An addendum to this Public Summary Document has been included at the end of the document.

7.06 ODEVIXIBAT,
Capsule 200 micrograms,
Capsule 400 micrograms,
Capsule 600 micrograms,
Capsule 1200 micrograms,
Bylvay®,
Ipsen Pty Ltd.

1 Purpose of submission

1.1 The Facilitated Resolution Pathway resubmission requested a Section 85, Authority Required listing for odevixibat 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).

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 (PFIC)
Intervention	Odevixibat 40 mcg/kg orally administered once daily with dose escalation to 120 mcg/kg/day if adequate clinical response [a] is not achieved in first month
Comparator	Standard of care (SoC) partial external biliary diversion (PEBD) and liver transplant (LT).
Outcomes	Serum bile acid (sBA) response, pruritus 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 1-2, p11 of the resubmission

[a] Defined as an average ≥1 grade improvement in pruritus score on the Prucision™ ObsRO Pruritus Scale, assessed over a one-week period prior to dose modification.

1.3 The timing for dose escalation was reduced from three months without adequate clinical response in the July 2024 submission, to after one month in the resubmission, which was consistent with the Facilitated Resolution Pathway Workshop discussion.

2 Background

Registration status

2.1 The TGA Delegate's Overview was available at the time of PBAC consideration. It was noted that a stop clock was implemented by the TGA following the evaluation process to enable a manufacturing site to undergo a good manufacturing practice (GMP) inspection. The proposed TGA indication for odevixibat was for treatment of PFIC in

patients aged six months or older, with registration expected by the end of March 2025.

Previous PBAC consideration

2.2 At the July 2024 PBAC meeting, the PBAC did not recommend odevixibat for the treatment of PFIC (paragraph 7.1, odevixibat Public Summary Document (PSD), July 2024 PBAC meeting). A Facilitated Resolution Pathway Workshop was held for odevixibat in September 2024 to explore feasible options to address the issues identified by the PBAC.

2.3 Table 2 summarises the key matters of concern from the July 2024 submission and how they were addressed in the resubmission.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Restriction	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 (paragraph 7.4, July 2024 PSD).	Partially addressed in resubmission; addressed in Pre-Sub-Committee Response (PSCR). The proposed restriction types included Authority Required (in writing only via post or HPOS upload) for initiation and continuing and Authority Required (telephone/electronic) for dose modification. The use of telephone/electric approvals was inconsistent with the Facilitated Resolution Pathway Workshop discussion. The PSCR confirmed that initial, dose modification and continuing restrictions should be Authority Required (in writing only via post of HPOS upload).
	The restriction should require prescription by a specialist experienced in the management of PFIC. (paragraph 7.4, July 2024 PSD).	Partially addressed. Amended for initial restriction, however proposed that continuing prescribing be expanded to a specialist 'acting under the supervision' of a specialist experienced in the management of PFIC, which was aligned with the Facilitated Resolution Pathway Workshop discussion.
	The initial restriction did not include genetic testing for diagnosis despite some patients with PFIC (e.g. PFIC2 *BSEP3* genotype and PFIC5) being unlikely to respond to odevixibat (paragraph 7.4, July 2024 PSD).	Partially addressed. The resubmission does not include genetic testing and instead proposed to rebate the cost of treating these patients under a RSA, in the form of annual expenditure caps.
	The initial restriction did not specify diagnostic criteria, lacking both the severity of symptomatic pruritus and a minimum level of serum bile acid (sBA) (paragraph 7.4, July 2024 PSD).	Addressed. The revised restriction restricted access to PFIC patients who had both a finding of elevated serum bile acids only (although not quantified using the ≥100 µmol/L criteria required in the registrational studies) and a pruritus score of ≥2 (using the Pruritus Item of the ObsRO instrument). This was consistent with the Facilitated Resolution Pathway Workshop discussion.
	No criteria for dose escalation were provided. (paragraph 7.4, July 2024 PSD).	Addressed. The resubmission included a new treatment criterion for dose escalation. However, the ESC considered that the criterion required further clarification to state that (i) dose escalation was allowed to occur between 1-3 months after initiation; and (ii) the continuation criteria needed to be met at 6 months post-initiation.

Component	Matter of concern	How the resubmission addresses it
	The continuing restriction did not include a response criteria or discontinuation rule if patients, for example, progress to SBD. (paragraph 7.4, July 2024 PSD).	Partially addressed. The continuation restriction was amended to require a once-off response criterion. However, loss of response was not considered.
	The PBAC considered it appropriate for the restriction to require initiation at age < 18 years. (paragraph 7.4, July 2024 PSD).	Not addressed. The resubmission maintained that the listing should not be age restricted. The Facilitated Resolution Workshop indicated that this may be feasible provided that the additional patients were managed in the RSA.
	The initial restriction did not exclude patients who had previously received surgical biliary diversion (SBD) or liver transplant (LT). (paragraph 7.4, July 2024 PSD).	Not addressed. The resubmission's financial estimates excluded patients with prior PEBD or LT, which was inconsistent with the proposed restriction, and inconsistent with the Facilitated Resolution Pathway Workshop discussion.
	The restriction criteria did not allow for patients to stop and restart treatment (paragraph 7.4, July 2024 PSD).	Addressed. The resubmission proposed enabling re-starting odevixibat treatment based on clinicians' discretion and consistent with the treatment initiation criteria.
Comparator	The submission appeared to position odevixibat largely as an alternative to SBD in the proposed clinical management algorithm and economic model. (paragraph 7.5, July 2024 PSD).	Partially addressed. The resubmission continued to present odevixibat largely as an alternative to SBD in the clinical algorithm. The economic model was revised to allow odevixibat patients to receive SBD, however the financial model excluded patients with prior SBD.
	The PBAC noted that placebo, which made up the control arm of PEDFIC 1 does not represent the nominated comparator of SOC [a] (paragraph 7.7, July 2024 PSD).	Not addressed. The resubmission did not present any further comparison of odevixibat versus SOC beyond OvEC part B in the July 2024 submission.
Clinical evidence	The ObsRO instrument was uncertain given 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 (paragraph 7.8, July 2024 PSD).	Not addressed. No further details of the development and validation of the ObsRO instrument were provided in the resubmission.
	The submission provided no comparative evidence for patients with PFIC3 or PFIC6 and no evidence for patients with PFIC4 and PFIC5 subtypes (paragraph 7.6, July 2024 PSD).	Not addressed. No comparative evidence was provided in the resubmission for these subtypes. In addition, an additional subgroup described as 'episodic PFIC' was introduced in the resubmission. There was no clinical evidence provided for this incremental population.
	The PBAC noted there were substantial transitivity issues with OvEC Part A and limited details were provided for OvEC Part B (paragraph 7.11, July 2024 PSD).	Not addressed. No additional details were provided in the resubmission.
	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 (paragraph 7.20, July 2024 PSD).	Partially addressed No further evidence for dose escalation was presented in the resubmission. The resubmission proposed that annual expenditure caps would address the uncertainty of dose escalation. This was inconsistent with the Facilitated Resolution Pathway Workshop discussion, which noted that a fixed treatment cost, via flat pricing between the 40 mcg/kg and 120 mcg/kg doses, together with discontinuation rules would be appropriate.

Component	Matter of concern	How the resubmission addresses it
Economic evaluation	Transition probabilities were primarily informed by data from OvEC which favoured odevixibat and could not be independently verified (paragraph 7.17, July 2024 PSD).	Partially addressed. Data from OvEC was maintained in the base case. The resubmission presented a sensitivity analysis that excluded OvEC inputs.
	The PBAC considered that odevixibat would not be cost-effective without a substantial price reduction, and that the higher price for the 120 mcg/kg/day dose vs. 40 mcg/kg/day was not supported by the clinical evidence (paragraphs 7.21 & 7.25, July 2024 PSD).	Partially addressed. A [redacted]% price reduction was proposed in the resubmission, resulting in the effective price per mcg being revised from $[redacted]/mcg to $[redacted]/mcg. A further [redacted]% price reduction was offered in the PSCR, to align the adult ICER with that for the under 18 population, reducing the effective price per mcg for the overall population to $[redacted]. The resubmission proposed that the RSA annual expenditure caps, calculated using a '[redacted] cost' approach, reflected a substantial cost reduction. The ESC noted that if the [redacted] cost was not achieved via the RSA, then the ICER increased further.
	The time horizon (100-years) was considered too long (paragraph 7.15, July 2024 PSD).	Partially addressed. The time horizon was revised to 50 years. It was unclear if this was a reasonable time horizon given comparative evidence from PEDFIC 1 was only for 24 weeks.
	The PBAC considered the assumption that odevixibat treated patients would not undergo PEBD after losing response implausible. (paragraph 7.18, July 2024 PSD).	Addressed. Subsequent PEBD rates from the PEDFIC 2 trial (3/113 over 115 weeks) was incorporated into the model.
	The 'no PEBD, no response' health state had higher utility (0.83) than the 'PEBD, response' state (0.659). This implied that patients preferred pruritus symptoms above achieving a response after PEBD, which was not plausible. (paragraph 7.19, July 2024 PSD).	Partially addressed. The 'PEBD, response' health state utility was revised to 0.761, which remained lower than the 'no PEBD, no response' health state, which was inconsistent with the Facilitated Resolution Pathway Workshop discussion which noted that the direction of utility values lacked face validity.
Financial estimates	The PBAC considered that a RSA would be required, given the level of uncertainty in the estimates, including uncertainty in the duration of use and uptake. (paragraph 7.23, July 2024 PSD).	Partially addressed. The resubmission proposed a RSA in the form of annual expenditure caps, which were adjusted to incorporate a '[redacted] cost' and exclusion of genetic non-responders. The ESC noted that patients were assumed to remain on treatment for the entirety of the estimates. The ESC considered that this overestimated duration of treatment.
	DUSC commented that applying the estimated prevalence rate of 0.05 to 0.07 per 10,000 people to the entire population may not have been reasonable (Table 21, July 2024 PSD).	Not addressed. There was no change to the prevalence rate and therefore the number of prevalent patients may be overestimated.
	DUSC considered that the incidence rate [of 6 patients per year] may be overestimated. (Table 21, July 2024 PSD).	Addressed. The incident rate was reduced to 4 patients per year, which aligned with the Facilitated Resolution Pathway Workshop discussion.

Component	Matter of concern	How the resubmission addresses it
	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. (paragraph 7.23, July 2024 PSD). DUSC considered that the submission had overestimated the average age of prevalent patients at initiation of treatment (paragraph 6.80, July 2024 PSD).	Partially addressed. The mean age of prevalent patients was increased from 12 to 13.8 in the resubmission based on EAP data (n=12). This was consistent with Facilitated Resolution Pathway Workshop discussion, although remains highly uncertain.
	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 (Table 21, July 2024 PSD).	Partially addressed. The resubmission reduced the proportion with prior LT from 80% to 54.1%. The revised eligibility calculations were consistent with Facilitated Resolution Pathway Workshop discussion, though it was unclear if this was reasonable due to the prevalence rate not being amended.
	DUSC noted that patients who have already undergone PEBD were not excluded from the PEDFIC1 trial and considered it may not be reasonable to exclude these patients from the estimates (Table 21, July 2024 PSD).	Not addressed. All patients with prior PEBD remained excluded in the resubmission's financial estimates, which was inconsistent with Facilitated Resolution Pathway Workshop outcomes.
	DUSC noted that 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 (Table 21, July 2024 PSD).	Not addressed. The Facilitated Resolution Pathway Workshop discussion document stated that response rates would align with economic model assumptions. However, the resubmission's economic model used a response rate of 43.5% (PEDFIC1 40 mcg/kg 24-week response) versus 58% in the financial estimates.

Source: Tables 1-1, 3-1 and 4-1 of the resubmission
Note: Italicised text reflects comments added during evaluation
Abbreviations: EAP = early access program; LT = liver transplant; para = paragraph; PEBD = partial external biliary diversion surgery; RSA = risk share arrangement; SOC = standard of care
[a] The nominated comparator of SOC included off-label use of medicines such as ursodeoxycholic acid and rifampicin, as well as PEBD, as a proxy for all SBDs, and LT.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№. of Rpts	Available brands
ODEVIXIBAT					
Odevixibat 200 microgram capsules,	$[redacted] (published) $[redacted] (effective)	12	30	2,4 or 5	Bylvay
Odevixibat. 400 microgram capsules,	$[redacted] (published) $[redacted] (effective)	6	30	2,4 or 5	Bylvay
Odevixibat. 600 microgram capsules,	$[redacted] (published) $[redacted] (effective)	12	30	2,4 or 5	Bylvay
Odevixibat 1200 micrograms capsules	$[redacted] (published) $[redacted] (effective)	6	30	2,4 or 5	Bylvay
Category / Program:	Section 85- General schedule				
Prescriber type:	☒ Medical Practitioners				
Restriction type:	☒ Authority Required (in writing only via post/HPOS upload)				

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№. of Rpts	Available brands
Condition:	Progressive familial intrahepatic cholestasis (PFIC)				
PBS Indication:	Progressive familial intrahepatic cholestasis (PFIC)				
Administrative advice:	No increase in the maximum quantity or number of units may be authorised				
	No increase in the maximum number of repeats may be authorised				
	Special Pricing Arrangements Apply				
	For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.				
	The Prucision™ ObsRO pruritus scale is available as a downloadable document at: [INSERT LINK]				
Treatment phase:	**Initial treatment**				
Treatment criteria:					
	Must be treated by a specialist or under the supervision of a specialist experienced in the management of PFIC, who is either a: (i) gastroenterologist, (ii) hepatologist				
Clinical criteria:					
	Patient must have/have had elevated serum bile acids at treatment initiation with this drug; **AND**				
	Patient must have/have had an average pruritus score of ≥2, on the Prucision™ ObsRO Pruritus Scale assessed over a one week period prior to treatment initiation with this drug.				
Population criteria:					
	Patient must be aged 6 months or older				
Prescribing Instructions:					
	The authority application must be made in writing via HPOS upload or mail and must include: (1) details of the proposed prescription; (2) details of the pruritus score using the completed Prucision™ ObsRO pruritus scale (3) details of serum bile acids (date and micromol/L including reference range)				
	Relapsing patient previously treated with this item may recommence treatment using initiation criteria if restrictions are satisfied.				
Treatment phase:	**Dose Modification**				
Restriction type:	☒ Authority Required ~~(telephone/electronic)~~ *(in writing only via post/HPOS upload)*				
Administrative advice:					
	The recommended dose of odevixibat for initial treatment is 40 micrograms/kg/day administered orally once daily. 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 at least 1 month of initial treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 mcg per day) for a total period of 6 months of treatment with odevixibat				
Treatment criteria:					
	Must be treated by a specialist or under the supervision of a specialist experienced in the management of PFIC, who is either a: (i) gastroenterologist, (ii) hepatologist				
	~~Patient must be undergoing dose modification with this drug at 120 micrograms/kg/day dose for 3 - 5 consecutive months~~				
Clinical criteria:					
	Patient must not have demonstrated an adequate clinical response to initial treatment at 40 mcg/kg/day after 1 month.				
Prescribing instructions:					
	An adequate clinical response to treatment is defined as an average ≥1 grade improvement in pruritus score on the Prucision™ ObsRO Pruritus Scale, assessed over a one week period prior to dose modification.				
	Any further authority applications occurring immediately after access through this dose modification listing are not to occur through the Initial Treatment listing.				

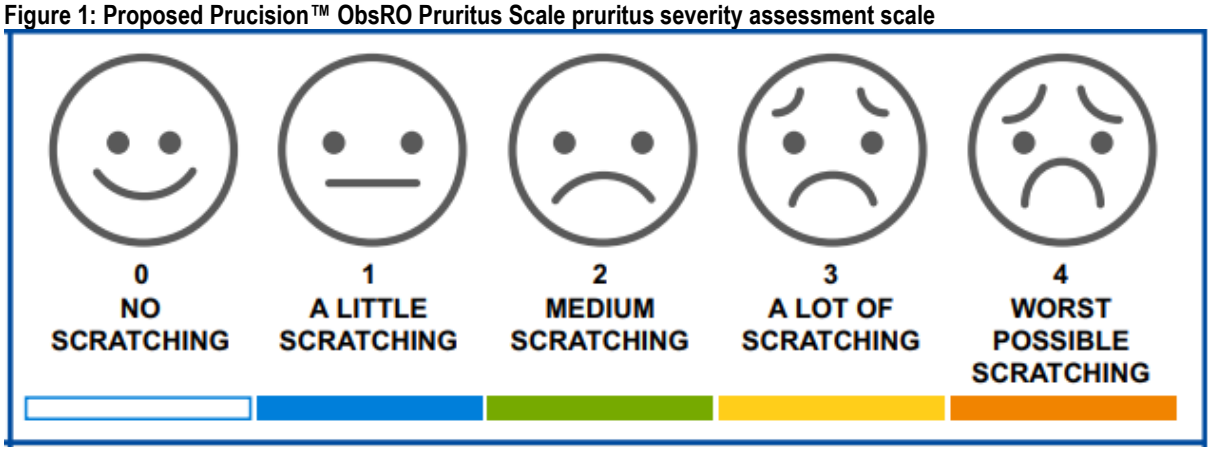
MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№. of Rpts	Available brands
	Dose modification Where the drug's Product Information indicates variable dosing regimens based on the individual's response/tolerance, apply under this listing to continue treatment with the new strength. Mark any remaining repeat prescriptions for the discontinued strength with the word 'cancelled'. This treatment phase listing recognises that a patient's optimal dose may not always be immediately apparent at the time of treatment initiation and therefore does not require confirmation of an objective, adequate response to the preceding supply of drug.				
Treatment phase:	**Continuing Treatment**				
Restriction type:	☒ Authority Required (in writing only via post/HPOS upload)				
Treatment criteria:					
	Must be treated by a specialist experienced in the management of PFIC, who is either: (i) gastroenterologist, (ii) hepatologist; **OR**				
	Must be treated by a medical practitioner under the supervision of a specialist experienced in the management of PFIC				
Clinical criteria:					
	Patient must have demonstrated an adequate clinical response to initial treatment at 40mcg/kg/day over 3 consecutive months; **OR**				
	Patient must have demonstrated an adequate clinical response to dose modification at 120mcg/kg/day at 6 months from commencing odevixibat treatment.				
Prescribing instructions:					
	If an adequate clinical response has been achieved after 3 consecutive months of initial treatment, odevixibat should be renewed at 40 mcg/kg/day through the continuing treatment phase. If an adequate clinical response has been achieved after dose modification at 6 months from commencing odevixibat treatment, should be renewed at 120 mcg/kg/day through the continuing treatment phase. Patients must meet the criteria outlined in the Prucision™ ObsRO Pruritus Scale for ongoing treatment at the lowest effective dose which achieves a response.				
	An adequate clinical response to treatment is defined as an average ≥1 grade improvement in pruritus score on the Prucision™ ObsRO Pruritus Scale, assessed over a one week period prior to dose modification.				
Treatment phase:	**Transitioning from non-PBS to PBS subsidised supply - Grandfather arrangements**				
Restriction type:	☒ Authority Required (in writing only via post/HPOS upload)				
Treatment criteria:					
	Must be treated by a specialist experienced in the management of PFIC, who is either: (i) gastroenterologist, (ii) hepatologist; OR				
	Must be treated by a medical practitioner under the supervision of a specialist experienced in the management of PFIC				
Clinical criteria:					
	Patient must have received treatment with this drug for this PBS indication prior to [insert date]; AND				
	Patient must have had, prior to initiating treatment with this drug, elevated serum bile acids at treatment initiation with this drug; AND				
	Patient must have had, prior to initiating treatment with this drug, an average pruritus score of ≥2, on the Prucision™ ObsRO Pruritus Scale assessed over a one week period prior to treatment initiation with this drug; AND				
	Patient must be in initial 3 months of treatment and continuing at treatment dose of 40mcg/kg/day; OR				
	Patient must have demonstrated an adequate clinical response to dose modification at 120mcg/kg/day at 6 months from commencing odevixibat treatment				

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№. of Rpts	Available brands
Prescribing Instructions:					
	If an adequate clinical response has been achieved after 3 consecutive months of initial treatment, odevixibat should be renewed at 40 mcg/kg/day through the continuing treatment phase. If an adequate clinical response has been achieved after dose modification at 6 months from commencing odevixibat treatment, should be renewed at 120 mcg/kg/day through the continuing treatment phase. Patients must meet the criteria outlined in the Prucision™ ObsRO Pruritus Scale for ongoing treatment at the lowest effective dose which achieves a response.				
	An adequate clinical response to treatment is defined as an average ≥1 grade improvement in pruritus score on the Prucision™ ObsRO Pruritus Scale, assessed over a one-week period prior to dose modification.				

Source: Tables 1-7 to 1-10, of the resubmission

3.1 The resubmission requested an attached document to the restriction, with the description "This document provides health professionals with the observer reported outcomes (ObsRO) pruritus scale for assessing patient scratching associated with PFIC. The scale runs in whole numbers from 0 to 4 with grade 0 representing no scratching to grade 4 representing worst possible scratching". The ObsRO Pruritus Scale is shown in Figure 1.

Figure 1: Proposed Prucision™ ObsRO Pruritus Scale pruritus severity assessment scale



Source: Figure 1-6, p32 of the resubmission

3.2 The requested effective ex-manufacturer price (EMP) of $[redacted]/mcg was [redacted]% lower than in the previous submission ($[redacted]/mcg), equating to an effective EMP of $[redacted] for the 200 mcg pack, $[redacted] for the 400 mcg pack, $[redacted] for the 600 mcg pack, and $[redacted] for the 1200 mcg pack. The Pre-Sub-Committee Response (PSCR) proposed a further [redacted]% price reduction to $[redacted]/mcg. The ESC, noting that there was no comparative clinical data supporting dose escalation, considered that it would be more appropriate if the cost of the higher strength capsules, used when patients escalated to 120 mcg/kg, were the [redacted] cost as the lower strength capsules, used when patients received 40 mcg/kg. Further, the ESC noted that this was previously requested by PBAC in July 2024.

3.3 The resubmission also proposed a Risk Sharing Arrangement (RSA) in the form of annual expenditure caps for the first five years of listing, which were calculated with a '[redacted]cost' assumption, which was implemented by assuming all patients received the [redacted]mcg/kg dose (i.e. [redacted] patients would be up titrated to 120 mcg/kg). The resubmission claimed that the '[redacted]cost' reflected a substantial cost reduction for odevixibat. The ESC noted that the '[redacted] cost' would only be achieved if the assumptions behind the utilisations are accurate and utilisation is reached.

3.4 A summary of the changes to the requested restriction in the resubmission is presented in Table 3.

Table 3: Summary of changes to odevixibat requested restriction

PBAC topic	July 2024 Submission	Resubmission
Authority prescribing	Authority Required (Streamlined)	Initial, dose modification and continuing: • Authority Required (in writing only via post/HPOS upload) (amended in PSCR, see Table 2)
Genetic testing.	Not required	Not required. Non-responder subtype patients accounted for in RSA.
Eligibility criteria (sBA and pruritus assessments)	Patient must have: • Elevated sBA; AND/OR • Symptomatic pruritus	Patient must have: • Elevated sBA at treatment initiation; AND • An average pruritus score of ≥2 on the Prucision™ ObsRO Pruritus Scale assessed over a one-week period prior to treatment initiation.
Dose escalation	Not described	Patient must not have demonstrated an adequate clinical response [a] to initial treatment at 40 mcg/kg/day after at least 1 month. The ESC considered that the criterion required further clarification and stated that (i) dose escalation was allowed to occur between 1-3 months after initiation; and (ii) the continuation criteria needed to be met at 6 months post-initiation.
Response criteria/ discontinuation rules, and stopping & restarting treatment	Not described	Patient must have demonstrated an adequate clinical response [a] to initial treatment at 40 mcg/kg/day over 3 consecutive months; OR 120 mcg/kg/day at 6 months from commencing odevixibat treatment. Relapsing patient previously treated with this item may recommence treatment using initiation criteria if restrictions are satisfied.
Initiation in adults	No age restriction	No age restriction. The ESC noted that there were no data for the initial treatment of patients diagnosed with PFIC as an adult. Further, these patients generally have a better prognosis compared to paediatric patients (see paragraph 4.4).The pre-PBAC response acknowledged the concerns regarding older, and therefore heavier, patients accessing odevixibat. The pre-PBAC response suggested that initiation of odevixibat in adults could be restricted to specialist hepatologists working in liver transplant centres to prevent use in other cholestatic liver diseases.
Use post-surgical treatment	Not excluded	Not excluded

Source: compiled during evaluation from Table 1-1, p10 and Tables 1-7 to 1-9 of the resubmission.
a An adequate clinical response to treatment is defined as an average ≥1 grade improvement in pruritus score on the Prucision™ ObsRO Pruritus Scale, assessed over a one-week period prior to dose modification.
Abbreviations: HPOS = Health Professional Online Services; ObsRO = observer reported outcomes; RSA = risk sharing arrangement; sBA = serum bile acids

3.5 The proposed restriction did not include a requirement for genetic testing. Instead, as per the Facilitated Resolution Pathway Workshop discussion, the resubmission proposed compensating the Commonwealth for use of odevixibat in patients that

would otherwise have been excluded on the basis of genetic testing. Following this, an estimated number of genetic non-responder patients was included as part of the expenditure caps comprising the proposed RSA (see paragraphs 6.67 to 6.69). The pre-PBAC response stated that genetic testing is considered helpful, but is not essential, for initiating treatment with odevixibat and that clinical advice is that the assessment of benefit versus risk supports a trial of odevixibat.

3.6 The amended clinical criteria for initiating treatment was in line with the Facilitated Resolution Pathway Workshop discussion document, which stated (Item 2.3) that participants believed it was reasonable to restrict access to PFIC patients who had both a finding of elevated serum bile acids only (i.e. not the ≥100 µmol/L level required in the registrational studies) and a pruritus score of ≥2 (using the Pruritus Item of the ObsRO instrument).

3.7 The Facilitated Resolution Pathway Workshop discussion document stated it was reasonable for 'Continuing' prescriptions to be allowed for patients who have demonstrated a positive pruritus response. The resubmission proposed that sBA assessment not be included as an eligibility requirement for continuing odevixibat treatment, based on clinical advice that there is day-to-day, intra-patient variability in serum bile acid measurements that occurs due to diurnal variation, diet and other factors (Steiner 2011). The resubmission argued that due to this intra-patient variability, sBA may not be a reliable marker for monitoring treatment effectiveness, and that the overwhelming objective of patients effected by PFIC and their families is to stop or reduce itching. The evaluation noted that sBA measurements were the primary outcome for PEDFIC 1 and the submission is still proposing that an elevated sBA be required at baseline for eligibility. Response based on sBA was also used in the economic evaluation to define response. The PSCR stated that patients who have a symptomatic response (i.e. relief from pruritus) may be excluded from continuing therapy if it was based on sBA response alone due to the vagaries in sBA response. Overall, the ESC considered that pruritus alone, if measured with a robust tool, was an acceptable criterion for assessing eligibility for continuing therapy. The PBAC noted that repeated blood tests could be distressing to children.

3.8 The resubmission defined an adequate clinical response to treatment as "an average ≥1 grade improvement in pruritus score on the Prucision™ ObsRO Pruritus Scale, assessed over a one-week period prior to dose modification." The proposed ObsRO scale for use of clinical response assessment is presented in Figure 1 above. The resubmission noted the ObsRO scale is not used in clinical practice.

3.9 The ESC noted that a 9-item ObsRO instrument was previously considered by the PBAC in the July 2024 submission. 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 (paragraph 7.8, odevixibat PSD, July 2024 PBAC Meeting). The ObsRO instrument has not been validated as a self-

assessment tool. The ESC noted that no further details on the development and validation of the ObsRO instrument were provided in the resubmission.

3.10 The resubmission's proposed ObsRO Pruritus Scale was a simplification of the 9-item ObsRO instrument used in PEDFIC1 and PEDFIC2, using a single Likert-scale item to measure the overall degree of itch as experience over a prior week, and it could be completed by a patient or carer. The ESC noted that the ObsRO Pruritus Scale, as proposed in the resubmission to assess eligibility and clinical response, relied on the answer to one question. Overall, the ESC considered that the ObsRO Pruritus Scale would be subject to high variability and may not be a meaningful measure of response. The ESC noted that the expanded ObsRO instrument, or one of the several other pruritus scales which had been validated, including the Worst itch numeric rating scale (WI-NRS) or the 5-D itch scale, could be applied in the restriction to measure response. The pre-PBAC response stated that, although none of the suggested tools were used in clinical practice, the sponsor was open to alternatives to the ObsRO Pruritus Scale being used as long as it does not place undue burden on prescribers, patients and caregivers.

3.11 The resubmission proposed that 'Continuing' prescriptions only be allowed for patients who have demonstrated an adequate clinical response (see paragraph 3.8) following treatment under 'Initial' treatment or 'Dose Modification' restrictions, that is:

- If an adequate clinical response is achieved after three months of initial treatment, odevixibat would continue at 40 mcg/kg/day through the continuing treatment phase;
- If there is an inadequate clinical response following one to three months of initial treatment at low dosage, patients can increase to the 120 mcg/kg/day dose. If an adequate clinical response has been achieved at six months post initiation with dose escalation to 120 mcg/kg/day, treatment should continue at 120 mcg/kg/day through the continuing treatment phase; or
- If a positive pruritus response is not achieved after 6 months, including after dose modification, then treatment would be discontinued.

3.12 The proposed response criteria only required the patient to have demonstrated an adequate clinical response to initial treatment but not in continuing treatment. That is, there was no requirement for patients in the continuation treatment phase to maintain response (or even a requirement for any objective assessment), nor any discontinuation criteria for patients who may subsequently lose response. This would allow for patients that are no longer receiving (adequate) benefit from odevixibat to continue treatment, which would be inappropriate. The ESC considered that patients should continue to demonstrate an adequate response (i.e. reduced pruritus) to odevixibat to continue receiving treatment, given the limited longer-term data available and the possibility that some patients may experience a loss of response. The

pre-PBAC response stated that treatment should continue for as long as a positive pruritus response is maintained.

3.13 There was no criterion in the resubmission's initial treatment restriction which would prevent non-responder patients who were not eligible for continuing treatment from receiving treatment under the initial treatment criteria again. The ESC considered that a patient should only be eligible to receive retreatment if they had previously satisfied the criteria for a clinical response and the reason for prior discontinuation was that it was considered that odevixibat was no longer required, not that the itch had worsened whilst on odevixibat. The pre-PBAC agreed in principle with the ESC's consideration that patients should only be eligible to receive retreatment if they had previously responded.

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 an accumulation of bile acid. 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 a portal hypertension, liver failure, cirrhosis, hepatocellular carcinoma, and extrahepatic manifestations (e.g., diarrhoea, risk of pancreatitis, hearing problems, and fat-soluble vitamin deficiencies). The ESC has previously noted that neonatal cholestasis affects 1 in 2,500 infants and ~13% of these infants have PFIC (paragraph 4.1, odevixibat PSD, July 2024 PBAC meeting).[1]

4.2 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.

4.3 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. 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; however, PFIC5 is noted to be a very rare subtype with only nine patients identified worldwide in the literature (paragraph 4.5, odevixibat PSD, July 2024 PBAC meeting). The resubmission proposed to account for the costs associated with treatment of

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

odevixibat in an estimated proportion of patients predicted to be PFIC2 *BSEP3* non-responders within the proposed RSA.

4.4 The resubmission also described 'episodic PFIC' where patients experience acute manifestations of severe pruritus lasting for several weeks or months followed by significant periods of remission. During periods of remission, liver function is restored and typically such patients do not progress to cirrhosis. Episodic PFIC may refer to benign recurrent intrahepatic cholestasis (BRIC), which is sometimes considered a milder form of PFIC characterised by periods of cholestasis interspersed with, usually much longer, periods with no cholestasis and without progression to chronic liver disease. Similar genes are implicated in BRIC1 and PFIC1 (ATP8B1), as well as among BRIC2 and PFIC2 patients (ABCB11); however, there is differentiation in gene expression, resulting in major clinical and prognostic differences between the two entities[2]. Whilst PFIC is typically diagnosed in infancy, the time of a first episode of BRIC varies widely, with records ranging from two months to 47 years[3]. The exact prevalence of episodic PFIC or BRIC is not known; however, it was noted in the Facilitated Resolution Pathway Workshop document that allowing patients with episodic exacerbations of PFIC over the age of 18 to initiate odevixibat would significantly increase the size of the prevalent pool. Notably, the efficacy of odevixibat in BRIC (or any 'episodic PFIC') is unknown, with no clinical data presented and the potential incremental benefit not captured in the economic modelling. The ESC also noted that these potential patients were not included in the financial estimates.

4.5 The ESC noted that additional data were requested by NICE during its review of odevixibat (published February 2022, page 39)[4], for its next review in 2025, including:

(i) the ongoing effect of odevixibat on serum bile acid levels and pruritus, survival outcomes, liver transplant rates and alternative utility values for people having high dose odevixibat in PEDFIC 2,

(ii) clinical effectiveness by PFIC subtypes from PEDFIC 2, particularly types 3 and 6;

(iii) the clinical effectiveness of odevixibat compared with PEBD from the sponsor's indirect treatment comparison;

(iv) UK-specific data on starting age and stopping rates for odevixibat; and

(v) alternative utilities for patients having a stoma bag.

The ESC requested that any available NICE data be provided for PBAC consideration.

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[2] Geladari EV, Vallianou NG, Margellou E, Kounatidis D, Sevastianos V, Alexopoulou A. Benign Recurrent Intrahepatic Cholestasis: Where Are We Now? Gastroenterology Insights. 2024; 15(1):156-167. https://doi.org/10.3390/gastroent15010011

[3] https://www.pfic.org/learn-about-pfic-disease/pfic-types-and-subtypes/

[4] *NICE. Odevixibat for treating progressive familial intrahepatic cholestasis. Highly specialised technologies guidance, HST17, published 22 February 2022. Available at: https://www.nice.org.uk/guidance/hst17*

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

5 Comparator

5.1 The comparator in the resubmission remains SoC. At the July 2024 PBAC Meeting, the PBAC considered the nomination of SoC, including off-label use of medicines such as ursodeoxycholic acid and rifampicin, as well as 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 (paragraph 7.5, odevixibat PSD, July 2024 PBAC Meeting). The resubmission continued to present odevixibat largely as an alternative to PEBD in the clinical algorithm.

5.2 The resubmission stated that the PBAC heard within the Sponsor Hearing at the July 2024 PBAC meeting that PEBD following odevixibat treatment is quite rare, with the clinician aware of only one case being considered in Australia. The PEDFIC-2 72-week clinical study report (CSR) reported that 3 of 116 patients (2.5%) underwent SBD and 15 of 116 patients (12.9%) underwent LT following treatment with odevixibat. The resubmission also stated that at the Facilitated Resolution Pathway Workshop, clinician input also noted this as a rare event, with very little PEBD being conducted now. It was unclear whether 'very little PEBD being conducted now' was applicable to all patients, or only odevixibat treated patients. That is, if PEBD was reduced in clinical practice for all patients, then the rate of surgery in the SoC arm may have been overestimated in the economic model and financial estimates.

5.3 No evidence was presented on the comparative rates of PEDB and LT in odevixibat non-responders versus patients untreated with odevixibat and it remains uncertain whether odevixibat will replace SBD and LT and to what degree.

5.4 The direct clinical evidence from PEDFIC 1 presented in the July 2024 submission compared odevixibat to placebo in mostly patients who have not undergone SBD, and there was no direct evidence of odevixibat compared to PEBD. The PBAC had considered the OvEC part B was the most relevant study as it compared odevixibat to SBD, but the study had significant limitations (paragraph 7.11, odevixibat PSD, July 2024 PBAC meeting). No additional clinical evidence comparing odevixibat against PEBD has been presented in the resubmission. The estimated rate of PEBD surgery had a substantial impact on both the resubmission's economic model and financial estimates.

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 primarily discussed the clinical perspective of treatment of adults with PFIC. The clinician stated that, although

a minority of patients are diagnosed in adulthood, it is becoming increasingly recognised. The clinician stated that adult patients generally have a more attenuated form of disease which is less rapidly progressing, and that patients with long standing disease generally presenting for diagnosis as their pruritus and jaundice become more severe. Diagnosis of these patients relies primarily on histology and symptoms and can usually be differentiated clinically from BRIC. The clinician further stated that pruritus can be burdensome to patients and that odevixibat, which is a directed antipruritic therapy, is effective and can positively impact a patients quality of life.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (4) and organisations (2) via the Consumer Comments facility on the PBS website associated with this resubmission. The PBAC also recalled that the July 2024 submission received input from individuals (35), health care professionals (4) and organisations (3). 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 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 “2 months after the first dose, we almost forgot about the itching” 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.

6.4 In March 2025, PFIC and Related Disorders Australia stated that there was a critical

need for odevixibat to be made available to adult patients, as well as paediatric patients. The groups stated that the adult population was likely to be very small (i.e. approximately 10 patients) and noted that many adults with PFIC experience episodic disease and may only require treatment during exacerbations.

Clinical studies/trials

6.5 The July 2024 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]) (paragraph 6.4, odevixibat PSD, July 2024 PBAC meeting).

6.6 As the final analysis for PEDFIC 1 was presented within the July 2024 submission, no new data was presented in the resubmission. However, the resubmission presented an updated 72-week treatment period analysis for PEDFIC 2 which included additional non-randomised patients recruited into Cohort 2 (N=116; median follow-up = 98.9 weeks).

6.7 In response to the PBAC's advice that any resubmission provide adequate details for validation (i.e., OvEC Part A and Part B) (paragraph 7.26, odevixibat PSD, July 2024 PBAC Meeting), the resubmission claimed that whilst additional information has been requested from the authors of the OvEC study, this was not available at the time of resubmission.

6.8 Details of the studies presented in the submission are provided in Table 4.

Table 4: Trials/studies and associated reports presented in the resubmission

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)	Week 72 CSR, February 2024 data cut, date of report 29 August 2024
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: Table 3, Odevixibat PSD, July 2024 PBAC Meeting and 'Large files" attachment to the submission
Blue shaded cells indicate studies previously considered by the PBAC

6.9 The key features of the included evidence are summarised in Table 5.

Table 5: 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	Odevixibat sBA response
PEDFIC 2 [b]	Cohort 1 = 56 Cohort 2 = 60 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	Discontinuation rates and rate of PEBD in odevixibat arm
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)	Rate of PEBD in SoC arm, PEBD response and LT transitions

Source: Table 4, odevixibat PSD, July 2024 PBAC Meeting.
Abbreviations: 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; PFS = progression-free survival; 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 analyses as of 29 Augst 2024 reporting on results at 72 weeks; 116 patients enrolled and 100% received at least 1 dose; 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.
Blue shaded cells indicate studies previously considered by the PBAC

6.10 Of the included evidence only OvEC Part B provided any information regarding the comparative efficacy of odevixibat to SBD. The ESC previously noted that as no baseline characteristics for OvEC Part B were reported, 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 (paragraph 6.16, odevixibat PSD, July 2024 PBAC Meeting).

Comparative effectiveness

6.11 Results for the primary endpoint, sBA response (defined as ≥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) and pruritus response for ≥50% of the time from PEDFIC 1 are presented in Table 6.

Table 6: 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 -Placebo)	-	**44.1 (23.61, 64.64)**	21.6 (-0.5, 43.8)	30.7 (12.6, 48.79)
1-sided unadjusted p-valued	-	0.0003	0.0174	0.0015
1-sided adjusted p-value	-	**0.0015**	0.0174	-
Proportion of positive pruritus assessments (primary)				
% 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-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)
One-sided p-value (unadjusted)	-	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/Placebo)	-	16.22 (2.54, 106.32)	3.14 (0.72, 18.70)	6.21 (1.54, 27.43)
One-Sided Unadjusted p-valued	-	0.0002	0.0391	0.0016

Source: Table 5, odevixibat PSD, July 2024 PBAC meeting
Abbreviations: CI = confidence interval; FAS = full analysis set; n = number; 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)
Blue shaded cells indicate data previously considered by the PBAC at the July 2024 PBAC meeting

6.12 The PBAC has previously 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 (paragraph 7.12, odevixibat PSD, July 2024 PBAC meeting) and that there was a high placebo response rate in pruritus assessment. Further, placebo was not the nominated comparator and therefore results of PEDFIC 1 may not be sufficient to support a clinical claim compared to the nominated comparator of SoC.

6.13 Results for the change from baseline in sBA concentration and the proportion of positive pruritus assessments from PEDFIC 2 is presented in Table 7. All patients in PEDFIC 2 were treated with odevixibat 120 mcg/kg/day.

Table 7: Summary of change from baseline in sBA concentration after 72 weeks of treatment, and the proportion of positive pruritus assessments in PEDFIC 2

	Cohort 1		Cohort 2 (N=60) [c]
	Placebo/ Odevixibat (N=19) [a]	Odevixibat/ Odevixibat (N=37) [b]	
Change in serum bile acid concentration (µmol/L)			
Baseline [d]			
n	19	37	60
Mean (SD)	280.58 (131.874)	248.11 (129.721)	220.93 (121.015)
Median	277.00	208.00	213.25
Week 22/24			
n patients with data (n/N)	11/19	21/34	5/16
Mean (SE)	155.59 (26.810)	85.10 (25.123)	213.20 (85.683)
Change from baseline, mean (SE)	-143.73 (48.601) [e]	-18.02 (11.892) [f]	-104.10 (38.770)
% change from baseline, mean (SE)	-36.78 (13.966)	-9.62 (18.429)	-48.20 (18.416)
Week 70/72 of PEDFIC 2, n/N			
n patients with data (n/N)	15/19	28/37	43/60
Mean (SD)	164.73 (124.647)	127.73 (131.868)	148.88 (147.416)
Median	171.00	82.50	105.00
Change from baseline [d], n	15	28	43
Mean (SD)	-104.00 (167.318)	-139.84 (172.070)	-57.97 (137.990)
Median	-61.00	-121.00	-46.00
% Change from baseline [d], n	15	28	43
Mean (SD) [g]	-16.62 (69.127) [g]	-50.29 (50.342)	-20.07 (105.278)
Median	-18.04	-58.47	-24.83
Proportion of Positive Pruritus Assessments [h]			
Week 22-24			
n patients with data (n/N)	11/19	26/34	5/16
% Mean (SE)	56.26 (10.869)	32.62 (6.510)	61.63 (19.866)
Week 0-72			
n patients with data n/N (%)	12/19 (63.2)	26/37 (70.3)	31/60 (51.7)
Mean (SD)	55.20 (38.733)	38.58 (34.877)	77.28 (28.084)
Median	62.84	36.88	88.35

Source: Table 2-1 and 2-2 p39, p49 of the resubmission, Table 2-18, p83 of the July 2024 submission
Abbreviations: Max: maximum; min: minimum; SD: standard deviation; SE = standard error
[a] Includes patients who received placebo in PEDFIC 1 and transitioned to odevixibat in PEDFIC 2.
[b] Includes patients who received odevixibat 40 or 120 µg/kg/day in PEDFIC 1 and transitioned to odevixibat in in PEDFIC 2
[c] Includes new patients who were not eligible for PEDFIC 1, that received odevixibat in Cohort 2 in PEDFIC 2
[d] For the Cohort 1 placebo/odevixibat and Cohort 2 groups, baseline is calculated as the average of last 2 values before the first dose of study drug in PEDFIC 2 (Baseline 2); Baseline 2 is used for the change from baseline analysis. For the Cohort 1 odevixibat/odevixibat group, baseline is calculated as the average of last 2 values before the first dose of study drug in PEDFIC 1 (Baseline 1); Baseline 1 is used for the change from baseline analysis.
[e] The mean (SE) baseline sBA level reported in the PEDFIC 2 24-week analysis for placebo patients enrolled from PEDFIC 1 was 270.79 (29.034), which differed to the PEDFIC 2 72-week analysis. It was unclear why there would be any differences as it should be the same 19 patients at both time points.
[f] A different baseline (mean 127.38) to the data presented in the resubmission was used in the July 2024 submission. This appeared to have been the sBA level at the end of PEDFIC 1, prior to entry into PEDFIC 2, and may not be comparable with the 72-week results which used sBA levels from prior to entry into PEDFIC 1.
[g] This is as reported in the CSR but could not be independently verified. For example, in placebo/odevixibat patients in Cohort 1, a mean % change from baseline of -16% was reported even though the mean change from baseline was -104 with a baseline of 280, suggesting a change of around -37% (before adjustments).
[h] A positive pruritus assessment was defined as a scratching score of ≤ 1 or at least a 1-point decrease from baseline on the ObsRO instrument.
Blue shaded cells indicate values previously considered by the PBAC at the July 2024 meeting

6.14 Patients in PEDFIC 2 with available data were observed at week 70/72 to have a mean reduction from baseline in sBA levels of -104.00 µmol/L (standard deviation [SD]: 167.32) for the odevixibat naïve patients in Cohort 1; -139.84 µmol/L (SD: 172.10) for the odevixibat experienced patients in Cohort 1; and -57.97 µmol/L (SD: 137.99) for Cohort 2.

6.15 Not all patients experienced a reduction in sBA, as the maximum values for change from baseline indicate some patients experienced worsening of sBA at week 70/72 despite odevixibat treatment. However, it was unclear how this compares to SoC as there was no comparator arm data in PEDFIC 2.

6.16 Only 63.2% (12/19), 70.3% (26/37) and 51.7% (31/60) of patients in Cohort 1 (odevixibat naïve from placebo arm of PEDFIC 1), Cohort 1 (odevixibat experienced from active treatment arm of PEDFIC 1) and Cohort 2 (PFIC patients ineligible for PEDFIC 1) respectively had pruritus data available for the 72-week analysis (i.e. 59.5% (69/116) of patients in PEDFIC 2). As such, there was a substantial risk of attrition bias. Carers of patients noticing a reduction in scratching may be more likely to record symptoms than those with persistent symptoms or who had worsening of symptoms. Cohort 2, which had the lowest number of patients with available data (n=31) was recorded as having a substantially higher proportion of positive pruritus scores than either group in Cohort 1, despite Cohort 2 being observed to have the smaller reduction in mean sBA levels.

6.17 The event free survival (EFS), native liver survival (NLS), SBD-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 8.

Table 8: 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 26, odevixibat PSD, July 2024 PBAC Meeting

CI = confidence interval; HR = hazard ratio; n = number of patients experiencing event; NE = not evaluable

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

Comparative harms

6.18 No new comparative harms data between odevixibat and SoC was reported in the resubmission. Safety data for the PEDFIC 1 trial remained unchanged from the July 2024 submission, presented in Table 9.

Table 9: Summary of safety results – PEDFIC 1 - 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 7, odevixibat PSD, July 2024 PBAC meeting

CI = confidence interval; TEAE = treatment emergent adverse event; RD = risk difference; RR = relative risk

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

c Comparisons were between all doses odevixibat vs placebo

6.19 The safety results at the interim analysis (data cutoff 31 July 2022, median follow-up 53.1 weeks) for PEDFIC 2 from the TGA's Clinical Evaluation Report for odevixibat, and

the Week-72 CSR (data cutoff 15 February 2024, median follow-up 98.9 weeks) from the resubmission are presented in Table 10.

Table 10: PEDFIC 2 overall summary of TEAEs

	Cohort 1				Cohort 2	Cohort 2 + placebo	Overall cohort
	40 µg/kg	120 µg/kg	All doses	Placebo			
Data cutoff 31 July 2022[a]	**N=21**	**N=16**	**N=37**	**N=19**	**N=56**	**N=75**	**N=112**
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)
Data cutoff 15 February 2024[b]	**N=21**	**N=16**	**N=37**	**N=19**	**N=60**	**N=79**	**N=116**
TEAE	NR	NR	37 (100)	18 (94.7)	**57 (95.0)**	NR	112 (96.6)
Drug-related TEAE	NR	NR	17[c] (45.9)	8 (42.1)	20 (33.3)	NR	45 (38.8)
Severe TEAE	NR	NR	3 (8.1)	2 (10.5)	15 (25.0)	NR	20 (17.2)
Serious TEAE	NR	NR	**35 (30.2)**	5 (26.3)	**23 (38.3)**	NR	**35 (30.2)**
Drug-related serious TEAE	NR	NR	2 (1.7)	0	1 (1.7)	NR	2 (1.7)
TEAE leading to death	NR	NR	0	0	0	NR	0
TEAE leading to treatment discontinuation	NR	NR	10 (8.6)	3 (15.8)	7 (11.7)	NR	10 (8.6)
TEAE leading to study treatment interruption	NR	NR	14 (37.8)	5 (26.3)	20 (33.3)	NR	39 (33.6)
Select TEAEs reported in ≥ 5% patients							
Investigations	NR	NR	20 (54.1)	11 (57.9)	29 (48.3)	NR	60 (51.7)
Blood bilirubin increased	NR	NR	10 (27.0)	4 (21.1)	14 (23.3)	NR	28 (24.1)
INR increased	NR	NR	5 (13.5)	3 (15.8)	11 (18.3)	NR	19 (16.4)
ALT increased	NR	NR	3 (8.1)	2 (10.5)	6 (10.0)	NR	11 (9.5)
AST increased	NR	NR	2 (5.4)	1 (5.3)	5 (8.3)	NR	8 (6.9)
Hepatobiliary disorders	NR	NR	10 (27.0)	4 (21.1)	8 (13.3)	NR	22 (19.0)
Hepatomegaly	NR	NR	4 (10.8)	1 (5.3)	1 (1.7)	NR	6 (5.2)
Jaundice	NR	NR	3 (8.1)	0	3 (5.0)	NR	6 (5.2)

Source: Table 9, odevixibat PSD, July 2024 PBAC meeting and Table 2-3, p42 of the resubmission
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; TEAE = treatment emergent adverse event; NR = not reported
[a] Median duration of exposure 53.1 weeks
[b] Median duration of exposure 98.9 weeks
[c] It appeared that 2 patients who had TEAEs recorded as drug-related at the time of the July 2022 interim analysis had been amended in the February 2024 data cut.
Bold values indicate percentages that increased by ≥10% from the July 2022 data cut to the February 2024 data cut.

6.20 Two patients, both in Cohort 2, had drug-related treatment emergent adverse events (TEAEs) that were reported as severe in intensity. One patient had increased alanine aminotransferase (ALT) increased and one patient had increased ALT, aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT). None of the drug-related TEAEs of hepatic function test abnormalities were assessed as serious by the investigator.

6.21 The TGA Delegate's Overview, which reviewed the July 2022 data cut noted that:

- "it was difficult to separate whether liver-related TEAEs were disease-related or drug-related. Cholestasis and elevated hepatic biochemical parameters, most excursions in ALT, AST, and total bilirubin values were considered by the investigators to be related to the underlying disease" (TGA Delegate's Overview, odevixibat, May 2024); and
- "from 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).

It was unclear whether the latest data cutoff of PEDFIC 2 sufficiently addressed uncertainties around long term safety, given odevixibat is intended to be a lifelong therapy.

Benefits/harms

6.22 As no new direct comparative evidence was presented in the resubmission, the summary of the comparative benefits for odevixibat versus placebo considered at the July 2024 PBAC meeting is presented in the Table 11. No statistically significant differences between odevixibat and placebo with respect to adverse events were observed.

Table 11: 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[1] (95% CI)
	40 mcg/kg	120 mcg/kg	All doses		40 mcg/kg	120 mcg/kg	All doses	Placebo	
Benefits									
sBA response	10/23	4/19	14/42	0/0	43.5%	21.1%	33.3%	0%	44.1% (23.61, 64.64)
Proportion of positive pruritic assessments for ≥50% of the time	17/23	9/19	26/42	4/20	73.9	47.4	47	20	53.9%

Source: Table 10, odevixibat PSD, July 2024 PBAC meeting
HR = hazard ratio; PBO = placebo; RD = risk difference; TEAE = treatment emergent adverse event; sBA = serum bile acid; NR = not reported; NE = not evaluable.
Note: RD for sBA response was the adjusted difference between the 40 mcg/kg and placebo as this was the only comparison demonstrating statistical significance.
1. adjusted RD 40 mcg/kg/day vs placebo

6.23 On the basis of direct comparison evidence presented, 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).
- Approximately 54 additional patients will achieve a positive pruritus assessment for ≥ 50% of the time.

6.24 On the basis of direct comparison evidence presented, for every 100 patients treated with odevixibat (120 mcg/kg/day) in comparison with placebo after 24 weeks of treatment:

- Approximately 21 additional patients will achieve a sBA response (at least a 70% reduction in sBA concentrations from baseline or reaching ≤70 µmol).
- Approximately 27 additional patients will achieve a positive pruritus assessment for ≥ 50% of the time.

Clinical claim

6.25 The resubmission described odevixibat as superior in terms of effectiveness compared to placebo.

6.26 The PBAC has previously 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 (paragraph 7.12, odevixibat PSD, July 2024 PBAC meeting). The PBAC noted that the clinical data did not support any incremental benefit of the 120 mcg/kg dose over the 40 mcg/kg dose and that the point estimates of benefit for the higher dose were lower (see Table 6). Further, placebo was not the nominated comparator and therefore results of PEDFIC 1 may not be sufficient to support a clinical claim compared to the nominated comparator of SoC. Given no new evidence was presented, the ESC considered that the same conclusion regarding comparative efficacy between odevixibat and placebo was reasonable.

6.27 The resubmission described odevixibat as superior in terms of effectiveness compared to SoC.

6.28 The PBAC has previously 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 (paragraph 7.13, odevixibat PSD, July 2024 PBAC meeting). Given no new evidence was presented, the ESC considered that the same conclusion regarding comparative efficacy between odevixibat and SoC was reasonable.

6.29 The resubmission described odevixibat as "having uncertain comparative safety compared with best supportive care given the lack of comparative data. However, the significance of surgical interventions including stoma are noted for the comparator".

6.30 The PBAC has previously 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 (paragraph 7.14, odevixibat PSD, July 2024 PBAC meeting). Given no new evidence was presented, the ESC considered the same conclusion regarding comparative safety between odevixibat and SoC was reasonable.

6.31 Given that no new comparative data were presented, the PBAC again considered that the claim of superior comparative effectiveness compared to placebo was supported, but the claim of superior comparative effectiveness compared to SoC was uncertain.

6.32 The PBAC again considered that the claim non-inferior comparative safety compared to SoC was not adequately supported by the data.

Economic analysis

6.33 The resubmission presented a cost-utility analysis (CUA) of odevixibat compared to SoC. The overall structure of the CUA model considered by the PBAC at its July 2024 meeting was unchanged, though the resubmission used different inputs and assumptions to address several issues raised by the PBAC. The ESC considered that the economic model presented in the resubmission was not reliable for decision making because of both implausible structural assumptions and continuing uncertainty in data inputs (see paragraph 6.49).

6.34 The key components of the economic evaluation are presented in Table 12.

Table 12: Summary of model structure, key inputs and rationale

<table>
<tr><th>Component</th><th>Resubmissions approach and comments</th></tr>
<tr><td>Treatments</td><td>Odevixibat vs SOC</td></tr>
<tr><td>Time horizon</td><td>50 years (reduced from 100 years from July 2024)</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. Liver Transplant (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 resubmission model maintained the use of OvEC data in the base case.
<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 was changed in the resubmission from 62.28% (OvEC) to 43.5% (PEDFIC 1, 24 weeks response)
SoC response was maintained at 0%.</td></tr>
<tr><td>1</td><td>No PEBD, no response (or loss of response)</td><td>Odevixibat annual discontinuation was increased in the resubmission, from 3.53% to 12.01% based on updated PEDFIC 2 data of 33 patients discontinuing over a total average follow up of 115.61 weeks.</td></tr>
<tr><td>2</td><td>PEBD, response</td><td>PEBD response based on OvEC data (32.3%).</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>
</table></td></tr>
</table>

<table>
<tr><th>Component</th><th>Resubmissions approach and comments</th></tr>
<tr><td></td><td>
<table>
<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>
<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 3-3 from the resubmission</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 PFIC 1 (27.4%) and PFIC2 (72.6%).</td></tr>
<tr><td>Health related quality of life</td><td>The resubmission maintained the utility for the ‘PEBD, response’ state as below that of the ‘no PEBD, no response’ state. However, the health state utility value was increased from 0.659 to 0.761 in the resubmission.
<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>0.761</td><td>A stoma disutility modifier (0.833), based on the average of Arseneau 2006 (0.722) and Hornbrook 2011 (0.945) was applied to the ‘No PEBD, response state’.</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</td><td>‘Post LT children’ from Parma 2017,</td></tr>
</table></td></tr>
<tr><td>Healthcare resource use and costs</td><td>The resubmission 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>The resubmission assumed a ‘[redacted] cost’. Specifically, all patients initiated at 40 mcg/kg and [redacted] dose escalation to 120 mg/kg was permitted. Thus, all patients received benefits and costs associated with the 40 mcg/kg dose. A per unit price reduction was also applied within this resubmission.
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>The proportion of use were 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>
<tr><td>PEBD costs (including surgery, reoperations, complications, and monitoring)</td><td>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</td></tr>
</table></td></tr>
</table>

Component	Resubmissions approach and comments	
		visits, and the proportion of patients who have clinical were informed by the HCD 2021 burden of illness study.
	AE	AE events included in the odevixibat arm were changed from PEDFIC 1 (24 weeks) to PEDFIC 2 (115 weeks) in the resubmission.
	Societal costs including lost productivity (scenario analysis only)	Lost productivity is based on the proportion of work impairment recorded in the burden of illness study (HCD 2021).

Source: Modified from Table 11, odevixibat PSD, July 2024 PBAC meeting. Added information from Table 3-3, p29, p53 of the resubmission and 'Transitions', 20241105 Bylvay PFIC CEM Resubmission excel workbook

Abbreviations: ABS = Australian Bureau of Statistics; AEs = adverse events; CDC = Centre for Disease Control; PEBD = Partial external biliary diversion; PFIC = Progressive familial intrahepatic cholestasis; PedsQL = Paediatric Quality of Life Inventory; EQ-5D = EuroQol-5 Dimension; SOC = standard of care; QALY = quality-adjusted life years; NHCDC = National Hospital Cost Data Collection; UDCA = Ursodeoxycholic acid

Note: Blue shaded cells indicate components that were unchanged from the July 2024 submission

6.35 It was assumed that sBA response was a surrogate for pruritus response in the model. The PBAC has previously considered that use of sBA as a surrogate was reasonable, noting there were a number of issues with the pruritus tool used in PEDFIC 1, the PRUCISION ObsRO instrument (paragraph 7.16, odevixibat PSD, July 2024 PBAC meeting). However, in the resubmission, pruritus response (based on a substantially modified version of the ObsRO scale) was proposed as the definition of clinical outcome in the restriction, with the resubmission arguing that sBA may be an unreliable marker for monitoring treatment effectiveness (see paragraph 3.7). As such, response in the economic evaluation did not align with the proposed clinical response in the requested restriction or likely use in the proposed PBS population.

6.36 The July 2024 submission assumed patients within the modelled evaluation could dose escalate from 40 mcg/kg to 120 mcg/kg if no response was observed. The resubmission proposed a '[redacted] cost' via an expenditure cap (see paragraph 6.67) and [redacted] the 40 mcg/kg/day dose was considered in the economic model. The ESC noted that the actual costs of the higher strength capsules remain greater under the requested listing, as the '[redacted] cost' would only be achieved if the expenditure cap was met. The ESC considered that the extent to which this was likely was uncertain, given the issues identified in the financial estimates (see paragraph 6.62). If the utilisation of odevixibat was below the estimates used to generate the expenditure cap, then there would be no '[redacted] cost' and the incremental cost effectiveness ratio (ICER) would be underestimated.

6.37 The '[redacted] cost' was implemented in the base case by not allowing any dose escalation. However, the resubmission also changed the assumed response rate from 62.28% (OvEC, 'combined doses' from internal sponsor data) to 43.5% (PEDFIC 1, 24 weeks response in patients treated with 40 mcg/kg/day). The PSCR stated that as the PBAC previously challenged the incremental effectiveness of dose escalation, the '[redacted] cost' intentionally assumes no incremental benefit. The ESC noted that this was not reasonable, and the response rate should not be impacted as the proposed PBS population would have access to the higher dosage. This reduction in response rate also unexpectedly led to a decrease in the ICER separate to the cost assumption of no

dose escalation. Increasing the response rate to 62.28% increased the ICER by %. This paradoxical reduction in the ICER following a reduction in the response rate was due to the model having a separate assumption of benefit for odevixibat treatment in the form of a reduced rate of PEBD surgery. Notably, in a hypothetical worse-case scenario where the response rate of odevixibat was set to 0%, the ICER decreased by % and still conferred an incremental quality adjusted life year (QALY) gain of 0.64. This suggested that, despite assuming a null treatment effect (0% response with odevixibat), the model still, implausibly, favoured treatment with odevixibat. This appeared to be largely driven by the difference in rate of PEBD between the SoC and odevixibat arm (see paragraph 6.40).

6.38 The resubmission utilised the discontinuation data from the updated 72-week data-cut of the PEDFIC 2 trial, where 33 of 116 patients had discontinued over a mean follow up of 115.61 weeks, to inform the loss of response. This equated to an annual probability of discontinuing of 12.01% per 1-year model cycle. It was unclear if it was reasonable to assume that discontinuation in PEDFIC 2 was equivalent to loss of response, as patients may have discontinued for other reasons. The ESC noted that, as with the response rate, assuming a lower loss of response paradoxically increased the ICER. Assuming a 3.53% annual loss of response (as used in the July 2024 submission) increased the ICER by %, with the higher drug acquisition costs due to lower discontinuation outweighed by the QALY gain from longer treatment. Paradoxically, this meant that a faster loss of response to treatment improved cost effectiveness, which was unreasonable and lacked face validity. This was because a permanent separate incremental benefit (i.e. lower rate of PEBD) was assumed, independent of continuing odevixibat treatment (see paragraph 6.40). The PSCR stated that the updated discontinuation data from PEDFIC 2 was more robust than the data applied in the July 2024 submission which was informed by a single patient discontinuing over a 24-week duration of follow-up.

6.39 In the July 2024 submission, it was assumed that odevixibat treated patients would not undergo PEBD after losing response. The PBAC considered this favoured odevixibat and was not likely to reflect clinical practice (paragraph 7.18, odevixibat PSD, July 2024 PBAC meeting). In the resubmission, subsequent PEBD was allowed in the odevixibat arm, based on the proportion of patients undergoing PEBD within PEDFIC 2 (3/116 patients with subsequent PEBD over an average follow up of 115 weeks).

6.40 Transitions to PEBD from non-responders in the SoC arm were unchanged from the July 2024 submission and based on data from the OvEC study, which could not be independently verified and were therefore highly uncertain. An annual rate of PEBD of 5.52% was applied to the SoC arm, compared to 1.16% in the odevixibat arm. The difference in rate of PEBD surgery was assumed to be constant over the 50-year time horizon, and irrespective of whether odevixibat arm patients responded to treatment, which did not appear to be clinically plausible. The reduced rate of PEBD for odevixibat patients was a key driver of the model. In addition, the proportion of patients

undergoing PEBD in current clinical practice is relatively uncertain (see paragraphs 5.2 and 5.3).

6.41 The resubmission maintained the use of data from OvEC in the base case, which were not verifiable, and had a substantially less favourable PEBD response compared to NAPPED (32.2% versus 60.15%, respectively). As patients in the SoC arm transitioned to PEBD at a higher rate than patients in the odevixibat arm, the lower response rate of PEBD favoured odevixibat. Assuming a 60.15% response rate instead of the 32.2% in the base case increased the ICER by %.

6.42 In the resubmission's base case the 'no PEBD, no response' health state utility remained higher than the 'PEBD, response' health state (0.83 vs 0.761), though the resubmission increased the utility in the 'PEBD, response' health state from 0.659 in July 2024 to 0.761. Within the Facilitated Resolution Pathway Workshop, the significant disutility of stoma in a child was acknowledged. It was suggested that providing additional context as to why utility values are in the direction they are would be required, as at face value these did not make sense regarding the 'no PEBD, no response' health state having higher utility (0.83) than the 'PEBD, response' state. The resubmission reemphasised the disutility associated with stoma. However, the magnitude of difference in comparison to being in response (i.e. pruritus controlled) was not addressed by the resubmission. The utility values applied still implied that patients prefer pruritus (and other symptoms accompanying worsening cholestasis) over achieving a response after PEBD with the associated stoma management, which may not be plausible. However, the impact of this difference was lower than the July 2024 model due to the difference in utility between health states being smaller in the resubmission and the resubmission's model allowing patients in the odevixibat arm to transition to PEBD.

6.43 The key drivers of the model are presented in Table 13.

Table 13: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1] /QALY [a]
PEBD in non-responders	The model assumed that: • odevixibat patients would undergo PEBD at a lower annual rate (1.16%) than SoC patients (5.52%). This difference in risk was constant over the 50-year time horizon, and irrespective of whether a patient responded to odevixibat • The 'PEBD, response' state had a lower utility than the 'no PEBD, no response', • PEBD response rate of 32.3% (OvEC) which was substantially lower than NAPPED data (60.15%).	High, favoured odevixibat. Changing the rate of PEBD in the odevixibat arm to equal SoC increased the ICER by [redacted]% to $[redacted][2]/QALY. Assuming utility of 'PEBD, response' to be the same as 'no PEBD, no response' increased the ICER by [redacted]% Increasing the PEBD response rate to 60.15% increased the ICER by [redacted]%
Starting age	The model base case assumed a starting age of 4.24 years. Due to the weight-based dosing of odevixibat, the drug acquisition costs were sensitive to patient's age. In the financial estimates, prevalent patients were assumed to have a starting age of 13.8 years.	High, favoured odevixibat. Increasing the mean age of prevalent patients to 7.62 years (Cohort 2 of PEDFIC 2) or 13.8 years (as used in the financial estimates) increased the ICER by [redacted]% ($[redacted][3]/QALY) and [redacted]% ($[redacted][4]/QALY), respectively.
Loss of response (i.e. treatment discontinuation)	The resubmission assumed patients would lose response and discontinue odevixibat at a rate of 12.01% per year, increased from 3.52% in the July 2024 submission, based on the 72-week PEDFIC 2 data.	High, a higher discontinuation rate unexpectedly favoured odevixibat (see paragraph 6.38) Reducing the loss of response rate to 3.52% as used in the July 2024 submission increased the ICER by [redacted]% to $[redacted][2]/QALY.
Use of OvEC data	The resubmission maintained the use of OvEC data in the base case which was previously considered by the PBAC to favour odevixibat (paragraph 7.17, odevixibat PSD, July 2024 PBAC meeting).	High, favoured odevixibat A scenario analysis that replaced OvEC inputs with PEDFIC/NAPPED data increased the ICER by [redacted]% to $[redacted][3]/QALY.
Response rate to odevixibat	The resubmission assumed a response rate to odevixibat based on the response rate of patients treated with 40 mcg/kg/day odevixibat in PEDFIC 1 (43.5%), instead of a 'combined' rate of 40 mcg and 120 mcg/kg/day response rate of 62.28% in the July 2024 submission.	Moderate, a lower response rate unexpectedly favoured odevixibat (see paragraph 6.37) Assuming a response rate of 62.28% increased the ICER by [redacted]% to $[redacted][1]/QALY. In a worst-case scenario where odevixibat sBA/pruritus response rate was set to 0% (i.e. a null treatment effect), the model maintained over half of the estimated incremental QALYs (0.64/1.21, 53%), and the ICER decreased by [redacted]% ($[redacted][5]/QALY).

Source: Compiled during evaluation from various sensitivity analysis conducted on the resubmission's economic model
Abbreviations: ICER = incremental cost effectiveness ratio; PEBD = partial biliary diversion surgery; QALY = quality adjusted life year
[a] The proposed price reduction was not applied to the 200mcg capsule formulation. This was corrected during the evaluation.
The redacted values correspond to the following ranges:
[1] *$355,000 to < $455,000*
[2] *$655,000 to < $755,000*
[3] *$555,000 to < $655,000*
[4] *$755,000 to < $855,000*
[5] *$25,000 to < $35,000*

6.44 The results of the base case of the economic evaluation are presented in Table 14. The ESC considered that the base case ICER was not reliable as several key drivers of the model lacked face validity (see Table 13). Given that the RSA annual expenditure caps may not be realised and the '[redacted] cost' may not be achieved, an alternative approach

which removed the '[redacted] cost', allowed patients to dose escalate and applied the combined dose response rate as in the July 2024 economic model (62.28%) is also presented below.

Table 14: Results of the economic evaluation

Component	Odevixibat	SoC	Incremental
Resubmission			
Total costs	$[redacted] [a]	$214,850	$[redacted]
LYG	16.39	15.82	0.57
QALYs	13.19	11.98	1.21
Incremental cost/extra LY gained			$[redacted] [1]
Incremental cost/extra QALY gained			**$[redacted] [2 a]**
Alternative approach: '[redacted] cost' removed, response rate returned to 'combined doses'			
Total costs	$[redacted]	$214,850	$[redacted]
LYG	16.55	15.82	0.73
QALYs	13.44	11.98	1.45
Incremental cost/extra LY gained			$[redacted] [3]
Incremental cost/extra QALY gained			**$[redacted] [4]**
July 2024 Submission			
Total costs	$[redacted]	$219,662	$[redacted]
LYG	18.22	16.69	1.53
QALYs	15.14	12.41	2.73
Incremental cost/extra LY gained			$[redacted] [3]
Incremental cost/extra QALY gained			**$[redacted] [3]**

Source: Table 3-8 of the resubmission, Table 17 odevixibat PSD, July 2024 PBAC meeting and November 2024 odevixibat economic model spreadsheet

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

Note: blue shaded cells reflect values previously considered by the PBAC

[a] The proposed price reduction was not applied to the 200mcg capsule formulation. This was corrected during the evaluation.

The redacted values correspond to the following ranges:

[1] *$755,000 to < $855,000*

[2] *$355,000 to < $455,000*

[3] *> $1,055,000*

[4] *$655,000 to < $755,000*

6.45 If the [redacted]% price reduction offered in the PSCR was applied, the base case ICER decreased from $355,000 to < $455,000 per QALY to $255,000 to < $355,000 per QALY. The [redacted]% price reduction applied to the alternative approach scenario above resulted in an ICER of $655,000 to < $755,000 per QALY.

6.46 The stepped changes from the July 2024 base case to the resubmission's base case is presented in Table 15.

Table 15: **Results of the economic evaluation**

Item	Description	Incremental cost	Incremental QALY	ICER $/QALY	Cumulative change from July 2024 ICER
0	Base case from July 2024 submission	[redacted]	2.73	[redacted][1]	[redacted]%
1	Reduced time horizon to 50 years	[redacted]	2.45	[redacted][1]	[redacted]%
2	Increased utility value for 'PEBD, response' health state (from 0.659 to 0.761)	[redacted]	2.31	[redacted][1]	[redacted]%
3	Reviewed Adverse Event data from updated PEDFIC 2 trial	[redacted]	2.31	[redacted][1]	[redacted]%
4	Increased discontinuation rate from updated PEDFIC 2 trial (from 3.53% to 12.01% per cycle)	[redacted]	1.66	[redacted][2]	-[redacted]%
5	Inclusion of subsequent PEBD for odevixibat treatment group (change from 0% to 1.16% per cycle)	[redacted]	1.45	[redacted][3]	-[redacted]%
6	Revised price (from $[redacted]/mcg to $[redacted]/mcg) [a]	[redacted]	1.45	[redacted][4]	-[redacted]%
7a	Remove costs associated with 120 mcg/kg/day dose [b]	[redacted]	1.45	[redacted][5]	-[redacted]%
7b	'[redacted] Cost' (as for 7A, plus lower response rate from 62.28% to 43.5%)	[redacted]	1.21	[redacted][5]	-[redacted]%

Source: constructed during evaluation using Table 3-7, p58 of the resubmission and the resubmission's economic model excel workbook
Abbreviation: CEA = cost effectiveness analysis; ICER = incremental cost effectiveness ration; PEBD = Partial external biliary diversion
a Includes correction to apply reduction in cost to 200mcg capsules
b Change cell C35 in 'Cost Data' sheet from July 2024 model to 0%.
The redacted values correspond to the following ranges:
[1] *> $1,055,000*
[2] *$755,000 to < $855,000*
[3] *$855,000 to < $955,000*
[4] *$655,000 to < $755,000*
[5] *$355,000 to < $455,000*

6.47 The results of key univariate and multivariate sensitivity analyses around the economic model are summarised in Table 16.

Table 16: Sensitivity analyses

	Inc. Cost	Inc. QALY	ICER ($/QALY)	% Δ
Resubmission Base Case	[redacted]	**1.21**	[redacted][1 a]	**-**
Sensitivity analyses conducted by the resubmission				
Transition probabilities - use PEDFIC/NAPPED data (base case - OvEC)	[redacted]	0.85	[redacted][2]	[redacted]%
Time horizon 40 years (BC= 50 years)	[redacted]	1.11	[redacted][1]	[redacted]%
Discount cost and outcomes = 0% (BC = 5%)	[redacted]	3.08	[redacted][3]	-[redacted]%
Discount cost and outcomes = 3.5% (BC = 5%)	[redacted]	1.54	[redacted][4]	-[redacted]%
Caregiver disutility included (BC = excluded)	[redacted]	1.48	[redacted][4]	-[redacted]%
Societal perspective adopted includes productivity losses (BC = excluded)	[redacted]	1.21	[redacted][4]	-[redacted]%
Age at baseline: 6 months old (BC = mean age of 4.25 years)	[redacted]	1.22	[redacted][4]	-[redacted]%
Additional sensitivity analyses conducted during evaluation				
'[redacted] cost' removed + Dose escalation from 40 mcg to 120 mcg allowed (response rate: combined dose = 62.28%)	[redacted]	1.45	[redacted][5]	[redacted]%
Odevixibat annual loss of response set to 3.53% (BC = 12.01%)	[redacted]	1.70	[redacted][5]	[redacted]%
Odevixibat annual loss of response set to 100%	[redacted]	0.72	[redacted][6]	-[redacted]%
Odevixibat sBA/pruritus response rate set to 62.28% (BC = 43.5%)	[redacted]	1.45	[redacted][1]	[redacted]%
Odevixibat sBA/pruritus response rate set to 0%	[redacted]	0.64	[redacted][7]	-[redacted]%
NAPPED PEBD response of 60.15% (BC = 32.3%)	[redacted]	1.04	[redacted][1]	[redacted]%

	Inc. Cost	Inc. QALY	ICER ($/QALY)	% Δ
Resubmission Base Case	[redacted]	**1.21**	[redacted][1] [a]	**-**
Utility of 'PEBD, response' set to 0.830 to equal 'no PEBD, loss of response' (BC = 0.761)	[redacted]	1.14	[redacted][1]	[redacted]%
6-year time on odevixibat treatment per financial estimates (BC = 3.39 years) [b]	[redacted]	1.45	[redacted][2]	[redacted]%
Annual rate of PEBD in odevixibat arm increased by 1% (BC = 1.16% [PEDFIC 2])	[redacted]	1.05	[redacted][1]	[redacted]%
Annual rate of PEBD in odevixibat arm reduced by 1%	[redacted]	1.40	[redacted][4]	[redacted]%
Annual rate of PEBD in SoC arm increased by 1% (BC = 5.52% [OvEC])	[redacted]	1.30	[redacted][4]	[redacted]%
Annual rate of PEBD in SoC arm reduced by 1%	[redacted]	1.10	[redacted][1]	[redacted]%
Annual rate of PEBD in odevixibat arm changed to equal SoC [c]	[redacted]	0.66	[redacted][5]	[redacted]%
Annual rate of PEBD in SoC arm changed to equal odevixibat [d]	[redacted]	0.57	[redacted][8]	[redacted]%
Starting age set to 7.62 years per the mean age of Cohort 2 in PEDFIC 2 (BC = 4.25)	[redacted]	1.18	[redacted][2]	[redacted]%
Starting age set to 13.8 years per the prevalent patients in the financial estimates	[redacted]	1.12	[redacted][8]	[redacted]%
Multivariate sensitivity analyses				
9% price reduction offered in PSCR + Alternate approach ([redacted] cost, response rate for combined doses + PEBD response utility = no PEBD, no response (i.e. 0.830)	[redacted]	0.99	[redacted][8]	[redacted]%
9% price reduction offered in PSCR + Alternate approach ([redacted] cost, response rate for combined doses + PEBD response utility = no PEBD, no response (i.e. 0.830) + Caregiver utilities included	[redacted]	1.27	[redacted][5]	[redacted]%

Source: Table 3-11 p60 of the resubmission and conducted during evaluation.
Abbreviations: BC = base case; QALY = quality adjusted life year; SOC = standard of care; PEBD = Partial external biliary diversion; LT = liver transplant;
a Corrected to include the cost reduction of 200 mcg capsules. Drug cost per pack list price in 'Cost data' E40 changed from $[redacted] to $[redacted] per Table 1.4.2.
b The model's base case discontinuation rate (12.01%; PEDFIC 2 72-week analysis) was reduced until a 6-year time on treatment (no PEBD, response) was met. The was reached with an annual probability of discontinuing of 6.67% in Cell K32, 'Clinical data – Efficacy'.
e Annual probability of PEBD in the odevixibat arm (G49:G50, ' Clinical data – Efficacy') set to equal that of the SoC arm (Column AA in 'OvEC data', 5.5202%).
c Column AA in OvEC data set to equal the annual probability of PEBD in the odevixibat arm (1.16%).
d Annual probability of PEBD in the odevixibat arm (G49:G50, ' Clinical data – Efficacy') set to equal that of the SoC arm minus 1% (Column AA in 'OvEC data', 5.5202%) – 1%.
The redacted values correspond to the following ranges:
[1] *$355,000 to < $455,000*
[2] *$555,000 to < $655,000*
[3] *$155,000 to < $255,000*
[4] *$255,000 to < $355,000*
[5] *$655,000 to < $755,000*
[6] *$35,000 to < $45,000*
[7] *$25,000 to < $35,000*
[8] *$855,000 to < $955,000*

6.48 The ESC noted that the base case ICER presented in the resubmission was likely underestimated, favoured odevixibat and was highly sensitive to changes in a number of inputs. The ESC also noted that the mean duration of treatment with odevixibat at 3.39 years was likely underestimated (see Table 18). The ESC considered that this also reduced the ICER.

6.49 Overall, the ESC considered that the economic model presented in the resubmission was not reliable for decision making as it lacked face validity regarding the change in ICER relative to the response rate and discontinuation rate of odevixibat (see paragraphs 6.37 and 6.38) and was driven by implausible structural assumptions and uncertainty in data inputs.

6.50 The ESC considered that an incremental cost per responder analysis might provide a reasonable alternative assessment of cost-effectiveness. The ESC noted that the PBAC has previously considered that cost per responder analyses were acceptable in the context of difficult to treat and relatively uncommon diseases and given the significant improvements in quality of life and symptom control that 'response' appeared to represent in this context.

6.51 The ESC noted the incremental cost per responder analyses based on the clinical outcomes in the PEDFIC 1 trial at 24 weeks and the price proposed in the PSCR presented in Table 17. The ESC noted that, given the weight-based dosing for odevixibat, the incremental cost per patient would be higher for older (heavier) patients.

Table 17: Cost and clinical outcome ratios: PEDFIC 1, mean age = 3.2 years (15.5 kg)[1]

Step and component	Odevixibat	Placebo	Increment
Odevixibat 40 mcg/kg/day			
Odevixibat cost per year[2]	$[redacted]	-	
Proportion of patients with an sBA response[3]	43.5%	0%	44.1%
Proportion of patients with a pruritus response[4] for ≥50% of the time	73.9%	20%	53.9%
Incremental cost per patient with an sBA response at 24 weeks [($[redacted]/52*24)/0.441]			$[redacted][a]
Incremental cost per patient with a pruritus response for ≥50% of the time at 24 weeks [($[redacted]/52*24)/0.539]			$[redacted][b]
Odevixibat 120 mcg/kg/day			
Odevixibat cost per year[5]	$[redacted][5]	-	
Proportion of patients with an sBA response[2]	21.1%	0%	21.6%
Proportion of patients with a pruritus response[3] for ≥50% of the time	47.4%	20%	27.4%
Incremental cost per patient with an sBA response at 24 weeks [($[redacted]/52*24)/0.216]			$[redacted][c]
Incremental cost per patient with a pruritus response for ≥50% of the time at 24 weeks [($[redacted]/52*24)/0.274]			$[redacted][d]

1. From published PEDFIC1 paper (Thompson 2022)
2. 40 mcg/kg/day x 15.5 kg x $[redacted]/mcg x 365.25
3. defined as ≥70% reduction in fasting sBA concentration from baseline to the end of treatment or reaching a level ≤ 70 µmol/L; results from Table 6
4. defined as a scratching score of ≤1 or at least a 1-point reduction from baseline on the Prucision ObsRO, results from Table 6
5. 120 mcg/kg/day x 15.5 kg x $[redacted]/mcg x 365.25

The redacted values correspond to the following ranges:

[a] *$95,000 to < S115,000*
[b] *$75,000 to < $95,000*
[c] *$555,000 to < $655,000*
[e] *$455,000 to < $555,000*

6.52 For the PBAC to rely on an ICER presented as a cost per responder it will need to value the benefits associated with a response. The ESC considered interpretation of the ICER

in the context of previous PBAC considerations would also be informative for the PBAC.

6.53 The pre-PBAC response stated that cost per responder analyses may oversimplify the complexity of issues and may not reflect a comprehensive value assessment as a cost per QALY analysis does. Further, the pre-PBAC response asks that the clinical value of a response be considered, as odevixibat significantly (i) reduces bile acid levels compared to placebo, which may be associated with a prolonged native liver survival; (ii) improves pruritus compared to placebo; and (iii) improves event-free survival in patients with PFIC.

Drug cost/patient/year

Table 18: Drug cost per patient for proposed and comparator drugs based on PEDFIC 2

	Odevixibat (40mcg/kg/day) [a]			
	Trial dose and duration	**Model**	**Financial estimates (RSA '[redacted] cost')**	
Mean duration	115.62 weeks [b] (2.22 years)	3.39 years	6 years	
Cost/patient/year	$[redacted] [c]	$[redacted] [d]	Responders $[redacted] (incident) [e] $[redacted] (prevalent) [f]	Non-responders $[redacted] (incident) [g] $[redacted] (prevalent) [h]

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

[a] A [redacted] cost was assumed for each estimate, i.e. [redacted] patients were assumed to receive 40mcgkg/day, per the resubmission's economic model assumptions and the proposed risk share arrangement. However, should the risk share arrangement not be realised, the shown cost/patient/year would be an underestimate.

[b] Mean duration of exposure in PEDFIC 2

[c] Cost per patient over the trial period was based on the mean baseline weight of 20.7 kg in PEDFIC 2 (n=116) and the corresponding daily cost from the model was $[redacted]/day for the 40mcg/kg/day dose. Cost at the 40mcg dose = (115.62 weeks x 7) x $[redacted] = $[redacted] divided by 2.22 years.

[d] Undiscounted cost of response state divided by time spent in response state for odevixibat arm = $[redacted]/ 3.39 years

[e] Cost per patient was based on the mean 400mcg daily cost (per the 'general population' sheet in the economic model) of an incident patient aged four (in year 1) to nine (in year 6), per the weight distribution estimates in the resubmission ($[redacted]/day). Responders were assumed to be treated for 12 months per year. The cost/patient/year = $[redacted] x 365.25

[f] Cost per patient was based on the mean 400mcg daily cost (per the 'general population' sheet in the economic model) of a prevalent patient aged 13 (in year 1) to 18 (in year 6), per the weight distribution estimates in the resubmission ($[redacted]/day). Responders were assumed to be treated for >12 months. The cost/patient/year = $[redacted] x 365.25.

[g] Cost per patient was based on the mean 400mcg daily cost (per the 'general population' sheet in the economic model) of an incident patient aged four, $[redacted]/day. Non-responders were assumed to be treated for 6 months. The cost/patient/year = $[redacted] x (365.25/2).

[h] Cost per patient was based on the mean 400mcg daily cost (per the 'general population' sheet in the economic model) of a prevalent patient aged 13, $[redacted]/day). Non-responders were assumed to be treated for 6 months. The cost/patient/year = $[redacted] x (365.25/2)

6.54 The cost per patient receiving 40 mcg/kg per year varied between the PEDFIC 2 trial, economic model, and the financial estimates. The difference in cost per patient per year were due to differences in the treatment duration of odevixibat (2.22 years vs 3.39 years vs 6 years in the trial, model and financial estimates, respectively), and differences in the mean age of patients, which impacts the weight-based dosing. The mean baseline age of patients in Cohort 2 of the PEDFIC 2 study (n=60) was 7.62 years, versus the model starting age of 4.25 years, and the financial estimates which assumed a mean age of 13.8 for prevalent patients, and 4 years for incident patients. The estimates assumed a '[redacted] cost' for patients receiving the 120 mcg/kg dose. If the expenditure caps in the resubmissions proposed RSA are not met, then the cost per patient per year would be higher.

6.55 The ESC noted that, in Year 1 of the financial model (using the price proposed in the PSCR and without implementing a ||| cost) the annual cost per responding prevalent patient at the 40 mcg/kg/day dose was $|[5] and at the 120 mcg/kg/day dose was $|[6].

Estimated PBS usage & financial implications

6.56 This resubmission was not considered by DUSC. In July 2024 the DUSC (Table 21, odevixibat PSD, July 2024 PBAC meeting) considered that the submission had likely overestimated the number of prevalent and incident patients as:

- Prevalence should not apply to entire population, but to the population aged 0-19 years and adult patients estimated separately; and
- An estimate of 2-3 incident patients per year based on applying 0.07/10,000 live births may be more reasonable than the 6 patients per year estimated.

As the resubmission applied the same method for estimating prevalence, the same likelihood of overestimation remains. However, the number of incident patients was reduced to 4 per year to align with the Facilitated Resolution Pathway Workshop discussion.

6.57 As in the July 2024 submission, the resubmission used an epidemiological approach to estimate the use and financial implication of listing odevixibat. The key data inputs and sources used to inform the financial estimates are presented in Table 19.

Table 19: Key inputs for financial estimates

Parameter	July 2024 submission	DUSC/PSD comment	Resubmission/Evaluation Comment
Prevalent patients	The PFIC prevalence rate of 0.07 per 10,000 people presented by Baker et al (Baker et al 2019) was used to estimate the Australian prevalent PFIC population.	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 LT or have died and considered that the utilisation in adults should be estimated separately. (Table 21, odevixibat PSD, July 2024 PBAC meeting)	The rate of 0.07 per 10,000 was maintained for the entire population, which appeared inconsistent with DUSC advice, and may overestimate the prevalent adult population. The DUSC previously noted that the prevalence estimate of 0.07 per 10,000 people was likely derived by multiplying the reported incidence of intrahepatic cholestasis (1 per 18,000 live births) by the estimated prevalence of PFIC among intrahepatic cholestasis patients (12.9%).
Incident patients	The PFIC incident patient population of 1 in every 50,000 was calculated from the rate presented by Davit Spraul 2009.	DUSC considered that the incidence rate may be overestimated. DUSC considered an estimate of 2-3 per year may be more reasonable than the estimated number of 6 in the submission (Table 21, odevixibat PSD, July 2024 PBAC meeting).	An incidence rate of 4 patients per year, an average of the two estimates was adopted in the resubmission.

[5] 63.39 packs of 400 mcg x $5,070.60
[6] 63.39 packs of 1200 mcg x $14,886.60

Parameter	July 2024 submission	DUSC/PSD comment	Resubmission/Evaluation Comment
PFIC2 *BSEP3* Subtype	The PFIC2 *BSEP3* genetic subtype group was excluded from patient estimates in the July 2024 submission. The proportion of patients with PFIC2 *BSEP3* (7%) was based on Alsohaibani 2023 and Van Wessel 2020.	The proposed restriction did not exclude patients according to PFIC subtype. DUSC considered this without genetic testing, patients with non-responsive subtypes were likely to initiate, but not response after 3 months of treatment. DUSC considered these estimates could instead inform continuation rates. (Table 21, odevixibat PSD, July 2024 PBAC meeting). 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.	The resubmission included these patients but proposed to rebate the cost of treating these patients under the proposed RSA. Only the PFIC2 *BSEP3* subtype was considered in estimating the number of genetic non-responders, and potentially underestimated based on NAPPED data.
Prior PEBD and LT	In the July 2024 submission, patients with prior PEBD or LT were excluded based on sponsor assumption: • % who have undergone previous PEBD = 50% • % who have undergone previous LT = 80%	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 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 (Table 21, odevixibat PSD, July 2024 PBAC meeting).	All patients with prior LT and prior PEBD remained excluded from the prevalent pool. [a] The percentage of patients with prior PEBD or LT was reduced from 50% and 80% in the July 2024 submission to 37.3% and 54.1%, respectively. This was based on a weighting prior PEBD or LT in patients 19 and under years of age (75% of the population) and over 20 years of age.
Responders and non-responders	The July 2024 submission used an overall response rate of 58%, with 43.5% assumed to respond to the 40 mcg/kg dose, based on PEDFIC 1 24-week response, and an additional 14.5% [c] assumed to escalate and respond to 120mcg/kg	DUSC noted that patients with other subtypes with unknown response will be eligible to initiate treatment thus, 43.5% might be an overestimate [of response] (Table 21, odevixibat PSD, July 2024 PBAC meeting) DUSC also noted that 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 and was therefore uncertain (Table 21, odevixibat PSD, July 2024 PBAC meeting).	A combined response rate of 58% as used in the July 2024 financial estimates was applied in the resubmission. This was inconsistent with both the resubmission's economic model which used 40 mcg/kg 22-week response rates from PEDFIC 1 (43.5%); and the 'doses combined' OvEC value of 62.28% used in the July 2024 economic model.

Parameter	July 2024 submission	DUSC/PSD comment	Resubmission/Evaluation Comment
Treatment duration	The July 2024 submission presented three treatment scenarios: 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	Initial and continuing treatment durations were not specified in the proposed restriction and may not be reasonable. (Table 21, odevixibat PSD, July 2024 PBAC meeting)	The same treatment durations were assumed in the resubmission. The 72 month (6 years) continuing treatment for responders remains inconsistent with the duration of treatment of responders over the first six years in the economic model (3.82 years). This may have led to an overestimate of the financial impact Under the proposed expenditure caps in the resubmission, treatment scenario two was appropriately not included. 'Relapsing PFIC' patients, which are expected by the resubmission to utilise a 6-month initial treatment period were not considered. Additionally, recommencement of initial treatment, which is allowed in the proposed restriction (see paragraph 3.13) was not considered
Mean age (units dispensed)	The July 2024 submission assumed the mean age of prevalent patients was 12 years and for incident patients it was 4 years (assumed from the model).	DUSC noted that the median age in PEDFIC 1 was 3.2 years, and that in PEDFIC 2 Cohort 2 the mean age of patients was 7.8 years. DUSC considered using a mean age of 12 years may overestimate utilisation. (Table 21, odevixibat PSD, July 2024 PBAC meeting)	The prevalent patient age was increased from 12 to 13.8 years based on early access data as per the Workshop outcomes (item 5.5) but DUSC had previously considered that the submission had overestimated the average age of prevalent patients at initiation of treatment (paragraph 6.80, odevixibat PSD, July 2024 PBAC meeting). A higher starting age would lead to a higher financial estimate due to more odevixibat being used. It was uncertain whether the mean age of the EAP (n=12) [b] would be reflective of the mean age for the entire prevalent pool.
Compliance and uptake	100% compliance and uptake rate assumed.	Likely conservative but consistent with the model (Table 21, odevixibat PSD, July 2024 PBAC meeting)	Unchanged and consistent with the economic model, however, treatment interruptions due to TEAEs in PEDFIC 2 were reported in 39/116 (34%) patients. Therefore 100% compliance may be an overestimate.
Grandfathered patients	The July 2024 submission included [redacted]1 patients from a compassionate access program.	DUSC considered it was reasonable to assume that grandfathered patients will all continue treatment (Table 21, odevixibat PSD, July 2024 PBAC meeting)	This assumption was unchanged in the resubmission.

Source: Table 21, odevixibat PSD, July 2024 PBAC Meeting, Table 37, p190 of PEDFIC 2 CSR 72-week analysis
Abbreviations: *BSEP* = bile salt export pump; DUSC = drug utilisation sub-committee; EAP = early access program; LT = liver transplant; PEBD = partial external biliary diversion; PFIC = progressive familial intrahepatic cholestasis; SoC = standard of care; TEAE = treatment emergent adverse event; RSA = risk share arrangement
a In the resubmission's financial model it was noted that '5% of prior PEBD [or prior LT] would benefit from treatment (clinical input from Facilitated Workshop)', and two additional eligibility proportions (98.14% and 97.3%, respectively) were applied to the overall eligibility. It was unclear how these proportions were calculated, and the application effectively reduced overall eligibility by 4.56% ([1-0.9814] +[1-0.973]).
b Patient numbers extracted from the 'Calculation for prior LT and PEBD eligibility based on EAP patient data' in the resubmission's

financial model which had <500 patients age >20 years and <500 patients age ≤19 years.
c Calculated as 24.5% x 58% where 24.5% = % high dose (internal data and PEDFIC response) and 58% = total responders
The redacted values correspond to the following ranges:
[1] < 500

6.58 The resubmission made the following changes based on input at the Facilitated Resolution Pathway Workshop:

- The total proportion of prevalent patients assumed to have prior LT was reduced from 80% to 54.1%, due to prior LT rates in the under 20 population being reduced to 45.5% from van Wessell 2020;
- The total proportion of prevalent patients assumed to have prior PEBD was reduced from 50% to 37.3%, due to prior PEBD rates in the under 20 population being reduced to 23% from van Wessell 2020;
- The number of incident patients was reduced from 6 per year to 4 per year;
- Patients with the PFIC2 *BSEP3* subtype, which were previously excluded, were included in the resubmission; and
- The age of prevalent patients was increased from 12 to 13.8 years, based on early access data (n=12).

6.59 The number of eligible prevalent patients was increased in the resubmission from <500 to <500 patients largely due to the reduction in the assumed proportion of prevalent patients with prior LT or prior PEBD surgery (see paragraph 6.58). All patients with prior LT or PEBD were excluded from the prevalent pool. It was acknowledged at the Facilitated Resolution Pathway Workshop that the changes to prior LT and prior PEBD rates would increase the eligibility and prevalent population. However, the ESC noted that DUSC has previously considered that the July 2024 submission had likely overestimated the number of prevalent and incident patients (see paragraph 6.56), and that applying the prevalence rate of 0.07 per 10,000 persons to the adult population may not have been appropriate. Therefore, it was unclear whether the increase in eligible patients was reasonable without any adjustment to the overall prevalence pool.

6.60 The mean age of prevalent patients was increased in the resubmission from 12 to 13.8 years, based on early access program data (n=12, individual patient ages not reported). This was noted in the Facilitated Resolution Pathway Workshop discussion document as being considered a reasonable approach. However, DUSC has previously considered that the average age at initiation (which was 12 years in the July 2024 submission) may overestimate utilisation for prevalent patients (Table 21 and paragraph 6.80, odevixibat PSD, July 2024 PBAC meeting). The mean age of prevalent patients remains highly uncertain as:

- Data from the early access program (n=12) may not be reflective of the entire prevalent pool;

- the proposed restriction does not limit the age of initiation, and the impact of 'episodic PFIC' patients over the age of 18 (see paragraph 4.4) on the prevalent pool was not considered by the resubmission; and
- the mean age of Cohort 2 in the PEDFIC 2 trial (n=60) was 7.62 years, with a median age of 4.75 years.

6.61 The estimated use and financial impacts of listing odevixibat as well as the proposed expenditure caps are summarised in Table 20.

Table 20: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Prevalent and incident patients						
Prevalent patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of patients eligible						
Prevalent patients	[redacted][1c]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Scripts (100% compliance and uptake)						
Total scripts [b]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net cost to PBS/RPBS						
Odevixibat	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Other medicines	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Net impact	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net impact (model corrected) [a]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Proposed annual expenditure caps	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
July 2024 submission						
Prevalent and incident patients						
Prevalent patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of patients eligible						
Prevalent patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Scripts (100% compliance and uptake)						
Total scripts	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net cost to PBS						
Odevixibat	[redacted][4]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][4]
Other medicines	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Net impact to PBS	[redacted][4]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][4]

Source: Table 4-2 and 4-5, p67 of the resubmission. Table 22, p45 odevixibat PSD, July 2024 PBAC Meeting.
Abbreviations: PBS = pharmaceutical benefits scheme; RPBS = repatriation pharmaceutical benefits scheme
Note: The resubmission appeared to have used the weight distribution of an 18 year old in year 6 of the incident patient dosage estimates. This was corrected during evaluation (Cell K210:K218 returned to July 2024 values).
[a] During the evaluation, it was noted that there was an error in the financial workbook in regard to the duration of treatment groups for affected medicines which was corrected
[b] Assuming <500 or <500 scripts per year for incident and prevalent patients respectively, treated with the 200mcg and 400mcg capsules; and <500 or <500 scripts per year for incident and prevalent patients respectively, treated with the 400mcg and 1200mcg capsules. Initial and continuing treatment durations of 3 and 72 months, respectively were assumed.
[c] <500 patients treated with 40 mcg/kg/day, <500 patients treated with 120 mcg/kg/day and <500 patients treated with 120 mcg/kg/day but do not respond.
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *500 to < 5000*
[3] *$20 million to < $30 million*
[4] *$10 million to < $20 million*
[5] *net cost saving*
[6] *$0 to < $10 million*

6.62 Odevixibat was estimated to cost (without the proposed annual expenditure caps) $20 million to < $30 million in Year 1, followed by $10 million to < $20 million in Year 2 and increasing to $10 million to < $20 million by Year 6 and totalling $100 million to < $200 million over the first 6 years ($80 million to < $90 million under the proposed RSA). This initial decrease in Year 2 was attributed to discontinuation of

treatment after Year 1 due to non-response in prevalent patients, who comprised the majority of patients treated in year 1.

6.63 The ESC noted that the age agnostic listing and the extension of the restriction to allow for treatment of patients with more benign episodic disease, without any confirmation via genetic testing, greatly increased the uncertainty around the financial estimates. Overall, the ESC considered that the resubmission's financial estimates remained highly uncertain and were likely overestimated as:

- The number of prevalent and incident patients may be overestimated based on previous DUSC advice;
- The combined 40 mcg/kg and 120 mcg/kg response rate of 58% (43.5% + 14.5%) remains uncertain because, as previously noted by ESC and DUSC, the response of patients who up-titrated could not be verified and as patients with other non-responder subtypes will be eligible to initiate treatment (Table 21, odevixibat PSD, July 2024 PBAC meeting);
- The mean age of prevalent patients was uncertain (see paragraph 6.60), and could result in higher or lower utilisation, depending on the direction of change;
- The assumed treatment duration of 6.25 years was uncertain as it exceeded that in the economic model's mean treatment duration of 3.39 years;
- 100% compliance was assumed for all patients. The ESC, noting that 34% of patients in PEDFIC 2 experienced dose interruptions due to adverse events, considered that this was overestimated;
- The estimates assumed that no treatment responders would discontinue treatment over the financial estimates. The ESC considered that this was unreasonable, particularly as 28% (<500/<500) of patients discontinued treatment over 2.2 years in PEDFIC2 (i.e., an average of 12% per year); and
- The estimates assumed an uptake of 100% in eligible patients from Year 1.

6.64 The ESC noted the financial model assumed one pack of odevixibat per script (see calculations in rows 296 to 311 in 3c. Impact – proposed (eff) worksheet); however, the requested listing was for 6 or 12 packs per script. This will overestimate the markups and AHI fees per script and overestimate the patient copayments.

Quality Use of Medicines

6.65 The resubmission did not present any information regarding the quality use of medicines. Given the cost of odevixibat and the financial risks associated with use outside the proposed restriction, this may not be reasonable.

Financial Management – Risk Sharing Arrangements

6.66 Within their July 2024 review of odevixibat in PFIC, the PBAC considered that an RSA would be required, given the level of uncertainty in the estimates, including

uncertainty in the duration of use and uptake (paragraph 7.23, odevixibat PSD, July 2024 PBAC Meeting).

6.67 The resubmission proposed an RSA in the form of annual expenditure caps for the first five years of listing. The resubmission proposed that the annual expenditure caps be adjusted for the treatment cost for patients escalating to the higher 120 mcg/kg dose from 40 mcg/kg. The purpose of this cap would be to maintain the cost for patients escalating to the 120 mcg/kg dose at the cost per patient as the 40 mcg/kg dose i.e. a 'cost'. In addition, as the resubmission argued genetic testing should not be a requirement for access to treatment, the expenditure cap would accommodate the eligibility of likely genetic non-responders, namely the PFIC2 *BSEP3* subtype. The resubmission stated that the annual expenditure caps are informed by DUSC / PBAC guidance on the utilisation estimates with a % rebate payable for Commonwealth expenditure above the caps.

6.68 The resubmission proposed a formal review of the annual expenditure caps via submission to the PBAC after 2 to 3 years to inform potential adjustments to the caps. Notably, as the dosage is weight based and incident patients are likely to be children, the cost in the first five years of listing (covered by the RSA) will be the lowest for all incident patients and will only increase over time, though the number of prevalent patients remaining on treatment could theoretically decrease over time. However, as discussed in paragraphs 3.12 and 3.13, there is nothing in the restriction which requires patients to stop treatment if they achieved a response with initial treatment but subsequently lost response, nor any criteria which prevents non-responders from re-initiating odevixibat. Further, the ESC noted that use in 'episodic PFIC' was not considered. As such, the cost beyond the five-year RSA remains uncertain.

6.69 The proposed annual expenditure caps were calculated by the resubmission from the base case by removing likely genetic non-responders (i.e. PFIC2 *BSEP3* subtype but not PFIC5) from the eligibility criteria (assumed to make up 7% of the prevalent pool) and incorporating a 'cost' by assuming % of patients would remain on the 40 mcg/kg dosage. However, this means that if the utilisation was lower than the assumptions used to generate the expenditure cap, the cap would not be exceeded and the proposed 'cost' would not be achieved.

6.70 During consideration by the ESC, it was noted that there was an error in the financial estimates model used for the proposed annual expenditure caps which assumed patients who do not respond to treatment in Year 1 (i.e. non-responders) continue to incur the cost of the 120 mcg/kg/day dose. In Year 1, the model assumed patients would incur the costs associated with the 1200 mcg strength capsules (cell F31 of sheet 3a). This was unable to be corrected for the ESC advice, but significantly overestimated the cost in Year 1. The expenditure caps in subsequent years were also overestimated as 12 prescriptions per year were assumed for patients continuing to receive 600 mcg capsules and 14 prescriptions per year were assumed for patients continuing to receive 1200 mcg capsules.

6.71 The calculation of the annual expenditure caps is shown in Table 21. These expenditure caps were based on the resubmission's financial estimates which include the error in the weight distribution of incident patients and the error regarding non-responders continuing to receive treatment at the 120 mcg/kg/day dose (see paragraphs 6.61 and 6.70).

Table 21: Calculation of annual expenditure caps

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Net impact (SPA - Effective Price) [a]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Exclusion of genetic non-responders (PFIC 2 *BSEP3*) [b]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
[redacted] cost	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Proposed annual expenditure caps [c]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]

a Uncorrected for the incident patient weight distribution, as presented in the resubmission
b Proportion eligible for odevixibat (no *BSEP3*) reduced from 100% to 93% in 2a. Patients – Incident and 2b. Patients – prevalent
c Both exclusion of genetic non-responders and the [redacted] 40 mcg/kg dosage applied.
The redacted values correspond to the following ranges:
[1] *$20 million to < $30 million*
[2] *$10 million to < $20 million*

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for odevixibat for the treatment of progressive familial intrahepatic cholestasis (PFIC). The PBAC requested draft restrictions which considered revisions to the following aspects: prescriber type for adults, instrument used for assessing pruritus, and criteria for ceasing treatment if no response, for retreatment and for dose escalation. The PBAC considered a reduced price for odevixibat would be required as it was not cost-effective at the price proposed in the resubmission. The PBAC requested revised financial estimates as they were overestimated and hence, when used as a basis for risk sharing arrangement, did not adequately manage the risk of dose escalation which would not be cost-effective, as well as continued use in non-responders.

7.2 The PBAC recognised that there is a high clinical need for treatment of this ultra rare condition. The PBAC noted the outcomes from the Facilitated Workshop which was held in September 2024. The PBAC noted that there was significant patient and clinician input at the Workshop relating to the symptoms of disease and the proposed patient population and PBS restriction criteria. The PBAC also noted and welcomed the consumer comments provided in support of odevixibat. The comments described the significant burden PFIC has on the quality of life of patients, carers and their families. The PBAC noted the comments received indicated that treatment with odevixibat improved both the symptoms of disease, such as severe itch, as well complications of the disease, such as anxiety, sleep, appetite, growth and energy and reduced the need for hospitalisations and surgical interventions. The PBAC further noted that adverse events associated with odevixibat were considered tolerable by

patients.

7.3 The PBAC noted that a number of the changes proposed at its July 2024 meeting and discussed at the Facilitated Workshop were incorporated into the restrictions. The PBAC noted that the revised restrictions expanded the eligible population to include patients diagnosed with PFIC as adults with the listing being age agnostic which would allow use in those with episodic disease who would likely use odevixibat intermittently. The PBAC considered that this may not be unreasonable, as it would allow greater patient access in this ultra rare disease, but noted that, as there was no clinical evidence for patients diagnosed as adults or for those with episodic disease, the cost effectiveness in this population was unknown. The PBAC considered that additional changes to the restrictions would be required to ensure that the appropriate patients received treatment, including:

- That the proposal in the pre-PBAC response to restrict initiation of treatment in adult patients to specialist hepatologists working in liver transplant centres would be appropriate to prevent use in other cholestatic liver diseases, particularly as adult patients will be older, and therefore heavier and require a higher dose of odevixibat
- Review of the ObsRO Pruritus Scale which was used to assess pruritis at treatment initiation and for continuation of therapy. The PBAC was concerned about the rigour of the ObsRO Pruritus Scale, particularly in terms of the assessment for continuing therapy, as it relied on the response to one question. Overall, the PBAC considered that the ObsRO Pruritus Scale would be subject to high variability and may not provide a meaningful measure of response. The PBAC noted that the pre-PBAC response advised that the sponsor was agreeable to alternatives to the ObsRO Pruritus Scale, as long as there was no undue burden on prescribers, patients or caregivers, but did not provide an alternative measure.
- Although the continuing restriction required patients to have an adequate clinical response to initial treatment, there was no requirement for patients to continue to demonstrate a benefit to receive continuing therapy. The PBAC considered that the continuing restriction should include a stopping rule to ensure that treatment only continues for as long as a positive pruritus response is maintained
- Amendments to the retreatment restriction to ensure only patients who have previously benefited from treatment and who stopped treatment for reasons other than loss of response could be retreated
- The criteria for, the timing of, and assessment of response to, dose escalation is clear. Dose escalation should be allowed to occur between 1-3 months after initiation and the continuation criteria should be met at 6 months post initiation of treatment.

7.4 The PBAC accepted that genetic testing for PFIC was inconclusive in some patients and considered that it was not required as a criterion for initial treatment. The PBAC noted

that costs of odevixibat in patients with a genetic subtype known to be unlikely to respond were appropriately removed from the expenditure caps in the proposed RSA (see paragraph 7.18).

7.5 The PBAC requested, if possible, review of the revised restrictions by clinical specialists, including those who attended the Facilitated Workshop, prior to PBAC reconsideration.

7.6 The PBAC noted the resubmission was again 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)).

7.7 The PBAC noted that updated data from the PEDFIC 2 study (a single arm study in which all patients received 120 mcg/kg/day) were presented. The PBAC noted that the updated data aligned with those previously presented.

7.8 The PBAC recalled that it had previously 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 (it only provided 24 weeks of comparative data).
- the claim of superior effectiveness against standard of care (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.
- the clinical claim that odevixibat is non-inferior in terms of safety to SoC to be inadequately supported, given the lack of comparative data.

7.9 The PBAC noted that no clinical evidence was provided for patients diagnosed with PFIC as an adult or for patients with episodic disease. Therefore, the PBAC was unable to determine the effectiveness or safety of odevixibat in these patients.

7.10 The PBAC noted that the resubmission presented a revised economic model that partially addressed the issues identified in July 2024 (see Table 2). The PBAC recalled that it had previously considered that the economic model was biased in favour of odevixibat and that odevixibat would not be cost effective without revisions to the economic model and a significant price reduction. The PBAC noted that the revised economic model presented in the resubmission resulted in an ICER of $355,000 to < $455,000 per quality adjusted life year (QALY). However, the PBAC noted that only the 40 mcg/kg/day dose was captured in the base case ICER, and if the cost and response of the 120 mcg/kg/day dose was included, the ICER increased to $655,000 to < $755,000 per QALY.

7.11 The PBAC noted that the revised model was sensitive to the response and loss of

response rates applied. The PBAC noted that, if response was increased, the ICER paradoxically increased, while assuming a lower loss of response, again paradoxically, increased the ICER. The PBAC also noted that the model assumed an average duration of treatment of 3.39 years, which was likely underestimated and which favoured odevixibat. The PBAC considered that the base case economic model presented in the resubmission could not be used to assess the cost-effectiveness of odevixibat. Noting the available clinical evidence, which reflected the rarity of the disease, the PBAC considered that the uncertainty with the cost-effectiveness was unlikely to be adequately resolved with further revision to the model inputs.

7.12 The PBAC acknowledged the high and urgent clinical need for effective PFIC treatments in the context of this ultra rare and life-limiting disease and the importance of clinical gains in reducing the need for surgery, including liver transplantation, as well as the significant quality of life improvements for patients and carers associated with reduced pruritus. The PBAC reflected on previous determinations made for other rare diseases. The PBAC compared the current resubmission in terms of the nature of the benefits with odevixibat, estimated ICERs and the number of patients expected to be treated with other treatments for rare diseases recommended for funding on the PBS. The PBAC noted that the ESC had considered that a cost per responder analysis might provide a reasonable alternative assessment of cost-effectiveness. The PBAC recalled that it had previously considered that cost per responder analyses were acceptable in the context of difficult to treat and relatively uncommon diseases. The PBAC noted that, based on the results of the PEDFIC 1 trial, the incremental cost per patient with a serum bile acid (sBA) response at 24 weeks for a 15.5 kg paediatric patient ranged from $ when receiving the 40 mcg/kg/day dose to $ when receiving the 120 mcg/kg/day dose. Given the weight-based dosing for odevixibat, the PBAC noted that the incremental cost per patient would be higher for prevalent patients who would be older, and therefore heavier.

7.13 The PBAC considered that in order to accept the value proposition, in the context of the high degree of uncertainty and bias in the economic model, and the potential long-term use of odevixibat, a price reduction would be required. Noting the estimated cost per responder was high compared with that previously accepted for other chronic therapies, the PBAC considered that for odevixibat to be considered cost effective the cost per patient per year would need to be in the order of $ for an average prevalent patient receiving 40 mcg/kg/day dosing. The PBAC noted that the average age of a prevalent patient entering the model was assumed to be 13 years and the average dose was 4.51 x 400 mcg tablets per day. The PBAC noted that dose escalation to the 120 mcg/kg/day dose would need to be managed by the RSA. Overall, the PBAC considered that this would be consistent with that for previously recommended treatments for ultra rare diseases funded on the PBS, when accounting for the clinical need, available evidence, nature of the benefits, range of estimated ICERs and size of the patient population so long as the financial estimates and RSA managed the risk of non-cost-effective use (i.e. those with non-responsive disease or requiring dose

escalation) and the risk of use where the cost effectiveness was unknown (i.e. patients diagnosed with PFIC as an adult and those with episodic disease).

7.14 In terms of the utilisation estimates, the PBAC noted that the number of incident patients with PFIC was decreased from 6 in the July 2024 submission to 4 in the resubmission and considered that this was reasonable.

7.15 The PBAC noted however, that the prevalent population was increased from <500 in the July 2024 submission to <500 in the resubmission due to changes in the proportion of patients with prior liver transplant or PEBD surgery to account for different rates in children and adults (which was then applied as a weighted rate across the prevalent population). The PBAC considered that although the changes in liver transplant and PEBD surgery were reasonable, it would be more appropriate to estimate use separately for children and adults. The PBAC noted that PFIC and Related Disorders, Australia stated that the prevalent adult population was likely to be approximately 10 patients.

7.16 The PBAC also considered that the financial impact of odevixibat was overestimated as the estimates assumed % uptake in Year 1 and 100% compliance for all patients. The PBAC considered that an uptake of % was uncertain and noted that treatment interruptions due to adverse events occurred in 34% of patients in PEDFIC 2.

7.17 The PBAC noted that patients diagnosed with PFIC as an adult and those with episodic disease were not included in the utilisation estimates. The PBAC considered that this was reasonable as no clinical evidence was provided for these patients.

7.18 As noted above, the resubmission proposed that cost associated with dose escalation from 40 mcg/kg/day to 120 mcg/kg/day would be managed through the RSA. In the absence of clinical data supporting dose escalation, the PBAC considered that flat pricing across doses would be the most appropriate way to manage this risk. However, in the absence of flat pricing, the PBAC considered managing this risk in the RSA was appropriate. The PBAC accepted that genetic testing for PFIC was inconclusive in some patients and noted that use in patients who had subtypes of disease known to be non-responsive were appropriately removed from the proposed RSA expenditure caps.

7.19 The PBAC considered that the sponsor should provide a revised cost-effective price for odevixibat, as per paragraph 7.13. This price should be included in revised financial estimates, as per paragraph 7.15, and a revised RSA proposal. The Secretariat advised that a revised restriction would be provided to the sponsor for review.

Outcome:
Deferred

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.

May Addendum to the March 2025 PBAC PSD:

4.01 ODEVIXIBAT
Capsule 200 micrograms,
Capsule 400 micrograms,
Capsule 600 micrograms,
Capsule 1200 micrograms,
Bylvay®,
Ipsen Pty Ltd.

10 Purpose

10.1 The Sponsor provided a proposal that sought to address the outstanding issues from the March 2025 PBAC deferral of odevixibat for the treatment of progressive familial intrahepatic cholestasis (PFIC).

10.2 The proposal addressed the issues raised by PBAC; see **Table 22** below.

Table 22: Summary of key matters addressed in the proposal

Matter of concern	Response	Addressed?
Restriction: - The Secretariat provided a revised restriction	- The Sponsor and clinical experts have provided comment on the Secretariat proposed restriction.	-
Cost effective price of odevixibat: - the PBAC considered that for odevixibat to be cost effective the cost per patient per year would need to be in the order of $[redacted] for an average prevalent patient receiving 40 mcg/kg/day (an average patient was assumed to be 13 years and the average dose was 4.51 x 400 mcg tablets/day) (paragraph 7.13, PSD, March 2025).	- The proposal proposed a revised price which resulted in a cost per patient per year for a patient requiring an average of 4.51 x 400 mcg tablets per day of $[redacted].	Yes
Financial estimates: - the PBAC requested estimates presented separately for children and adults and noted that the prevalent adult population was likely to be approximately [redacted][1] patients (paragraph 7.15, PSD, March 2025).	The proposal: - provided separate adult and paediatric utilisation estimates and appropriately applied a prevalence rate of 0.07 per 10,000 people to the 0-19 year population only. - assumed a prevalent adult population of [redacted][1] patients. - used an incident population of [redacted][1] paediatric and [redacted][1] adult patient - amended the uptake rate in prevalent patients from [redacted]% in Year 1 to [redacted]% in Year 1 and [redacted]% in Year 2.	Yes
Risk Sharing Arrangement: - the PBAC noted that dose escalation would be managed through the RSA. Although the PBAC considered that flat pricing across the doses would be the most appropriate way to manage the risk, in the absence of flat dosing, management via the RSA was appropriate. The PBAC noted that patients who had subtypes of disease that were non-responsive to odevixibat should be removed from the proposed expenditure caps (paragraph 7.18, PSD, March 2025)	- In the context of the price proposed and the adjustments to the patient numbers, the proposal has proposed expenditure caps that are [redacted]% higher than the financial estimates. - The proposal has proposed a [redacted]% rebate for use above the proposed expenditure caps	Partially

Source: July 2025 proposal RSA = risk sharing arrangement
The redacted values correspond to the following ranges:
[1] < 500

11 Requested listing

11.1 Following the March 2025 meeting, the Secretariat drafted proposed restrictions for odevixibat. At the March 2025 meeting, the PBAC considered that:

- There should be a review the ObsRO Pruritus Scale which was proposed by the sponsor to assess pruritus at treatment initiation and for continuation of therapy. The PBAC was concerned that the ObsRO Pruritus Scale was highly variable and may not provide a meaningful measure, particularly in terms of assessment of response for continuing therapy, as it relied on the response to one question;

- The restriction should restrict the initiation of treatment in adult patients to specialist hepatologists working in liver transplant centres to prevent use in other cholestatic liver diseases;
- The continuing restriction should include a stopping rule to ensure that treatment only continues for as long as a positive pruritus response is maintained;
- The restrictions should only allow retreatment in patients who have previously benefited from treatment and who stopped treatment for reasons other than loss of response (e.g. pregnancy);
- The restrictions be clear as to the timing of and assessment of response to dose escalation. The PBAC advised that dose escalation should occur between 1-3 months after initiation and the continuation criteria should be met at 6 months post initiation of treatment.

11.2 There are separate restrictions for patients diagnosed before and after 18 years of age. This will allow utilisation in each population to be tracked, noting patients diagnosed as adults are more likely to have episodic disease (see paragraph 4.4). The initial and continuing restriction for patients diagnosed under 18 years of age is presented below. A dose modification criteria for each population is also proposed (not presented below).

Initial or grandfather supply:

MEDICINAL PRODUCT medicinal product pack	DPMQ	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ODEVIXIBAT					
odevixibat 200 mcg capsule, 30	Published: $67,122.96 Effective: $[redacted]	12	360	2	Bylvay
odevixibat 400 mcg capsule, 30	Published: $67,122.90 Effective: $[redacted]	6	180	2	Bylvay
odevixibat 600 mcg capsule, 30	Published: $201,042.96 Effective: $[redacted]	12	360	2	Bylvay
odevixibat 1200 mcg capsule, 30	Published: $201,042.90 Effective: $[redacted]	6	180	2	Bylvay

Restriction Summary [new] Treatment of Concept: [new]		
Concept ID (for internal Dept. use)		**Category / Program:** Section 85 - General Schedule
		Prescriber type: ☒ Medical Practitioners
		Restriction type: ☒ Authority Required (in writing via post/HPOS upload or Online PBS Authorities system)
Prescribing rule level		**Administrative advice:** No increase in the maximum quantity or number of units may be authorised
		Administrative advice: No increase in the maximum number of repeats may be authorised
		Administrative Advice: Special Pricing Arrangements Apply
		Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au

		Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
		Administrative Advice: The recommended dose of odevixibat for initial treatment is 40 micrograms/kg/day. 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 been achieved after 3 consecutive months since commencement of treatment, odevixibat should be renewed at 40 micrograms/kg/day through the continuing treatment phase. Dose Modification (where dose escalation occurs during initial treatment) If an adequate clinical response has not been achieved after at least 1 month and up to 3 months of initial treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the dose modification treatment phase for up to a total period of 6 months from the date of treatment commencement with odevixibat. If an adequate clinical response is demonstrated following the balance of up to 6 months of treatment at the higher dose of 120 micrograms/kg/day, odevixibat can be renewed at the same dose through the continuing treatment phase. If a patient fails to demonstrate a response after 6 months of treatment with this drug for this condition (inclusive of initial and dose modification treatment), they will no longer be eligible to receive PBS-subsidised treatment with this drug for this condition. Continuing Treatment (where dose escalation occurs during continuing treatment) If an adequate clinical response is unable to be maintained at the lower dose (40 micrograms/kg/day) during continuing treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the continuing treatment phase. If an adequate clinical response is demonstrated following XX months of treatment at the higher dose of 120 micrograms/kg/day, odevixibat can continued to be renewed at the same dose through the continuing treatment phase. Patients who are unable to demonstrate an adequate clinical response to continuing treatment at the higher dose will be ineligible for further PBS-subsidised treatment with this drug for this condition. Recommencing treatment Patients who have demonstrated an adequate clinical response and have ceased treatment for reasons other than a lack of response may recommence treatment through the continuing treatment phase.
		Administrative Advice: See the following article for details on the XXX Scale: [INSERT ARTICLE] The XXX Scale is available as a downloadable document at: [INSERT LINK]
		Episodicity: n/a
		Severity: n/a
		Condition: Progressive familial intrahepatic cholestasis (PFIC)
		Indication: Progressive familial intrahepatic cholestasis (PFIC)
		Treatment Phase: Initial treatment (PFIC diagnosed under 18 years of age)

	Clinical criteria:
	Patient must not have received prior PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have a clinical diagnosis of PFIC
	AND
	Clinical criteria:
	Patient must have elevated serum bile acids at treatment initiation with this drug
	AND
	Clinical criteria:
	Patient must be experiencing itch at treatment initiation with this drug, with other factors causing pruritus excluded through both: (i) physical examination and (ii) patient history
	AND
	Clinical criteria:
	Patient must have a baseline score of XXX on the XXXX scale
	Treatment criteria:
	Must be treated by a specialist experienced in the management of PFIC, who is either a: (i) gastroenterologist, (ii) hepatologist
	Population criteria:
	Patient must be aged between 6 months and 17 years inclusive; OR
	Patient must be/have been diagnosed prior to 18 years of age
	Prescribing Instructions: The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include: (1) details of the pruritus score using the XXXX scale (2) details of serum bile acids (date and micromol/L)
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) details of the proposed prescription; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: Prescriber must exclude any other causes of pruritus which include any of the following: (i) drug related (e.g., opioid-related pruritus) (ii) drug hypersensitivity or adverse effect; contact dermatitis; allergy (iii) differential diagnoses (e.g., xerosis; infestations; iron deficiency; chronic kidney disease; polycythaemia vera/leukemia/lymphoma; hypothyroidism; uncontrolled diabetes).
	Prescribing Instructions: At the time of the authority application, the prescriber should request the appropriate strength(s) and quantity based on the patients' weight, according to the dosing schedule in the TGA approved Product Information to provide sufficient drug for one month's supply with 2 repeats. A separate authority approval is required for each strength requested
	Prescribing Instructions: An application for continuing treatment must occur following an assessment of response conducted up to 3 months of therapy. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
	Prescribing Instructions:

	An application for dose modification treatment must occur following an assessment of response conducted from 1 month of therapy up to 3 months of therapy. This will enable ongoing treatment for those who meet the dose modification restriction criteria for PBS-subsidised treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug after 1 month, they will be eligible to receive PBS-subsidised treatment at a higher dose with this drug for this condition under the dose modification treatment phase for a maximum of 5 months; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs within this treatment phase.
	Prescribing Instructions: All diagnostic reports/tools must be documented in the patient's medical records.
	Prescribing Instructions: An adequate clinical response to initial treatment is defined as an XXX grade improvement on the XXXX Scale,
	Prescribing Instructions: Eligible patients must not be recommencing treatment directly through this treatment phase;

Continuing supply:

MEDICINAL PRODUCT medicinal product pack	DPMQ	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ODEVIXIBAT					
odevixibat 200 mcg capsule, 30	Published: $67,122.96 Effective: $[redacted]	12	360	5	Bylvay
odevixibat 400 mcg capsule, 30	Published: $67,122.90 Effective: $[redacted]	6	180	5	Bylvay
odevixibat 600 mcg capsule, 30	Published: $201,042.96 Effective: $[redacted]	12	360	5	Bylvay
odevixibat 1200 mcg capsule, 30	Published: $201,042.90 Effective: $[redacted]	6	180	5	Bylvay

Restriction Summary [new] Treatment of Concept: [new]		
Concept ID (for internal Dept. use)		**Category / Program:** Section 85 - General Schedule
		Prescriber type: ☒ Medical Practitioners
		Restriction type: ☒ Authority Required (telephone/electronic)
Prescribing rule		**Administrative advice:** No increase in the maximum quantity or number of units may be authorised
		Administrative advice: No increase in the maximum number of repeats may be authorised
		Administrative Advice: Special Pricing Arrangements Apply
		Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
		Administrative Advice: The recommended dose of odevixibat for initial treatment is 40 micrograms/kg/day. 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 been achieved after 3 consecutive months since commencement of treatment, odevixibat should be renewed at 40 micrograms/kg/day through the continuing treatment phase. Dose Modification (where dose escalation occurs during initial treatment) If an adequate clinical response has not been achieved after at least 1 month and up to 3 months of initial treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the dose modification treatment phase for up to a total period of 6 months from the date of treatment commencement with odevixibat.

		If an adequate clinical response is demonstrated following the balance of up to 6 months of treatment at the higher dose of 120 micrograms/kg/day, odevixibat can be renewed at the same dose through the continuing treatment phase. If a patient fails to demonstrate a response after 6 months of treatment with this drug for this condition (inclusive of initial and dose modification treatment), they will no longer be eligible to receive PBS-subsidised treatment with this drug for this condition. Continuing Treatment (where dose escalation occurs during continuing treatment) If an adequate clinical response is unable to be maintained at the lower dose (40 micrograms/kg/day) during continuing treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the continuing treatment phase. If an adequate clinical response is demonstrated following XX months of treatment at the higher dose of 120 micrograms/kg/day, odevixibat can continued to be renewed at the same dose through the continuing treatment phase. Patients who are unable to demonstrate an adequate clinical response to continuing treatment at the higher dose will be ineligible for further PBS-subsidised treatment with this drug for this condition. Recommencing treatment Patients who have demonstrated an adequate clinical response and have ceased treatment for reasons other than a lack of response may recommence treatment through the continuing treatment phase.
		Administrative Advice: See the following article for details on the XXX Scale: [INSERT ARTICLE] The XXX Scale is available as a downloadable document at: [INSERT LINK]
		Episodicity: n/a
		Severity: n/a
		Condition: Progressive familial intrahepatic cholestasis (PFIC)
		Indication: Progressive familial intrahepatic cholestasis (PFIC)
		Treatment Phase: Continuing Treatment (PFIC diagnosed under 18 years of age)
		Clinical criteria:
		Patient must have previously received PBS-subsidised treatment with this drug for this condition
		AND
		Clinical criteria:
		Patient must have previously demonstrated an adequate clinical response to treatment; or
		Patient must be undergoing dose escalation to 120 micrograms/kg/day if they were unable to maintain a previously demonstrated adequate clinical response at 40 micrograms/kg/day in continuing treatment
		AND
		Clinical criteria:
		Patient must not be undergoing treatment with this drug for this condition, where an adequate clinical response was unable to be maintained at 120 micrograms/kg/day
		Treatment criteria:
		Must be treated by a specialist experienced in the management of PFIC, who is either: (i) gastroenterologist, (ii) hepatologist; OR
		Must be treated by a medical practitioner under the supervision of a specialist experienced in the management of PFIC

	Prescribing Instructions: An adequate clinical response under this treatment phase is defined as an XXX grade improvement on the XXXX Scale
	Prescribing Instructions: Confirmation of eligibility for continuing treatment must be documented in the patient's medical records (include assessment of adequate clinical response to preceding supply)
	Prescribing Instructions: A patient may be eligible for treatment at the higher dose (120 micrograms/kg/day), if a loss of response or an adequate response was unable to be maintained at the lower dose (40 micrograms/kg/day) during continuing treatment. To be eligible for continuing treatment at the higher dose (120 micrograms/kg/day), the patient must demonstrate and maintain an adequate clinical response after undergoing XXX months of treatment at the higher dose.

11.3 The proposed restrictions were sent to clinical experts for comment. The input received included that:

- the ObsRO pruritus scale was a suitable and time efficient tool which was validated in paediatric patients;
- initial prescribing for patients diagnosed after 18 years of age by a hepatologist was reasonable;
- serum bile acid levels at initiation of treatment should be elevated but no level should be specified;
- the criterion requiring prescribers to exclude other causes of itch was reasonable, but the addition of eczema and scabies to the list of possible causes would make it more applicable to children;
- response was generally observed within 3 to 6 months of commencing therapy; and
- maintenance of response should be assessed with each continuing supply.

For more detail on PBAC's view, see section 11 PBAC outcome.

12 Consideration of the evidence

Drug cost/patient/year

12.1 The proposal included an updated price for odevixibat that represented a reduction of [redacted]% from the March 2025 resubmission and [redacted]% from the original July 2024 submission. The proposed pricing is based on an ex-manufacturer (EMP) price per microgram of $[redacted].

Table 23: Proposed pricing per pack (30 tablets)

Tablet strength	200 mcg	400 mcg	600 mcg	1,200 mcg
Published EMP	$5,580.00	$11,160.00	$16,740.00	$33,480.00
Effective EMP	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source Table 2, p4 of the July 2025 proposal
EMP = ex-manufacturer price

12.2 The updated price results in a cost per patient per year of $[redacted] for an average patient who is assumed to be 13 years of age and receive 4.51 x 400 mcg tablets per day (see **Table 24**).

Table 24: Updated cost per patient per year

	July 2025 proposal	March 2025 resubmission
Tablet strength	400 mcg	400 mcg
Tablets per day	4.51	4.51
Per tablet cost	$[redacted]	$[redacted]
Per day cost	$[redacted]	$[redacted]
Cost per year*	$[redacted]	$[redacted]

Source: Table 1, p4 of the July 2025 proposal
*Calculated based on DPMQ for one pack of 400 mcg presentation. The cost per patient per year using the DPMQ presented in Section 9 (i.e., for 6 packs) is $[redacted].

Estimated PBS usage & financial implications

12.3 The proposal provided revised utilisation and financial implication estimates. The key changes are outlined in **Table 25**.

Table 25: Key changes to the financial estimates

Parameter	March 2025 PBAC minute comment	July 2025 proposal
Utilisation models	It would be more appropriate to estimate use separately for children and adults (paragraph7.15).	Separate models were provided for the paediatric and adult populations.
Prevalent patients – Paediatric	DUSC commented that applying the estimated prevalence rate of 0.05 to 0.07 per 10,000 should be applied to the population aged 0-19 years old (Table 19).	A prevalence rate of 0.07 per 10,000 people has been applied to the 0 to 19 population.
Prevalent patients – Adults	PFIC and Related Disorders, Australia stated that the prevalent adult population was likely to be approximately 10 patients (paragraph 7.15).	Whilst unsure of the basis for this estimate, the proposal used this estimate to inform the prevalent patient population in adults.
Incident patients	The number of incident patients with PFIC was decreased from [redacted][1] in the July 2024 submission to [redacted][1] in the March 2025 resubmission and this was considered reasonable (paragraph **Error! Reference source not found.**).	The proposal assumed [redacted][1] incident patients, [redacted][1] paediatric and [redacted][1] adult.
Post PEBD and liver transplant	Although the changes in liver transplant and PEBD surgery were reasonable, it would be more appropriate to estimate use separately for children and adults (paragraph 7.15).	The proposal has applied the prior PEBD and liver transplant rates in the paediatric model and has estimated the adult utilisation separately.
Uptake	The financial impact of odevixibat was overestimated as the estimates assumed [redacted]% uptake in Year 1 and 100% compliance for all patients (paragraph **Error! Reference source not found.**).	Amended uptake rates of [redacted]% in Year 1 and [redacted]% in Year 2 for prevalent patients have been applied. Dose interruption data was not reported in the trial; however, this was expected to be minimal given severity of symptoms experienced by patients and the generally minor adverse events reported.
Response	Overall response rate of 58%, with 43.5% assumed to respond to the 40 mcg/kg dose and an additional 14.5%[a] assumed to escalate and respond to 120mcg/kg	Same response rates applied

Source: Table 3, p5 of the July 2025 proposal
DUSC = Drug Utilisation Sub-Committee; PEBD = partial external biliary diversion; PFIC = progressive familial intrahepatic cholestasis
[a] Calculated as 24.5% x 58% where 24.5% = % high dose (internal data and PEDFIC response) and 58% = total responders
The redacted values correspond to the following ranges:
[1] < 500

12.4 The proposal stated that the eligible prevalent patient population has been reduced from <500 in the March 2025 resubmission to <500 (<500 adult patients and <500 paediatric patients). A summary of the number of prevalent patients and treated patients and how this compares to the March 2025 resubmission is presented in **Table 26** and **Table 27**.

Table 26: Prevalent patients

	Year 1	Comment
July 2025 proposal		
Adults		
Number of patients with PFIC who are treated with odevixibat	[redacted][1]	As outlined in paragraph 7.15 of March 2025 PSD
Paediatric		
Number of patients with PFIC	[redacted][1]	0.07 per 10,000 population applied to number of people aged 0 to 19 years
Number of patients who have not had LT/ PEBD and are treated with odevixibat	[redacted][1]	34.87%. Includes a very small proportion of patients who have had surgery that may also be treated with odevixibat (~5%)
March 2025 submission		
Number of patients with PFIC	[redacted][1]	0.07 per 10,000 population applied to whole population
Number of patients who have not had LT/ PEBD and are treated with odevixibat	[redacted][1]	27.5%

LT = liver transplant; PEBD = partial external biliary diversion; PFIC = progressive familial intrahepatic cholestasis
The redacted values correspond to the following ranges:
[1] < 500

Table 27: Estimated treated patient population

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
July 2025 proposal						
Patients receiving treatment with odevixibat						
Paediatric patients: - Prevalent - Incident	[redacted][1] [redacted][1]	[redacted][1] [redacted][1]	[redacted][1] [redacted][1]	[redacted][1] [redacted][1]	[redacted][1] [redacted][1]	[redacted][1] [redacted][1]
Adult patients: - Prevalent - Incident	[redacted][1] [redacted][1]	[redacted][1] [redacted][1]	[redacted][1] [redacted][1]	[redacted][1] [redacted][1]	[redacted][1] [redacted][1]	[redacted][1] [redacted][1]
March 2025 resubmission						
Patients receiving treatment with odevixibat						
Prevalent patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]

Source: Table 4, p6 of the July 2025 proposal
PFIC = progressive familial intrahepatic cholestasis
The redacted values correspond to the following ranges:
[1] < 500

12.5 **Table 28** presents the revised financial implication of listing odevixibat on the PBS/RPBS.

The financial estimates offset the use of ursodeoxycholic acid, cholestyramine, rifampicin and naltrexone.

Table 28: Net financial impact of the proposed listing at effective price – July 2025 updates to price and utilisation

Year	2025	2026	2027	2028	2029	2030
Paediatric population						
Cost to PBS/RPBS	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Cost offsets	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Net impact to PBS/RPBS	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Adult population						
Cost to PBS/RPBS	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Cost offsets	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Net impact to PBS/RPBS	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Total population						
Cost to PBS/RPBS	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Cost offsets	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Net impact to PBS/RPBS	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
March 2025 resubmission						
Cost to PBS/RPBS	[redacted]3	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4
Cost offsets	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Net impact to PBS/RPBS	[redacted]3	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4

Source: Tables 5 and 6, pp6-7 of the July 2025 proposal

The redacted values correspond to the following ranges:

[1] *$0 to < $10 million*

[2] *net cost saving*

[3] *$20 million to < $30 million*

[4] *$10 million to < $20 million*

12.6 The net cost to the PBS/RPBS of listing odevixibat was estimated to be $0 to < $10 million in Year 1, $0 to < $10 million in Year 6 and total $$40 million to < $50 million over the first 6 years. The revised estimates were [redacted]% lower than those presented in March 2025, which estimated a total cost of $100 million to < $200 million over the first 6 years of listing.

Financial Management – Risk Sharing Arrangements

12.7 The proposal stated that due to the revision of the utilisation parameters, the utilisation and financial impact estimates were considerably lower than those presented in March 2025. The response stated that as PFIC is an ultra-rare condition, the utilisation estimates are uncertain. Thus, at the price and utilisation proposed, the proposal:

- Requested a formal review of the expenditure cap within 2 years, with more accurate utilisation data to inform the expenditure caps for the balance of the deed period;
- Proposed a [redacted]% rebate for any expenditure exceeding the agreed caps; and
- Stated that within the context of the price proposed by PBAC, it would not be possible for the sponsor to agree to the level of expenditure cap informed by the

proposed utilisation estimates. Thus, the response proposed setting the expenditure cap on average [redacted]% higher than the estimated financial impact, noting that this would provide tolerance to treat an additional <500-<500 eligible patients per year within the cap.

12.8 As per the March 2025 resubmission, the proposed RSA excluded patients who are likely to be genetic non-responders (i.e. patients with PFIC2 *BSEP3* subtype assumed to be 7% of the population) and incorporated a 'f[redacted]' cost by assuming that [redacted]% of patients would remain on the 40 mcg/kg/day dose.

12.9 The proposed RSA expenditure caps are presented in Table 29. The estimated cost to the PBS/RPBS over 5 years is $[redacted] million compared to $[redacted] million in the March 2025 resubmission.

Table 29: Revised annual expenditure caps

	Year 1	Year 2	Year 3	Year 4	Year 5[1]
Net impact to PBS/RPBS ($)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted]
Exclusion of genetic non-responders and application of flat treatment cost ($)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Additional expenditure requested	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Final proposed annual expenditure caps ($)	[redacted]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Potential additional patients within cap (at $[redacted] per patient cost)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
% additional expenditure requested	[redacted]				

Source: Table 7, p9 of the July 2025 proposal

The redacted values correspond to the following ranges:

[1] $0 to < $10 million

[2] <500

For more detail on PBAC's view, see section 11 PBAC outcome.

13 PBAC Outcome

13.1 The PBAC recommended the PBS listing of odevixibat for the treatment of progressive familial intrahepatic cholestasis (PFIC). The PBAC recognised that there was a high clinical need for treatments for this rare condition and recalled that it had previously considered that odevixibat was superior compared to the nominated comparator, standard of care. The PBAC considered that the outstanding issues from the March 2025 resubmission had been addressed, including revised restrictions, a reduced price, which resulted in a cost per patient per year that was considered cost-effective, and revised financial estimates. Further, the PBAC considered that a risk sharing arrangement (RSA) would mitigate financial risks associated with utilisation that is not cost-effective such as dose escalation and in patients who do not respond to treatment.

13.2 The PBAC considered that the proposed restrictions were reasonable, noting that:

- the clinical experts considered that the ObsRO Pruritus Scale was an appropriate tool to measure response to treatment. The Sponsor should provide advice on how

this tool can be freely accessed by clinicians prior to listing;

- initial prescribing for patients diagnosed with PFIC over 18 years of age by a hepatologist;
- possible other causes of pruritis that should be excluded before prescribing odevixibat should include eczema and scabies; and
- maintenance of response should be assessed with the ObsRO Pruritus scale prior to each continuing supply.

13.3 The PBAC recalled the issues associated with the previous economic models presented in July 2024 and March 2025 and that the uncertainty with the cost effectiveness was unlikely to be adequately resolved with further revisions to model inputs (see paragraphs **Error! Reference source not found.** to **Error! Reference source not found.**). The PBAC again acknowledged the high and urgent clinical need for effective PFIC treatments and that in the context of PFIC being a rare disease, recalled that in March 2025 it had considered that for odevixibat to be cost effective, the cost per patient per year would need to be in the order of $[redacted] for an average prevalent patient receiving 40 mcg/kg/day dosing (see paragraph **Error! Reference source not found.**). The PBAC considered that the prices proposed in the proposal were reasonable (see **Table 23**) and resulted in a cost per patient per year that was considered cost effective.

13.4 In terms of the revised financial estimates, the PBAC noted that the proposal had appropriately provided separate utilisation estimates for the paediatric and adult populations, assumed <500 paediatric and <500 adult incident patients per year, reduced the prevalent adult population to <500 patients and reduced the uptake rate in response to the advice received in March 2025. For the paediatric patient utilisation estimates, the PBAC noted that the proposal applied the prevalence rate of 0.07 PFIC patients per 10,000 to the population aged 0 to 19 years. However, the PBAC considered that there would be some additional young adult patients diagnosed as paediatric patients who were not captured by the revised estimates and recommended applying the prevalence rate to the population aged 0 to 25 years. The PBAC noted the error discussed in paragraph **Error! Reference source not found.** needs to be corrected (i.e., DPMQ calculated based on maximum quantity dispensed and number of scripts dispensed revised accordingly).

13.5 Regarding the proposed RSA, the PBAC noted that patients who are likely to be genetic non-responders (i.e. patients with PFIC2 *BSEP3* subtype assumed to be 7% of the population) were excluded and a '[redacted]' cost was incorporated by assuming [redacted] patients would receive the 40 mcg/kg/day dose. The PBAC considered that this was an appropriate basis for RSA subsidisation caps. The PBAC did not agree to the submission's proposal to set RSA caps at a level based on an arbitrary [redacted]% increase to the financial impact estimates; however, noted that the suggested changes to the paediatric prevalence rate would result in an additional <500 patients included in the utilisation estimates. The PBAC noted that a [redacted]% rebate for any expenditure that

exceeded the RSA caps was proposed and considered this was reasonable.

13.6 The PBAC advised that the utilisation of odevixibat should be reviewed after 2 years, as part of the standard utilisation review process.

13.7 The PBAC advised that odevixibat is not suitable for prescribing by nurse practitioners.

13.8 The PBAC advised that odevixibat should not be exempt from the Early Supply Rule.

13.9 The PBAC advised that under section 101(3BA) of the *National Health Act 1953*, odevixibat should not be treated as interchangeable on an individual patient basis with any other drug.

13.10 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A met. Specifically, the PBAC found that in the circumstances of its recommendation for odevixibat:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, or reduction in toxicity, over placebo;

b) The treatment is expected to address a high and urgent unmet clinical need as there are currently no treatments for PFIC listed on the PBS;

c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings

13.11 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

14 Recommended listing

14.1 Add new items:

PFIC diagnosed under 18 years of age:

Initial and grandfather

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ODEVIXIBAT					
odevixibat 200 mcg capsule, 30	NEW	12	360	2	Bylvay
odevixibat 400 mcg capsule, 30	NEW	6	180	2	Bylvay
odevixibat 600 mcg capsule, 30	NEW	12	360	2	Bylvay
odevixibat 1200 mcg capsule, 30	NEW	6	180	2	Bylvay
Restriction Summary [new] Treatment of Concept: [new]					
Concept ID (for internal Dept. use)	**Category / Program:** Section 85 - General Schedule				
	Prescriber type: ☒ Medical Practitioners				
	Restriction type: ☒ Authority Required (in writing via post/HPOS upload or Online PBS Authorities system)				

Prescribing rule level		**Administrative advice:** No increase in the maximum quantity or number of units may be authorised
		Administrative advice: No increase in the maximum number of repeats may be authorised
		Administrative Advice: Special Pricing Arrangements Apply
		Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
		Administrative Advice: The recommended dose of odevixibat for initial treatment is 40 micrograms/kg/day. 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 been achieved after 3 consecutive months since commencement of treatment, odevixibat should be renewed at 40 micrograms/kg/day through the continuing treatment phase. **Dose Modification (where dose escalation occurs during initial treatment)** If an adequate clinical response has not been achieved after at least 1 month and up to 3 months of initial treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the dose modification treatment phase for up to a total period of 6 months from the date of treatment commencement with odevixibat. If an adequate clinical response is demonstrated following the balance of up to 6 months of treatment at the higher dose of 120 micrograms/kg/day, odevixibat can be renewed at the same dose through the continuing treatment phase. If a patient fails to demonstrate a response after 6 months of treatment with this drug for this condition (inclusive of initial and dose modification treatment), they will no longer be eligible to receive PBS-subsidised treatment with this drug for this condition. **Continuing Treatment (where dose escalation occurs during continuing treatment)** If an adequate clinical response is unable to be maintained at the lower dose (40 micrograms/kg/day) during continuing treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the continuing treatment phase. If an adequate clinical response is demonstrated at the higher dose of 120 micrograms/kg/day, odevixibat can continue to be renewed at the same dose through the continuing treatment phase. Patients who are unable to demonstrate an adequate clinical response to continuing treatment at the higher dose will be ineligible for further PBS-subsidised treatment with this drug for this condition. **Recommencing treatment** Patients who have demonstrated an adequate clinical response and have ceased treatment for reasons other than a lack of response may recommence treatment through the continuing treatment phase.
		Administrative Advice:

	The Prucision™ ObsRO Pruritus Scale is available as a downloadable document at: [INSERT LINK]
	Episodicity:n/a
	Severity: n/a
	Condition: Progressive familial intrahepatic cholestasis (PFIC)
	Indication: Progressive familial intrahepatic cholestasis (PFIC)
	Treatment Phase: Initial treatment (PFIC diagnosed under 18 years of age)
	Clinical criteria:
	Patient must not have received prior PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have a clinical diagnosis of PFIC
	AND
	Clinical criteria:
	Patient must have elevated serum bile acids at treatment initiation with this drug
	AND
	Clinical criteria:
	Patient must be experiencing itch at treatment initiation with this drug, with other factors causing pruritus excluded through both: (i) physical examination and (ii) patient history
	AND
	Clinical criteria:
	Patient must have had an average pruritus score of ≥2 on the Prucision™ ObsRO Pruritus Scale assessed on three occasions over a one week period prior to treatment initiation with this drug.
	Treatment criteria:
	Must be treated by a specialist experienced in the management of PFIC, who is either a: (i) gastroenterologist, (ii) hepatologist
	Population criteria:
	Patient must be aged between 6 months and 17 years inclusive; OR
	Patient must be/have been diagnosed prior to 18 years of age
	Prescribing Instructions: The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include: (3) details of the pruritus score using the Prucision™ ObsRO Pruritus scale (4) details of serum bile acids (date and micromol/L)
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) details of the proposed prescription; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: Prescriber must exclude any other causes of pruritus which include any of the following: (i) drug related (e.g., opioid-related pruritus) (ii) drug hypersensitivity or adverse effect; contact dermatitis; allergy (iii) differential diagnoses (e.g., xerosis; infestations; iron deficiency; chronic kidney disease; polycythaemia vera/leukemia/lymphoma; hypothyroidism; uncontrolled diabetes, eczema, scabies).
	Prescribing Instructions: At the time of the authority application, the prescriber should request the appropriate strength(s) and quantity based on the patients' weight, according to the dosing schedule in the TGA approved Product Information to

	provide sufficient drug for one month's supply with 2 repeats. A separate authority approval is required for each strength requested
	Prescribing Instructions: An application for continuing treatment must occur following an assessment of response conducted up to 3 months of therapy. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
	Prescribing Instructions: An application for dose modification treatment must occur following an assessment of response conducted from 1 month of therapy up to 3 months of therapy. This will enable ongoing treatment for those who meet the dose modification restriction criteria for PBS-subsidised treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug after 1 month, they will be eligible to receive PBS-subsidised treatment at a higher dose with this drug for this condition under the dose modification treatment phase for a maximum of 5 months; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs within this treatment phase.
	Prescribing Instructions: All diagnostic reports/tools must be documented in the patient's medical records.
	Prescribing Instructions: An adequate clinical response to initial treatment is defined as an average ≥1 grade improvement in pruritus score on the Prucision™ ObsRO Pruritus Scale, assessed on 3 occasions over a one week period prior to assessment of response.
	Prescribing Instructions: Eligible patients must not be recommencing treatment directly through this treatment phase;

Dose modification

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
ODEVIXIBAT					
odevixibat 200 mcg capsule, 30	NEW	12	360	4	Bylvay
odevixibat 400 mcg capsule, 30	NEW	6	180	4	Bylvay
odevixibat 600 mcg capsule, 30	NEW	12	360	4	Bylvay
odevixibat 1200 mcg capsule, 30	NEW	6	180	4	Bylvay

Restriction Summary [new] Treatment of Concept: [new]		
Concept ID (for internal Dept. use)		**Category / Program:** Section 85 - General Schedule
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒ Authority Required (telephone/electronic)
Prescribing		**Administrative advice:** No increase in the maximum quantity or number of units may be authorised
		Administrative advice: No increase in the maximum number of repeats may be authorised
		Administrative Advice: Special Pricing Arrangements Apply
		Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
		Administrative Advice: The recommended dose of odevixibat for initial treatment is 40 micrograms/kg/day. 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 been achieved after 3 consecutive months since commencement of treatment, odevixibat should be renewed at 40 micrograms/kg/day through the continuing treatment phase.

		Dose Modification (where dose escalation occurs during initial treatment) If an adequate clinical response has not been achieved after at least 1 month and up to 3 months of initial treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the dose modification treatment phase for up to a total period of 6 months from the date of treatment commencement with odevixibat. If an adequate clinical response is demonstrated following the balance of up to 6 months of treatment at the higher dose of 120 micrograms/kg/day, odevixibat can be renewed at the same dose through the continuing treatment phase. If a patient fails to demonstrate a response after 6 months of treatment with this drug for this condition (inclusive of initial and dose modification treatment), they will no longer be eligible to receive PBS-subsidised treatment with this drug for this condition. **Continuing Treatment (where dose escalation occurs during continuing treatment)** If an adequate clinical response is unable to be maintained at the lower dose (40 micrograms/kg/day) during continuing treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the continuing treatment phase. If an adequate clinical response is demonstrated at the higher dose of 120 micrograms/kg/day, odevixibat can continue to be renewed at the same dose through the continuing treatment phase. Patients who are unable to demonstrate an adequate clinical response to continuing treatment at the higher dose will be ineligible for further PBS-subsidised treatment with this drug for this condition. **Recommencing treatment** Patients who have demonstrated an adequate clinical response and have ceased treatment for reasons other than a lack of response may recommence treatment through the continuing treatment phase.
		Administrative Advice: The Prucision™ ObsRO Pruritus Scale is available as a downloadable document at: [INSERT LINK]
		Episodicity:n/a
		Severity: n/a
		Condition: Progressive familial intrahepatic cholestasis (PFIC)
		Indication: Progressive familial intrahepatic cholestasis (PFIC)
		Treatment Phase: Dose Modification (Dose escalation from initial treatment phase; for PFIC diagnosed under 18 years of age)
		Clinical criteria:
		Patient must have previously received PBS-subsidised treatment with this drug for this condition
		AND
		Clinical criteria:
		Patient must not have demonstrated an adequate clinical response after at least 1 month and up to 3 months following commencement of treatment at 40 micrograms/kg/day
		Treatment Criteria:
		Patient must be undergoing treatment with this drug for this condition at 120 micrograms/kg/day
		Treatment criteria:
		Must be treated by a specialist experienced in the management of PFIC, who is either: (i) gastroenterologist, (ii) hepatologist; OR
		Must be treated by a medical practitioner under the supervision of a specialist experienced in the management of PFIC

	Prescribing Instructions: At the time of the authority application, the prescriber should request sufficient quantity and repeats to provide for the balance to complete up to 6 months of treatment (inclusive of initial and dose modification treatment), if dose modification is being accessed following initial treatment.
	Prescribing Instructions: An application for the continuing treatment must occur following an assessment of response conducted up to a maximum of 6 months from initiation of therapy. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment 6 months after initiating treatment with this drug for this condition (inclusive of initial and dose modification treatment), they will no longer be eligible to receive PBS-subsidised treatment with this drug for this condition.
	Prescribing Instructions: An adequate clinical response **under this treatment phase** is defined as an average ≥1 grade improvement in pruritus score on the Prucision™ ObsRO Pruritus Scale, assessed on 3 occasions over a one week period prior to assessment of response.
	Prescribing Instructions: Confirmation of eligibility for dose modification treatment must be documented in the patient's medical records (include assessment of response score after at least 1 month and up to 3 months after commencing initial treatment)
	Prescribing Instructions: Any further authority applications occurring immediately after access through this dose modification listing are not to occur through the Initial treatment listing.
	Prescribing Instructions: **Dose modification** Where the drug's Product Information indicates variable dosing regimens based on the individual's response/tolerance, apply under this listing to continue treatment with the new strength. Mark any remaining repeat prescriptions for the discontinued strength with the word 'cancelled'. This treatment phase listing recognises that a patient's optimal dose may not always be immediately apparent at the time of treatment initiation and therefore does not require confirmation of an objective, adequate response to the preceding supply of drug.
	Prescribing Instructions: Eligible patients must not be recommencing treatment directly through this treatment phase;

Continuing

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ODEVIXIBAT					
odevixibat 200 mcg capsule, 30	NEW	12	360	5	Bylvay
odevixibat 400 mcg capsule, 30	NEW	6	180	5	Bylvay
odevixibat 600 mcg capsule, 30	NEW	12	360	5	Bylvay
odevixibat 1200 mcg capsule, 30	NEW	6	180	5	Bylvay

Restriction Summary [new] Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** Section 85 - General Schedule
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required (telephone/electronic)
Prescribing	**Administrative advice:** No increase in the maximum quantity or number of units may be authorised
	Administrative advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Special Pricing Arrangements Apply

		Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
		Administrative Advice: The recommended dose of odevixibat for initial treatment is 40 micrograms/kg/day. 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 been achieved after 3 consecutive months since commencement of treatment, odevixibat should be renewed at 40 micrograms/kg/day through the continuing treatment phase. **Dose Modification (where dose escalation occurs during initial treatment)** If an adequate clinical response has not been achieved after at least 1 month and up to 3 months of initial treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the dose modification treatment phase for up to a total period of 6 months from the date of treatment commencement with odevixibat. If an adequate clinical response is demonstrated following the balance of up to 6 months of treatment at the higher dose of 120 micrograms/kg/day, odevixibat can be renewed at the same dose through the continuing treatment phase. If a patient fails to demonstrate a response after 6 months of treatment with this drug for this condition (inclusive of initial and dose modification treatment), they will no longer be eligible to receive PBS-subsidised treatment with this drug for this condition. **Continuing Treatment (where dose escalation occurs during continuing treatment)** If an adequate clinical response is unable to be maintained at the lower dose (40 micrograms/kg/day) during continuing treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the continuing treatment phase. If an adequate clinical response is demonstrated at the higher dose of 120 micrograms/kg/day, odevixibat can continue to be renewed at the same dose through the continuing treatment phase. Patients who are unable to demonstrate an adequate clinical response to continuing treatment at the higher dose will be ineligible for further PBS-subsidised treatment with this drug for this condition. **Recommencing treatment** Patients who have demonstrated an adequate clinical response and have ceased treatment for reasons other than a lack of response may recommence treatment through the continuing treatment phase.
		Administrative Advice: The Prucision™ ObsRO Pruritus Scale is available as a downloadable document at: [INSERT LINK]
		Episodicity:n/a
		Severity: n/a
		Condition: Progressive familial intrahepatic cholestasis (PFIC)
		Indication: Progressive familial intrahepatic cholestasis (PFIC)
		Treatment Phase: Continuing Treatment (PFIC diagnosed under 18 years of age)
		Clinical criteria:
		Patient must have previously received PBS-subsidised treatment with this drug for this condition
		AND
		Clinical criteria:
		Patient must have demonstrated an adequate clinical response to the most recent course of treatment; or
		Patient must be undergoing dose escalation to 120 micrograms/kg/day if they were unable to maintain a previously demonstrated adequate clinical response at 40 micrograms/kg/day in continuing treatment

	AND
	Clinical criteria:
	Patient must not be undergoing treatment with this drug for this condition, where an adequate clinical response was unable to be maintained at 120 micrograms/kg/day
	Treatment criteria:
	Must be treated by a specialist experienced in the management of PFIC, who is either: (i) gastroenterologist, (ii) hepatologist; OR
	Must be treated by a medical practitioner under the supervision of a specialist experienced in the management of PFIC
	Prescribing Instructions: An adequate clinical response **under this treatment phase** is defined as an average ≥1 grade improvement in pruritus score on the Prucision™ ObsRO Pruritus Scale, assessed on 3 occasions over a one week period prior to assessment of response.
	Prescribing Instructions: Confirmation of eligibility for continuing treatment must be provided with the authority application and documented in the patient's medical records (include assessment of adequate clinical response to preceding supply)
	Prescribing Instructions: A patient may be eligible for treatment at the higher dose (120 micrograms/kg/day), if a loss of response or an adequate response was unable to be maintained at the lower dose (40 micrograms/kg/day) during continuing treatment. To be eligible for continuing treatment at the higher dose (120 micrograms/kg/day), the patient must demonstrate and maintain an adequate clinical response at the higher dose.

PFIC diagnosed over 18 years of age:

Initial and grandfather

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ODEVIXIBAT					
odevixibat 200 mcg capsule, 30	NEW	12	360	2	Bylvay
odevixibat 400 mcg capsule, 30	NEW	6	180	2	Bylvay
odevixibat 600 mcg capsule, 30	NEW	12	360	2	Bylvay
odevixibat 1200 mcg capsule, 30	NEW	6	180	2	Bylvay

Restriction Summary [new] Treatment of Concept: [new]		
Concept ID (for internal Dept. use)		**Category / Program:** Section 85 - General Schedule
		Prescriber type: ☒ Medical Practitioners
		Restriction type: ☒ Authority Required (in writing via post/HPOS upload or Online PBS Authorities system)
Prescribing rule level		**Administrative advice:** No increase in the maximum quantity or number of units may be authorised
		Administrative advice: No increase in the maximum number of repeats may be authorised
		Administrative Advice: Special Pricing Arrangements Apply
		Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au

		Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
		Administrative Advice: The recommended dose of odevixibat for initial treatment is 40 micrograms/kg/day. 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 been achieved after 3 consecutive months since commencement of treatment, odevixibat should be renewed at 40 micrograms/kg/day through the continuing treatment phase. **Dose Modification (where dose escalation occurs during initial treatment)** If an adequate clinical response has not been achieved after at least 1 month and up to 3 months of initial treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the dose modification treatment phase for up to a total period of 6 months from the date of treatment commencement with odevixibat. If an adequate clinical response is demonstrated following the balance of up to 6 months of treatment at the higher dose of 120 micrograms/kg/day, odevixibat can be renewed at the same dose through the continuing treatment phase. If a patient fails to demonstrate a response after 6 months of treatment with this drug for this condition (inclusive of initial and dose modification treatment), they will no longer be eligible to receive PBS-subsidised treatment with this drug for this condition. **Continuing Treatment (where dose escalation occurs during continuing treatment)** If an adequate clinical response is unable to be maintained at the lower dose (40 micrograms/kg/day) during continuing treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the continuing treatment phase. If an adequate clinical response is demonstrated at the higher dose of 120 micrograms/kg/day, odevixibat can continue to be renewed at the same dose through the continuing treatment phase. Patients who are unable to demonstrate an adequate clinical response to continuing treatment at the higher dose will be ineligible for further PBS-subsidised treatment with this drug for this condition. **Recommencing treatment** Patients who have demonstrated an adequate clinical response and have ceased treatment for reasons other than a lack of response may recommence treatment through the continuing treatment phase.
		Administrative Advice: The Prucision™ ObsRO Pruritus Scale is available as a downloadable document at: [INSERT LINK]
		Episodicity:n/a
		Severity: n/a
		Condition: Progressive familial intrahepatic cholestasis (PFIC)
		Indication: Progressive familial intrahepatic cholestasis (PFIC)
		Treatment Phase: Initial treatment (PFIC diagnosed over 18 years of age)
		Clinical criteria:
		Patient must not have received prior PBS-subsidised treatment with this drug for this condition

	AND
	Clinical criteria:
	Patient must have a clinical diagnosis of PFIC
	AND
	Clinical criteria:
	Patient must have elevated serum bile acids at treatment initiation with this drug
	AND
	Clinical criteria:
	Patient must be experiencing itch at treatment initiation with this drug, with other factors causing pruritus excluded through both: (i) physical examination and (ii) patient history
	AND
	Clinical criteria:
	Patient must have had an average pruritus score of ≥2 on the Prucision™ ObsRO Pruritus Scale assessed on three occasions over a one week period prior to treatment initiation with this drug.
	Treatment criteria:
	Must be treated by a specialist hepatologist experienced in the management of PFIC
	Population criteria:
	Patient must be/have been diagnosed after 18 years of age;
	Prescribing Instructions: The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include: (i) details of the pruritus score using the Prucision™ ObsRO Pruritus scale (ii) details of serum bile acids (date and micromol/L)
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) details of the proposed prescription; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: Prescriber must exclude any other causes of pruritus which include any of the following: (i) drug related (e.g., opioid-related pruritus) (ii) drug hypersensitivity or adverse effect; contact dermatitis; allergy (iii) differential diagnoses (e.g., xerosis; infestations; iron deficiency; chronic kidney disease; polycythaemia vera/leukemia/lymphoma; hypothyroidism; uncontrolled diabetes, eczema, scabies).
	Prescribing Instructions: At the time of the authority application, the prescriber should request the appropriate strength(s) and quantity based on the patients' weight, according to the dosing schedule in the TGA approved Product Information to provide sufficient drug for one month's supply with 2 repeats. A separate authority approval is required for each strength requested
	Prescribing Instructions: An application for continuing treatment must occur following an assessment of response conducted up to 3 months of therapy. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
	Prescribing Instructions: An application for dose modification treatment must occur following an assessment of response conducted from 1 month of therapy up to 3 months of therapy. This will enable ongoing treatment for those who meet the dose modification restriction criteria for PBS-subsidised treatment.
	Prescribing Instructions:

	If a patient fails to demonstrate a response to treatment with this drug after 1 month, they will be eligible to receive PBS-subsidised treatment at a higher dose with this drug for this condition under the dose modification treatment phase for a maximum of 5 months; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs within this treatment phase.
	Prescribing Instructions: All diagnostic reports/tools must be documented in the patient's medical records.
	Prescribing Instructions: An adequate clinical response **to initial treatment** is defined as an average ≥1 grade improvement in pruritus score on the Prucision™ ObsRO Pruritus Scale, assessed on 3 occasions over a one week period prior to assessment of response.
	Prescribing Instructions: Eligible patients must not be recommencing treatment directly through this treatment phase;

Dose modification

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
ODEVIXIBAT					
odevixibat 200 mcg capsule, 30	NEW	12	360	4	Bylvay
odevixibat 400 mcg capsule, 30	NEW	6	180	4	Bylvay
odevixibat 600 mcg capsule, 30	NEW	12	360	4	Bylvay
odevixibat 1200 mcg capsule, 30	NEW	6	180	4	Bylvay

Restriction Summary [new] Treatment of Concept: [new]		
Concept ID (for internal Dept. use)		**Category / Program:** Section 85 - General Schedule
		Prescriber type: ☒ Medical Practitioners
		Restriction type: ☒ Authority Required (telephone/electronic)
Prescribing		**Administrative advice:** No increase in the maximum quantity or number of units may be authorised
		Administrative advice: No increase in the maximum number of repeats may be authorised
		Administrative Advice: Special Pricing Arrangements Apply
		Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
		Administrative Advice: The recommended dose of odevixibat for initial treatment is 40 micrograms/kg/day. 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 been achieved after 3 consecutive months since commencement of treatment, odevixibat should be renewed at 40 micrograms/kg/day through the continuing treatment phase. **Dose Modification (where dose escalation occurs during initial treatment)** If an adequate clinical response has not been achieved after at least 1 month and up to 3 months of initial treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the dose modification treatment phase for up to a total period of 6 months from the date of treatment commencement with odevixibat. If an adequate clinical response is demonstrated following the balance of up to 6 months of treatment at the higher dose of 120 micrograms/kg/day, odevixibat can be renewed at the same dose through the continuing treatment phase.

		If a patient fails to demonstrate a response after 6 months of treatment with this drug for this condition (inclusive of initial and dose modification treatment), they will no longer be eligible to receive PBS-subsidised treatment with this drug for this condition. **Continuing Treatment (where dose escalation occurs during continuing treatment)** If an adequate clinical response is unable to be maintained at the lower dose (40 micrograms/kg/day) during continuing treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the continuing treatment phase. If an adequate clinical response is demonstrated at the higher dose of 120 micrograms/kg/day, odevixibat can continue to be renewed at the same dose through the continuing treatment phase. Patients who are unable to demonstrate an adequate clinical response to continuing treatment at the higher dose will be ineligible for further PBS-subsidised treatment with this drug for this condition. **Recommencing treatment** Patients who have demonstrated an adequate clinical response and have ceased treatment for reasons other than a lack of response may recommence treatment through the continuing treatment phase.
		Administrative Advice: The Prucision™ ObsRO Pruritus Scale is available as a downloadable document at: [INSERT LINK]
		Episodicity:n/a
		Severity: n/a
		Condition: Progressive familial intrahepatic cholestasis (PFIC)
		Indication: Progressive familial intrahepatic cholestasis (PFIC)
		Treatment Phase: Dose Modification (Dose escalation from initial treatment phase; for PFIC diagnosed over 18 years of age)
		Clinical criteria:
		Patient must have previously received PBS-subsidised treatment with this drug for this condition
		AND
		Clinical criteria:
		Patient must not have demonstrated an adequate clinical response after at least 1 month and up to 3 months following commencement of treatment at 40 micrograms/kg/day
		Treatment Criteria:
		Patient must be undergoing treatment with this drug for this condition at 120 micrograms/kg/day
		Treatment criteria:
		Must be treated by a specialist hepatologist experienced in the management of PFIC
		Must be treated by a medical practitioner under the supervision of a specialist experienced in the management of PFIC
		Prescribing Instructions: At the time of the authority application, the prescriber should request sufficient quantity and repeats to provide for the balance to complete up to 6 months of treatment (inclusive of initial and dose modification treatment), if dose modification is being accessed following initial treatment.
		Prescribing Instructions: An application for the continuing treatment must occur following an assessment of response conducted up to a maximum of 6 months from initiation of therapy. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
		Prescribing Instructions: If a patient fails to demonstrate a response to treatment 6 months after initiating treatment with this drug for this condition (inclusive of initial and dose modification treatment), they will no longer be eligible to receive PBS-subsidised treatment with this drug for this condition.

	Prescribing Instructions: An adequate clinical response **under this treatment phase** is defined as an average ≥1 grade improvement in pruritus score on the Prucision™ ObsRO Pruritus Scale, assessed on 3 occasions over a one week period prior to assessment of response.
	Prescribing Instructions: Confirmation of eligibility for dose modification treatment must be documented in the patient's medical records (include assessment of response score after at least 1 month and up to 3 months after commencing initial treatment)
	Prescribing Instructions: Any further authority applications occurring immediately after access through this dose modification listing are not to occur through the Initial treatment listing.
	Prescribing Instructions: **Dose modification** Where the drug's Product Information indicates variable dosing regimens based on the individual's response/tolerance, apply under this listing to continue treatment with the new strength. Mark any remaining repeat prescriptions for the discontinued strength with the word 'cancelled'. This treatment phase listing recognises that a patient's optimal dose may not always be immediately apparent at the time of treatment initiation and therefore does not require confirmation of an objective, adequate response to the preceding supply of drug.
	Prescribing Instructions: Eligible patients must not be recommencing treatment directly through this treatment phase;

Continuing

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ODEVIXIBAT					
odevixibat 200 mcg capsule, 30	NEW	12	360	5	Bylvay
odevixibat 400 mcg capsule, 30	NEW	6	180	5	Bylvay
odevixibat 600 mcg capsule, 30	NEW	12	360	5	Bylvay
odevixibat 1200 mcg capsule, 30	NEW	6	180	5	Bylvay

Restriction Summary [new] Treatment of Concept: [new]		
Concept ID (for internal Dept. use)		**Category / Program:** Section 85 - General Schedule
		Prescriber type: ☒ Medical Practitioners
		Restriction type: ☒ Authority Required (telephone/electronic)
Prescribing		**Administrative advice:** No increase in the maximum quantity or number of units may be authorised
		Administrative advice: No increase in the maximum number of repeats may be authorised
		Administrative Advice: Special Pricing Arrangements Apply
		Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
		Administrative Advice: The recommended dose of odevixibat for initial treatment is 40 micrograms/kg/day. 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 been achieved after 3 consecutive months since commencement of treatment, odevixibat should be renewed at 40 micrograms/kg/day through the continuing treatment phase. **Dose Modification (where dose escalation occurs during initial treatment)**

		If an adequate clinical response has not been achieved after at least 1 month and up to 3 months of initial treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the dose modification treatment phase for up to a total period of 6 months from the date of treatment commencement with odevixibat. If an adequate clinical response is demonstrated following the balance of up to 6 months of treatment at the higher dose of 120 micrograms/kg/day, odevixibat can be renewed at the same dose through the continuing treatment phase. If a patient fails to demonstrate a response after 6 months of treatment with this drug for this condition (inclusive of initial and dose modification treatment), they will no longer be eligible to receive PBS-subsidised treatment with this drug for this condition. **Continuing Treatment (where dose escalation occurs during continuing treatment)** If an adequate clinical response is unable to be maintained at the lower dose (40 micrograms/kg/day) during continuing treatment, the dose may be increased to 120 micrograms/kg/day (maximum of 7,200 micrograms per day) through the continuing treatment phase. If an adequate clinical response is demonstrated at the higher dose of 120 micrograms/kg/day, odevixibat can continue to be renewed at the same dose through the continuing treatment phase. Patients who are unable to demonstrate an adequate clinical response to continuing treatment at the higher dose will be ineligible for further PBS-subsidised treatment with this drug for this condition. **Recommencing treatment** Patients who have demonstrated an adequate clinical response and have ceased treatment for reasons other than a lack of response may recommence treatment through the continuing treatment phase.
		Administrative Advice: The Prucision™ ObsRO Pruritus Scale is available as a downloadable document at: [INSERT LINK]
		Episodicity:n/a
		Severity: n/a
		Condition: Progressive familial intrahepatic cholestasis (PFIC)
		Indication: Progressive familial intrahepatic cholestasis (PFIC)
		Treatment Phase: Continuing Treatment (PFIC diagnosed over 18 years of age)
		Clinical criteria:
		Patient must have previously received PBS-subsidised treatment with this drug for this condition
		AND
		Clinical criteria:
		Patient must have demonstrated an adequate clinical response to the most recent course of treatment; or
		Patient must be undergoing dose escalation to 120 micrograms/kg/day if they were unable to maintain a previously demonstrated adequate clinical response at 40 micrograms/kg/day in continuing treatment
		AND
		Clinical criteria:
		Patient must not be undergoing treatment with this drug for this condition, where an adequate clinical response was unable to be maintained at 120 micrograms/kg/day
		Treatment criteria:
		Must be treated by a specialist hepatologist experienced in the management of PFIC
		Must be treated by a medical practitioner under the supervision of a specialist experienced in the management of PFIC

	Prescribing Instructions: An adequate clinical response **under this treatment phase** is defined as an average ≥1 grade improvement in pruritus score on the Prucision™ ObsRO Pruritus Scale, assessed on 3 occasions over a one week period prior to assessment of response.
	Prescribing Instructions: Confirmation of eligibility for continuing treatment must be provided with the authority application and documented in the patient's medical records (include assessment of adequate clinical response to preceding supply)
	Prescribing Instructions: A patient may be eligible for treatment at the higher dose (120 micrograms/kg/day), if a loss of response or an adequate response was unable to be maintained at the lower dose (40 micrograms/kg/day) during continuing treatment. To be eligible for continuing treatment at the higher dose (120 micrograms/kg/day), the patient must demonstrate and maintain an adequate clinical response at the higher dose.

DIBR	Listed drug	Description of document	Document access
ObsRo Pruritus Scale	Odevixibat	This document provides health professionals with the observer reported outcomes (ObsRO) pruritus scale for assessing patient scratching associated with PFIC. The scale runs in whole numbers from 0 to 4 with grade 0 representing no scratching to grade 4 representing worst possible scratching	Website URL to be advised

These restrictions may be subject to further review. Should there be any changes made to the restrictions the sponsor will be informed.

15 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.

16 Sponsor's Comment

The sponsor had no comment.