case	Scenarios 1, 4, 6, 8b, 3.53% loss of response to SoC and NHS perspective
C2b			Scenarios 1, 4, 6, 8b, 3.53% loss of response to SoC and societal perspective
C3a	Company suggested combined scenarios	Base case	Scenarios 6, 8b and NHS perspective
C3b			Scenarios 6, 8b and societal perspective

Abbreviations: EFS: event-free survival; kg: kilogram; LTx: liver transplant; NHS: National Health Service; PEBD: partial external biliary diversion; ScHARR: Sheffield Centre for Health and Related Research; sBA: serum bile acid; SoC: standard of care

5.3. Key strengths:

- A range of analyses were presented to test the sensitivity of the model outputs including probabilistic sensitivity analysis, one-way deterministic sensitivity analysis and scenario analyses.
- The choice of model was suitable.
- The inclusion of OvEC data in the reassessment allowed for long-term extrapolation of results where odevixibat was compared to more relevant comparators than placebo.[12]

5.4. Key uncertainties:

- It is uncertain if the choice of comparator in the model is appropriate. It may be inappropriate to have PEBD and odevixibat as mutually exclusive pathways in the model. A scenario analysis considered including PEBD in the odevixibat arm (Scenario 1) which resulted in a large increase in the incremental cost-effectiveness ratio (ICER).
- There remains no direct evidence that treatment with odevixibat delays biliary diversion surgery or liver transplant. Although the OvEC data has enabled comparisons with treatments other than placebo, several uncertainties were noted in this study.[12] Therefore, scenario analyses were conducted using the response rate from PEDFIC1 (Scenario 10), as well as by fully excluding the OvEC data (Scenario 11). The company have noted, however, that Scenario 11 is based on NAPPED PFIC natural history data

used in the 2021 SMC submission and has not been adjusted to match the PEDFIC trial population, which may make this result less robust than the base case which uses OvEC.

- There was uncertainty regarding the assumed response to off-label SoC medicines in the model. In the base case, a 0% response rate was applied, informed by clinical expert opinion and the placebo arm of PEDFIC1.[1, 4] However, SoC response was observed in OvEC Part A.[12] The company considered the SoC arm data from OvEC to have limited generalisability. To explore this uncertainty, a 10% SOC response rate was tested in sensitivity analysis (Scenario 4), although this may be considered conservative.
- Some utility values seemed unrealistically high given the severity of the disease profile for PFIC. The company used utility values derived from patient populations with different conditions and from adult populations and did not indicate that they had conducted a literature review to source alternative values for the reassessment. Alternative utility values were available from PEDFIC1 (Scenario 8a).[1, 4] The company viewed these as not robust as the sample size was small and based on only one sBA response record at baseline. To further explore this uncertainty, the company provided a supplementary scenario analysis using PEDFIC1 utilities based on change from baseline (Scenario 8b); this method was developed by Sheffield Centre for Health and Related Research (ScHARR).[22]
- The clinical studies underpinning the clinical data used in the model were not entirely based in the UK, for example, rates of surgery applied in the model may depend on treatment pathways in varying countries. Additionally, a meta-analysis was conducted to estimate liver transplant mortality probability, using non-UK studies. Scenario 6 was conducted using NHS source for liver transplant mortality (however, this is not specific to PFIC patients), and this was found to have an upwards impact on results.

6. Conclusions

The Committee considered the benefits of odevixibat in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as odevixibat is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted odevixibat for use in NHSScotland.

7. Costs to NHS and Personal Social Services

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

8. Guidelines and protocols

The European Association for the Study of the Liver (EASL) published EASL Clinical Practice Guidelines on genetic cholestatic liver diseases in 2024.[23]

9. Additional information

9.1. Product availability date

19 April 2022

Table 9.1 List price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Odevixibat	**40 micrograms/kg/day orally**	**112,294**

Costs from BNF online on 26 January 2026. Costs calculated assuming a mean weight of 14 kg based on a 3 year old child (median age in PEDFIC1). Costs do not take any patient access schemes into consideration.

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This assessment is based on data submitted by the applicant company up to and including 13 March 2026.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC includes Scottish national contract prices in its decision-making. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient Access Schemes (PAS): A PAS is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG

operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees prior to publication of SMC advice.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.