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

# 5.11 SELADELPAR, Capsule 10 mg, Livdelzi®, Gilead Sciences Pty Ltd

## 1 Purpose of submission

1.1 The Category 2 submission requested Authority Required (STREAMLINED) listing for seladelpar as treatment for primary biliary cholangitis (PBC).

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus best supportive care (BSC), a cost-effectiveness analysis versus obeticholic acid (OCA), and a cost-minimisation approach versus elafibranor. Table 1 summarises the components of the clinical claim addressed by the submission.

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

| Component | Description |
|---|---|
| Population | Patients with primary biliary cholangitis, who have had an inadequate response to UDCA or are intolerant to UDCA. |
| Intervention | Seladelpar at a dose of 10 mg/day in combination with UDCA (if UDCA is tolerated).<br>Seladelpar monotherapy at a dose of 10 mg/day (if UDCA is not tolerated). |
| Comparator[a] | • BSC consisting of:<br>  ○ Background therapy with UDCA (if UDCA is tolerated).<br>  ○ Placebo (if UDCA is not tolerated).<br>• OCA 5-10 mg/day +UDCA (if UDCA is tolerated).<br>• ELA 80 mg/day + UDCA (if UDCA is tolerated). |
| Outcomes | Primary outcome<br>• Biochemical response (ALP < 1.67x ULN and total bilirubin within normal limits, and ALP decrease of ≥ 15%).<br>Secondary/exploratory/safety outcomes<br>• ALP normalisation (ALP ≤ 1.0 x ULN).<br>• Change from baseline in weekly average Pruritus NRS.<br>• Change from baseline in PBC-40 QoL.<br>• Change from baseline in PBC-40 QoL itch domain.<br>• Change from baseline in 5-D itch.<br>• Frequently reported AEs.<br>• Treatment-emergent serious AEs. |
| Clinical claim | Seladelpar is superior to BSC in terms of efficacy and non-inferior to BSC in terms of safety.<br>Seladelpar is superior to OCA in terms of efficacy and safety.<br>Seladelpar is non-inferior to elafibranor in terms of efficacy and safety. |

Source: Table 1, p8 of the submission.

5-D = 5 dimensions (degree, duration, direction, disability, distribution); AE = adverse event; ALP = alkaline phosphatase; BSC = best supportive care; ELA = elafibranor; NRS = numeric rating scale; OCA = obeticholic acid; PBC = primary biliary cholangitis; QoL = quality of life; UDCA = ursodeoxycholic acid; ULN = upper limit of normal.

[a] Table 1 of the submission did not specify whether OCA and ELA were provided with or without UDCA. However, the evidence presented in Section 2 was for OCA + UDCA (if UDCA is tolerated) and ELA + UDCA (if UDCA is tolerated).

# 2 Background

## *Registration status*

2.1 The submission was made under the TGA/PBAC Parallel Process. At the time of ESC consideration, the TGA planning letter was available. The TGA Clinical Evaluator's Report (CER) was received on 8 July 2025 and the Delegate's overview was expected on 4 November 2025.

## *Previous PBAC consideration*

2.2 The PBAC has not previously considered seladelpar for any indication.

2.3 The PBAC recommended the listing of elafibranor for the treatment of PBC at its March 2025 meeting[1]. The PBAC considered that elafibranor was non-inferior in terms of effectiveness and safety compared to obeticholic acid (OCA) and therefore considered that a cost-minimisation approach versus OCA to be appropriate. The PBAC considered that a price premium for elafibranor would be reasonable given the potential reduction in PBC-related pruritus compared to OCA. The PBAC considered that elafibranor should join the risk sharing arrangement for OCA.

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

# 3 Requested listing

3.1 The requested listing for seladelpar is provided below. Secretariat suggestions and additions proposed are shown in italics and deletions are in strikethrough.

| **MEDICINAL PRODUCT medicinal product pack** | | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of Rpts** | **Available brands** |
|---|---|---|---|---|---|---|
| SELADELPAR | | | | | | |
| seladelpar 10 mg capsule, 30 | | NEW | 1 | 30 | 5 | Livdelzi |
| | | | | | | |
| Restriction Summary [16121] / Treatment of Concept: [16132] | | | | | | |
| **Concept ID** (for internal Dept. use) | **Category / Program:** ☒ GENERAL - General Schedule (Code GE) | | | | | |
| | **Prescriber type:** ☒ Medical Practitioners | | | | | |
| | **Restriction type:** ☒ Authority Required: ~~Streamlined~~ *immediate assessment (telephone/online)* | | | | | |
| Prescribing rule level | *2* | ***Caution:*** *Hepatic decompensation and failure, in some cases fatal, have been reported in post-marketing reports in patients with moderate to severe hepatic impairment when dosed incorrectly.* | | | | |
| | | ***Administrative Advice:*** *Not for use in the treatment of sclerosing cholangitis ~~or cholelithiasis.~~* | | | | |
| | | ***Administrative Advice:*** | | | | |

[1] Pharmaceutical Benefits Advisory Committee (PBAC) Meeting Outcomes, March 2025 PBAC meeting. https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2025-03/pbac-web-outcomes-03-2025.pdf

| | | |
|---|---|---|
| | | *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 888 333.* |
| | | ***Administrative Advice:***<br>*No increase in the maximum quantity or number of units may be authorised.* |
| | | ***Administrative Advice:***<br>*No increase in the maximum number of repeats may be authorised.* |
| | | ***Administrative Advice:***<br>*Special Pricing Arrangements apply.* |
| | | **Indication:** Primary biliary cholangitis (previously known as Primary biliary cirrhosis) |
| | | **Treatment Phase:** Initial treatment |
| | | **Treatment criteria:** |
| | | Must be treated by a prescriber who is either: (i) a gastroenterologist, (ii) a hepatologist; |
| | | **OR** |
| | | Must be treated by a medical practitioner who has consulted at least one of the above mentioned specialist types~~, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion~~ |
| | | **AND** |
| | | **Treatment criteria:** |
| | | Patient must be undergoing concurrent treatment with ursodeoxycholic acid~~, following this authority application~~; |
| | | **OR** |
| | | Patient must be undergoing treatment with this drug as monotherapy ~~following this authority application,~~ because ~~combination~~ treatment with ursodeoxycholic acid is not tolerated*/contraindicated* |
| | | **AND** |
| | | **Treatment criteria:** |
| | | Patient must not be undergoing ~~concomitant PBS-subsidised~~ *concurrent* treatment with obeticholic acid (or elafibranor) |
| | | **Clinical criteria:** |
| | | Patient must have experienced an inadequate response to ursodeoxycholic acid, despite treatment with ursodeoxycholic acid for at least 52 weeks at a therapeutic dose, prior to initiating treatment with this drug; |
| | | **OR** |
| | | Patient must have experienced an intolerance*/contraindication* to ursodeoxycholic acid of a severity requiring permanent treatment discontinuation, prior to initiating treatment with this drug |
| | | **AND** |
| | | **Clinical criteria:** |
| | | Patient must not have*/be each of*: *(i)* severe liver disease, *(ii) immunocompromised* |
| | | **AND** |
| | | **Clinical criteria:** |
| | | Patient must have an alkaline phosphatase (ALP) level of at least 1.67 times the upper limit of normal (ULN) having accounted for each of: (i) age, (ii) gender, (iii) laboratory to laboratory variances in the definition of 'normal', despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks; |
| | | **OR** |
| | | Patient must have a total bilirubin level between 1 to 2 times the ULN, despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks; |
| | | **OR** |
| | | Patient must have abnormal readings of at least one of: (i) alkaline phosphatase (ii) total bilirubin, in the presence of an intolerance of a severity requiring treatment discontinuation with ursodeoxycholic acid |
| | | **Population criteria:** |

| | |
|---|---|
| | Patient must be ~~aged~~ *at least* 18 years of age |
| | **Prescribing Instructions:**<br>Document and retain in the patient's medical records the qualifying baseline laboratory reading for the purpose of assessing response to treatment under the 'Continuing treatment' restriction. |
| | ***Administrative Advice:***<br>*Laboratory readings requested in this authority application must be no older than 52 weeks.* |
| | |
| | |
| Restriction Summary [12138] / Treatment of Concept: [12138] | |
| **Concept ID** (for internal Dept. use) | **Category / Program:** ☒ GENERAL - General Schedule (Code GE) |
| | **Prescriber type:** ☒ Medical Practitioners ☒ *Nurse Practitioners* |
| | **Restriction type:** ☒ Authority Required: Streamlined |
| Prescribing rule level | ***Caution:***<br>*Hepatic decompensation and failure, in some cases fatal, have been reported in post-marketing reports in patients with moderate to severe hepatic impairment when dosed incorrectly.* |
| | ***Administrative Advice:***<br>*Not for use in the treatment of sclerosing cholangitis.* |
| | ***Administrative Advice:***<br>***Continuing Therapy Only:***<br>*For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.* |
| | ***Administrative Advice:***<br>*No increase in the maximum quantity or number of units may be authorised.* |
| | ***Administrative Advice:***<br>*No increase in the maximum number of repeats may be authorised.* |
| | **Indication:** Primary biliary cholangitis (previously known as Primary biliary cirrhosis) |
| | **Treatment Phase:** Continuing treatment |
| | **Treatment criteria:** |
| | Must be treated by a prescriber who is either: (i) a gastroenterologist, (ii) a hepatologist; |
| | **OR** |
| | Must be treated by an eligible practitioner type who has consulted at least one of the above mentioned specialist types~~, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion~~ |
| | **AND** |
| | ***Treatment criteria:*** |
| | *Patient must be undergoing continuing PBS-subsidised treatment with this drug, with treatment having commenced through one of: (i) the 'Initial treatment' listing, (ii) 'Grandfather' arrangements, (iii) 'Switching treatment' listing* |
| | **AND** |
| | **Treatment criteria:** |
| | Patient must be undergoing concurrent treatment with ursodeoxycholic acid~~, following this authority application;~~ |
| | **OR** |
| | Patient must be undergoing treatment with this drug as monotherapy ~~following this authority application,~~ because combination treatment with ursodeoxycholic acid is not tolerated/*contraindicated* |
| | ***AND*** |
| | ***Treatment criteria:*** |
| | *Patient must not be undergoing concurrent treatment with obeticholic acid [or elafibranor]* |
| | **Clinical criteria:** |

| | | |
|---|---|---|
| | | Patient must have achieved an adequate response to this drug, defined as having at least one of: (i) an alkaline phosphate (ALP) level less than 1.67 times the upper limit of normal (ULN), (ii) a reduction in the ALP reading of at least 15% compared to the baseline level provided with the initial authority application, (iii) a total bilirubin level within the normal reference range |
| | | **Prescribing Instructions:**<br>The improvement in the qualifying laboratory reading(s) has/have been documented in the patient's medical records. |
| | | **Administrative Advice:**<br>Laboratory readings requested in this authority application must be no older than 52 weeks. |
| | | |
| | | |
| **Restriction Summary [NEW] / Treatment of Concept: [NEW]** | | |
| **Concept ID** (for internal Dept. use) | | **Category / Program:** ☒ GENERAL - General Schedule (Code GE) |
| | | **Prescriber type:** ☒ Medical Practitioners ☒ *Nurse Practitioners* |
| | | **Restriction type:** ☒ Authority Required: ~~Streamlined~~ *immediate assessment (telephone/online)* |
| *Prescribing rule level* | | ***Caution:***<br>*Hepatic decompensation and failure, in some cases fatal, have been reported in post-marketing reports in patients with moderate to severe hepatic impairment when dosed incorrectly.* |
| | | ***Administrative Advice:***<br>*Not for use in the treatment of sclerosing cholangitis* |
| | | ***Administrative Advice:***<br>***Continuing Therapy Only:***<br>*For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.* |
| | | ***Administrative Advice:***<br>*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 888 333.* |
| | | ***Administrative Advice:***<br>*No increase in the maximum quantity or number of units may be authorised.* |
| | | ***Administrative Advice:***<br>*No increase in the maximum number of repeats may be authorised.* |
| | | ***Administrative Advice:***<br>*Special Pricing Arrangements apply.* |
| | | **Indication:** Primary biliary cholangitis (previously known as Primary biliary cirrhosis) |
| | | **Treatment Phase:** Transitioning from non-PBS to PBS subsidised supply - Grandfather arrangements |
| | | ***Clinical criteria:*** |
| | | *Patient must have received treatment with this drug for this PBS indication prior to [Date]* |
| | | **Treatment criteria:** |
| | | Must be treated by a prescriber who is either: (i) a gastroenterologist, (ii) a hepatologist; |
| | | **OR** |
| | | Must be treated by an eligible practitioner type who has consulted at least one of the above mentioned specialist types~~, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion~~ |
| | | **AND** |
| | | **Treatment criteria:** |
| | | Patient must be undergoing concurrent treatment with ursodeoxycholic acid~~, following this authority application~~; |
| | | **OR** |

| | |
|---|---|
| | Patient must be undergoing treatment with this drug as monotherapy ~~following this authority application,~~ because combination treatment with ursodeoxycholic acid is not tolerated/*contraindicated* |
| | ***AND*** |
| | ***Treatment criteria:*** |
| | *Patient must not be undergoing concurrent treatment with obeticholic acid (or elafibranor)* |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have experienced an inadequate response to ursodeoxycholic acid, despite treatment with ursodeoxycholic acid for at least 52 weeks at a therapeutic dose, prior to initiating treatment with this drug; |
| | **OR** |
| | Patient must have experienced an intolerance/*contraindication* to ursodeoxycholic acid of a severity requiring permanent treatment discontinuation, prior to initiating treatment with this drug |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must not have/*be each of (i)* severe liver disease *(ii) immunocompromised* |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have had, prior to initiating treatment with this drug, an alkaline phosphatase (ALP) level of at least 1.67 times the upper limit of normal (ULN) having accounted for each of: (i) age, (ii) gender, (iii) laboratory to laboratory variances in the definition of 'normal', despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks; |
| | **OR** |
| | Patient must have had, prior to initiating treatment with this drug, a total bilirubin level between 1 to 2 times the ULN, despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks; |
| | **OR** |
| | Patient must have had, prior to initiating treatment with this drug, abnormal readings of at least one of: (i) alkaline phosphatase (ii) total bilirubin, in the presence of an intolerance of a severity requiring treatment discontinuation with ursodeoxycholic acid |
| | **Population criteria:** |
| | Patient must be at least 18 years of age |
| | **Prescribing Instructions:**<br>Document and retain in the patient's medical records the qualifying baseline laboratory reading for the purpose of assessing response to treatment under the 'Continuing treatment' restriction. |
| | ***Administrative Advice:***<br>*Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.* |
| | ***Administrative Advice:***<br>*This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.* |

3.2 The submission did not explicitly propose a published or effective price for seladelpar. Given that two approaches to the economic evaluation of seladelpar have been presented: i) a cost-effectiveness analysis to OCA which is subject to a confidential special pricing arrangement (SPA); and ii) a cost minimisation approach to elafibranor which, at present, has no established pricing, there is no anchor on which to base the prices for seladelpar. The submission proposed a placeholder DPMQ of $ per pack for the sole purpose of enabling the assessment of the economic evaluation and financial estimates. It was noted that this was an unusual approach to take for a cost utility analysis when a comparator is subject to special pricing arrangements, as the

incremental cost effectiveness ratio (ICER) was deliberately overestimated in the submission.

3.3 The submission proposed that while OCA has an 'Authority Required – immediate assessment' initial restriction, an 'Authority Required (Streamlined)' initial restriction was sufficient for seladelpar because the OCA restriction excluded patients who were immunocompromised whereas the proposed seladelpar restriction did not. Given there are multiple other clinical criteria in the seladelpar restriction (including qualifying baseline laboratory readings) the evaluation suggested a restriction listing, consistent with the initial OCA restriction (PBS item 12623J), may be more appropriate. Furthermore, the proposed restriction which does not exclude immunocompromised patients was inconsistent with the seladelpar RESPONSE trial, which excluded participants who were immunocompromised.

3.4 To allow treatment switching, the proposed text regarding intolerance to OCA or elafibranor could be incorporated into the initial restriction text regarding intolerance to ursodeoxycholic acid (UDCA). Regarding inadequate response, patients who are unable to meet the ALP or total bilirubin (TB) response criteria for continuing treatment with OCA or elafibranor would meet the initial criteria for seladelpar.

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

# 4 Population and disease

4.1 PBC is a rare but serious and potentially life-limiting autoimmune disease characterised by the destruction of intrahepatic bile ducts, leading to the build-up of bile acids. These bile acids accumulate, causing cholestasis-mediated tissue damage, inflammation and further blockage of remaining biliary ducts. The progressive worsening of liver function is reflected by increasing levels of ALP and TB. Untreated PBC is characterised by progressive cholestasis, biliary fibrosis, and culminating in end-stage biliary cirrhosis.

4.2 The submission stated that PBC has a global estimated prevalence of 14.6 per 100,000 and an incidence of 1.76 per 100,000 per year. The submission further noted that one Australian study estimated the 2013 prevalence of PBC in Victoria to be 18.9 per 100,000 (French 2020).[2] PBC predominantly (95%) affects women aged over 40 years, with the most common age between 45 and 65 years. The female predominance of PBC remains unexplained but it is thought to involve poorly characterised epigenetic factors.

4.3 The characteristic symptoms of PBC are significant fatigue and chronic cholestatic pruritus, both of which are debilitating conditions that can have marked effects on a patient's quality of life.

[2] French J, van der Mei I, et al. 2020. Increasing prevalence of primary biliary cholangitis in Victoria, Australia, Journal of Gastroenterology and Hepatology, 35:673-679. doi:10.1111/jgh.14924673

4.4 The goal of treatment and management of PBC is to prevent progressive liver disease and ameliorate associated symptoms that reduce patient quality of life. UDCA is the main disease-modifying treatment available in Australia and the established first-line treatment for PBC. The European Association for the Study of the Liver (EASL) guidelines (2017)[3] recommend that patients with PBC (including those with asymptomatic disease) should be treated with UDCA on a long-term basis. Approximately 30–40% of patients fail to achieve an adequate biochemical response to UDCA. Intolerance to UDCA is seen in up to 5% of patients.

4.5 The submission stated that in Australia, clinical practice for assessing treatment response was influenced by access to Pharmaceutical Benefits Scheme (PBS)-subsidised second-line treatment with OCA and incorporated measurements of both ALP and TB. To initiate PBS-subsidised treatment with OCA, patients must have had an inadequate response to treatment with UDCA, defined as meeting either of the following criteria despite 52 weeks of therapy: (i) ALP level ≥1.67 x upper limit of normal (ULN) or (ii) TB level ≥1 x ULN.

4.6 The submission claimed that it was likely that seladelpar would replace the use of OCA as an add-on therapy in patients who have failed to achieve an adequate response to an optimised dose of UDCA after at least a year of treatment. In addition, seladelpar could be used as an alternative to OCA monotherapy in patients who are intolerant to UDCA.

4.7 The submission claimed that seladelpar would replace BSC for patients contraindicated for OCA because of pre-existing pruritus or cirrhosis and patients eligible for but not taking OCA due to concerns around its benefit-to-risk profile. The submission noted that in November 2024 the European Medicines Agency (EMA) revoked the conditional marketing authorisation for OCA because its benefits no longer outweighed its risks as a treatment for PBC.

4.8 The submission noted that if elafibranor was approved by the PBAC for the second-line treatment of PBC, it was expected, given the comparable efficacy and safety profiles, that seladelpar and elafibranor would share the same position within the proposed treatment algorithm.

4.9 Seladelpar is a novel, potent and selective peroxisome proliferator-activated receptor delta (PPARδ) agonist that targets multiple cell types in the liver leading to anticholestatic, anti-inflammatory, anti-pruritic, and antifibrotic effects. Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors with a key role in the regulation of genes involved in bile acid metabolism, inflammation, and metabolic pathways, including glycaemic control and lipid metabolism. There are 3 isoforms of

[3] European Association for the Study of the Liver (EASL). 2017. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. Journal of hepatology, 67(1), 145–172. https://doi.org/10.1016/j.jhep.2017.03.022

PPARs (PPARα, PPARγ, and PPARδ). Elafibranor is a mixed-PPAR agonist that was considered by the PBAC for the treatment of PBC at the March 2025 PBAC meeting.

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

# 5 Comparator

5.1 The submission nominated OCA and BSC as the main comparators and elafibranor as a relevant near-market comparator. The main arguments provided in support of these nominations were:

- OCA is the only second-line treatment for PBC that is currently reimbursed on the PBS.
- Given the recent decision by the EMA to revoke marketing approval for OCA and by the FDA to recommend against full approval of OCA for the treatment of PBC, BSC was nominated as a comparator in the instance that OCA is removed from the PBS It was noted that BSC would also be a comparator for patients who are intolerant to OCA.
- Elafibranor was considered by the PBAC at the March 2025 meeting for the same indication as seladelpar.

5.2 The submission stated that BSC would consist of therapies to treat symptoms (such as pruritus and fatigue) and lifestyle changes (including diet and exercise) only.

5.3 The ESC considered that the nominated comparators were reasonable.

5.4 The submission proposed that sequential treatment with OCA, elafibranor, and seladelpar should be permitted. No clinical evidence regarding sequential treatment with elafibranor and seladelpar was presented in the submission. Sequential treatment was not considered in the economic analysis or financial estimates.

5.5 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

*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 presented a clinical perspective on the need for multiple agents for treatment of PBC in a second-line setting, following UDCA. It was raised that a proportion of patients either don't respond to or tolerate UDCA, and it was important to have treatment options to target

less pruritis. The clinician described the debilitating symptoms PBC and the impact on patients' quality of life, including lack of sleep and depression. A patient perspective was also presented. The patient described the experience of living with the PBC, including the fatigue and loss of livelihood associated with the symptoms, particularly severe itching. After a trial period on seladelpar the patient experienced life changing benefits and was able to return to her normal life. Her Stage 3 fibrosis was also reversed and now classed as Stage 1.

6.2 The PBAC considered that the hearing was informative as it provided a clinical perspective on the clinical place of seladelpar and the patient perspective was very clear on the severity of the symptoms and the benefit of reducing pruritis.

## *Consumer comments*

6.3 The PBAC noted and welcomed the input from one organisation, the Liver Foundation via the Consumer Comments facility on the PBS website. The comment supported the listing of seladelpar on the PBS.

6.4 The comments described the significant impact of PBC on quality of life, particularly chronic fatigue and severe itching, which can be debilitating, relentless and indescribable, with no effective relief.

## *Clinical trials*

6.5 The submission was based on one RCT, the RESPONSE trial, comparing seladelpar to BSC to inform the comparison to BSC. Additional evidence from the POISE and ELAIVE trials was provided to inform indirect treatment comparisons (ITCs) with OCA and elafibranor:

- The RESPONSE trial (N=193) compared:
- Seladelpar ± UDCA (n=128) versus placebo ± UDCA (n=65) in participants with PBC and inadequate response or intolerance to UDCA.
- The POISE trial (N=144) compared:
  - OCA 5-10 mg ± UDCA (n=71) versus placebo ± UDCA (n=73) in participants with PBC and inadequate response or intolerance to UDCA.
- The ELATIVE trial (N=161) compared:
  - Elafibranor 80 mg ± UDCA (n=102) versus placebo ± UDCA (n=51) in participants with PBC and inadequate response or intolerance to UDCA.

6.6 The proportion of participants in each trial receiving treatment or placebo without concomitant UDCA was small (RESPONSE n=12, POISE n=10, ELATIVE n=10).

6.7 The submission also identified one systematic review of second-line treatments for PBC (Giannini 2024).

6.8 Details of the trials presented in the submission are provided in Table 2. The submission identified multiple conference abstracts, *post hoc* analyses, and subgroup

analyses for the included trials (5 for the RESPONSE trial, 35 for the POISE trial, and 4 for the ELATIVE trial). These abstracts and analyses were not relied upon for the clinical claim, so are not presented below.

**Table 2: Trials and associated reports presented in the submission**

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| **Seladelpar** | | |
| RESPONSE<br>NCT04620733 | RESPONSE: A Placebo-controlled, Randomized, Phase 3 Study to Evaluate the Efficacy and Safety of Seladelpar in Patients with Primary Biliary Cholangitis (PBC) and an Inadequate Response to or an Intolerance to Ursodeoxycholic Acid (UDCA)<br>Hirschfield GM, Bowlus CL, Mayo MJ, et al. A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis | 30 November 2023<br><br>*NEJM.* 2024; 390(9):783-94 |
| **OCA** | | |
| POISE<br>NCT01473524<br>EUCTR2011-004728-36-BE | Nevens F, Andreone P, Mazzella G, et al. A Placebo-controlled trial of obeticholic acid in primary biliary cholangitis. | *NEJM.* 2016; 375(7):631-43. |
| **Elafibranor** | | |
| ELATIVE<br>NCT04526665<br>EUCTR2019-004941-34-BE | Kowdley KV, Bowlus CL, Levy C, et al. Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. | *NEJM.* 2024a; 390(9):795-805 |
| **Systematic reviews** | | |
| Giannini 2024 | Giannini, E. G., Pasta, A., Calabrese, F., Labanca, S., Marenco, S., Pieri, G., Plaz Torres, M. C., & Strazzabosco, M. (2024). Second-Line Treatment for Patients With Primary Biliary Cholangitis: A Systematic Review With Network Meta-Analysis. | *Liver International: official journal of the International Association for the Study of the Liver.* 45(1), e16222. |

Source: Tables 16 & 17, pp48-53 of the submission.
OCA = obeticholic acid, PBC = Primary Biliary Cholangitis, UDCA = ursodeoxycholic acid.

6.9 The submission also noted 3 long-term safety extension studies as studies of interest: the seladelpar ASSURE study, the OCA POISE LTSE study, and the elafibranor ELATIVE OLE study. The POISE and ELATIVE trials and the POISE LTSE and ELATIVE OLE studies were previously considered by the PBAC, most recently as part of the elafibranor submission at the March 2025 PBAC meeting.

6.10 The key features of the direct randomised trials are summarised in Table 3.

**Table 3: Key features of the included evidence – indirect comparison**

| Trial | N | Design/ duration | Risk of bias | Participant population | Outcome(s) | Use in modelled evaluation |
|---|---|---|---|---|---|---|
| **Seladelpar vs placebo** | | | | | | |
| RESPONSE | 193 | R, DB, MC 12 months | Low | Adults 18-75 with PBC.<br>Liver function tests:<br>• ALP: ≥ 1.67 x ULN;<br>• AST: ≤ 3 x ULN;<br>• ALT: ≤ 3 x ULN; and<br>• TB: ≤ 2 x ULN<br>Additional requirements for renal function, coagulation status, and platelet count.<br>Inadequate response to or unacceptable side effects with UDCA. | Primary: Biochemical response (ALP <1.67 x ULN and TB ≤ULN and ALP decrease of ≥15%).<br>Secondary: ALP normalisation; Pruritus NRS, PBC-40 total; PBC-40 itch domain, 5-D itch.<br>Safety: TEAEs, Pruritus events | ALP normalisation, discontinuations, pruritus, utilities |
| **OCA vs placebo** | | | | | | |
| POISE | 143[a] | R, DB, MC 12 months | Moderate[b] | Adults 18+ with PBC.<br>Liver function tests: at least one of<br>• ALP ≥ 1.67 x ULN<br>• TB > ULN but < 2 x ULN<br>Inadequate response to or unacceptable side effects with UDCA. | Primary: Biochemical response (ALP <1.67 x ULN and TB ≤ULN and ALP decrease of ≥15%).<br>Secondary: ALP normalisation; PBC-40 total; PBC-40 itch; 5-D itch.<br>Safety: TEAEs, Pruritus events | ALP normalisation (calibrated HR vs seladelpar based on ITC), discontinuations, pruritus |
| **Elafibranor vs placebo** | | | | | | |
| ELATIVE | 161 | R, DB, MC 12 months | Low | Adults 18-75 with PBC.<br>Liver function tests:<br>• ALP ≥ 1.67 x ULN; and<br>• TB ≤ 2 x ULN<br>>8 available values for WI-NRS in the 14 days before randomisation.<br>Inadequate response to or unacceptable side effects with UDCA. | Primary: Biochemical response (ALP <1.67 x ULN and TB ≤ULN and ALP decrease of ≥15%).<br>Secondary: ALP normalisation; Pruritus NRS; PBC-40, PBC-40 itch; 5-D itch.<br>Safety: TEAEs, Pruritus events | Not used |

Source: Tables 21, 22, 27, 28, 81, 86, 87 & 99 pp67 & 71-73, 85-86, 89-90, 180, 185, 187 & 201 of the submission, pp53, 62 & 181 of the submission.

5-D = 5 dimensions (degree, duration, direction, disability, distribution); ALP = alkaline phosphatase; ALT = alanine transferase; AST = aspartate aminotransferase; DB = double-blind; HR = hazard ratio; ITC = indirect treatment comparison; MC = multi-centre; NRS = numeric rating scale; OCA = obeticholic acid; PBC = primary biliary cholangitis; R = randomised; TB = total bilirubin; UDCA = ursodeoxycholic acid; ULN = upper limit of normal; WI-NRS = worst itch numeric rating scale.

[a] The POISE trial included 217 participants; however, the OCA 10 mg arm (73 participants) was excluded from this submission because the OCA dose used in the trial arm is not recommended for use in Australia.

[b] The ESC and PBAC previously considered that unblinding due to the occurrence of pruritus introduced a moderate potential for bias in the POISE trial (paragraph 6.9, obeticholic acid, Public Summary Document (PSD), November 2018 PBAC meeting).

6.11 The submission noted that the RESPONSE trial required participants to meet the following additional laboratory values for inclusion, compared to the POISE and ELATIVE trials: aspartate aminotransferase (AST) levels ≤ 3 x ULN; alanine aminotransferase (ALT) levels ≤ 3 x ULN; estimated glomerular filtration rate (eGFR) > 45 mL/min/1.73 $m^2$; international normalised ratio (INR) below 1.1 x ULN; and a

platelet count of ≥ 100 x 103/µL. The submission concluded that the additional criteria meant that the RESPONSE trial excluded participants with severe liver disease, significant renal disease, or who were immunocompromised, which was in line with the existing PBS restriction for OCA and the proposed restriction for seladelpar. However, the proposed seladelpar restriction did not exclude patients who were immunocompromised (see paragraph 3.2).

6.12 There were also differences between the trials in terms of how ULN was defined for ALP and TB. The different ULN thresholds for each trial are presented in Table 4. The submission stated that to prevent confounding resulting from these differences, key effectiveness results and the indirect comparisons were based on recalculated response rates using individual patient data from the RESPONSE trial and the thresholds defined in the POISE and ELATIVE trials.

**Table 4: Thresholds of normal ALP and TB across the included trials.**

| Threshold | RESPONSE | POISE | ELATIVE |
|---|---|---|---|
| ALP, IU/L | 116 | Females: 118; Males: 124 | Females: 104; Males: 129 |
| TB, µmol/L | 18.8 | Females: 19.32; Males: 25.48 | 20.5 |

Source: Table 19, p61 of the submission.
ALP = alkaline phosphatase; TB = total bilirubin; ULN = upper limit of normal.

6.13 Participants were similar across the trials in terms of age, sex, race, and prior UDCA use. Participants were different across the trials in terms of pruritus history, cirrhosis, and baseline laboratory values for ALP, TB, AST, and gamma-glutamyl transferase (GGT); however, the ESC considered that using matching-adjusted indirect comparisons (MAICs) could potentially resolve most of these issues. It was noted that more participants in the RESPONSE trial had a history of pruritus (72%), compared to between 53% and 64% in relevant arms of the POISE trial. The ELATIVE trial did not report the percentage of participants with a history of pruritus. However, the mean baseline pruritus numeric rating scale score in the ELATIVE trial (3.3) was similar to the RESPONSE trial (3.0) meaning that participants in the RESPONSE and ELATIVE trials may be similar in terms of pruritus severity.

6.14 The submission concluded that there were small differences in baseline characteristics across the trials, particularly relating to cirrhosis and laboratory values, which may indicate differences in baseline severity between the trials. The submission noted that baseline ALP was found to be a key effect modifier in the National Institute for Health and Care Excellence (NICE) evaluation of elafibranor (TA1016).[4]

6.15 The patient-reported outcomes of Pruritus Numeric Rating Scale (NRS), Primary Biliary Cholangitis-40 (PBC-40) and 5-Dimension itch (5-D itch) were presented for a subgroup of participants with moderate to severe pruritus at baseline (defined as a baseline NRS score ≥ 4), described as the moderate to severe pruritus (MSPN)

[4] National Institute for Health and Care Excellence (NICE), 2024, Elafibranor for previously treated primary biliary cholangitis: Technology appraisal guidance (TA1016). https://www.nice.org.uk/guidance/ta1016

population. Baseline characteristics for the MSPN population were not presented for the RESPONSE and ELATIVE trials.

6.16 The submission noted that OCA 5–10 mg was recommended based on an absolute difference of 36% compared to placebo in the proportion of participants achieving a biochemical response. The submission stated that given no non-inferiority margin was identified from the available Public Summary Documents, non-inferiority in this submission was claimed based on p-values > 0.05 indicating no significant differences between treatments. No MCID was nominated for the superiority claims versus BSC and OCA or the non-inferiority claim versus elafibranor. No non-inferiority margin was nominated for the non-inferiority claim versus elafibranor.

6.17 The primary outcome (biochemical response) and one key secondary outcome (ALP normalisation) were surrogate outcomes. The submission claimed that standard serum liver tests such as ALP and TB have been extensively validated as simple and robust prognostic tools in PBC. The submission conducted a systematic review of endpoints in PBC that identified 80 studies reporting an association between ALP response, composite responses, and other surrogate endpoints with hard clinical outcomes, including liver transplantation, death, and hepatocellular carcinoma (HCC) development. Of these, 2 studies considered biochemical response as defined in the RESPONSE, POISE, and ELATIVE trials and 7 studies looked at ALP normalisation.

## *Comparative effectiveness*

### Whole trial analyses and indirect comparisons

6.18 The submission presented whole trial results for the RESPONSE, POISE, and ELATIVE trials and Bucher indirect comparisons for the outcomes described in Table 3. The submission also presented:

- For the comparison between seladelpar and OCA: A Bayesian network meta-analysis (NMA) based on the RESPONSE and POISE trials.
- For the comparison between seladelpar and elafibranor: an anchored matched adjusted indirect comparison (MAIC) for the outcomes of biochemical response, ALP normalisation, adverse events, and pruritus events based on the RESPONSE and ELATIVE trials. The submission presented a Bayesian network meta-analysis for the patient-reported outcomes of Pruritus NRS, PBC-40 itch domain, and 5-D itch based on the RESPONSE and ELATIVE trials. This was because baseline characteristics for the MSPN population were not available, making a MAIC unfeasible.

6.19 The submission justified using an anchored MAIC to compare seladelpar and elafibranor based on the difference in baseline ALP observed between the RESPONSE and ELATIVE trials. The MAIC adjusted for 4 key effect modifiers (age at screening, baseline ALP, baseline TB, and the proportion of participants with cirrhosis at baseline).

6.20 Table 5 summarises the RESPONSE, POISE and ELATIVE whole trial results and indirect comparisons for the primary outcome of biochemical response.

**Table 5: Summary of the RESPONSE, POISE and ELATIVE whole trial results and indirect comparisons for biochemical response (ITT population).**

| Trial ID | Intervention n /N (%) | Placebo n/N (%) | Treatment effect | | |
|---|---|---|---|---|---|
| | | | OR [95% CI]; p-value | RR [95% CI]; p-value | RD [95% CI]; p-value |
| **Seladelpar vs OCA 5-10 mg** | | | | | |
| **Bucher ITC per individual trial thresholds** | | | | | |
| RESPONSE | 79/128 (61.7) | 13/65 (20.0) | **6.45 [3.19, 13.05]** | **3.09 [1.86, 5.11]** | **0.42 [0.29, 0.55]** |
| POISE | 32/70 (45.7) | 7/73 (9.6) | **7.94 [3.20, 19.73]** | **4.77 [2.25, 10.08]** | **0.36 [0.23, 0.5]** |
| Indirect estimate of effect adjusted for the common reference | | | 0.812 [0.26, 2.57]; 0.723 | 0.65 [0.26, 1.60]; 0.347 | 0.06 [-0.13, 0.25]; 0.530 |
| **Bucher ITC per POISE threshold** | | | | | |
| RESPONSE | 81/128 (63.3) | 13/65 (20.0) | **6.89 [3.40, 13.97]** | **3.16 [1.91, 5.24]** | **0.43 [0.3, 0.56]** |
| POISE | 32/70 (45.7) | 7/73 (9.6) | **7.94 [3.20, 19.73]** | **4.77 [2.25, 10.08]** | **0.36 [0.23, 0.5]** |
| Indirect estimate of effect adjusted for the common reference | | | 0.87 [0.27, 2.75]; 0.809 | 0.66 [0.27, 1.64]; 0.372 | 0.07 [-0.12, 0.26]; 0.464 |
| **Bayesian NMA per POISE threshold** | | | | | |
| Indirect estimate of effect adjusted for the common reference | | | NR | 0.93 [95% CrI: 0.53, 1.62] | NR |
| **Seladelpar vs elafibranor** | | | | | |
| **Bucher ITC per individual trial thresholds** | | | | | |
| RESPONSE | 79/128 (61.7) | 13/65 (20.0) | **6.45 [3.19, 13.05]** | **3.09 [1.86, 5.11]** | **0.42 [0.29, 0.55]** |
| ELATIVE | 55/108 (50.9) | 2/53 (3.8) | **26.46 [6.13, 114.21]** | **13.5 [3.42, 53.22]** | **0.47 [0.36, 0.58]** |
| Indirect estimate of effect adjusted for the common reference | | | 0.24 [0.05, 1.24]; 0.088 | **0.23 [0.05, 0.99]; 0.048** | -0.05 [-0.22, 0.12]; 0.565 |
| **Bucher ITC per ELATIVE threshold** | | | | | |
| RESPONSE | 73/128 (57.0) | 6/65 (9.2) | **13.05 [5.25, 32.42]** | **6.18 [2.84, 13.44]** | **0.48 [0.37, 0.59]** |
| ELATIVE | 55/108 (50.9) | 2/53 (3.8) | **26.46 [6.13, 114.21]** | **13.5 [3.42, 53.22]** | **0.47 [0.36, 0.58]** |
| Indirect estimate of effect adjusted for the common reference | | | 0.49 [0.09, 2.76]; 0.421 | 0.46 [0.10, 2.22]; 0.332 | 0.01 [-0.15, 0.17]; 0.900 |
| **Anchored MAIC (4 effect modifiers) per ELATIVE threshold (ESS=70)** | | | | | |
| Indirect estimate of effect adjusted for the common reference | | | 0.73 [0.11, 4.72] | 0.70 [0.13, 3.78] | -0.01 [-0.19, 0.17] |

Source: Tables 55 & 60, pp132 & 135 of the submission; Table 17, p29, Attachment 7 of the submission.
CI = confidence interval; CrI = credible interval; ESS = effective sample size; ITC = indirect treatment comparison; ITT = intention to treat; n = number of participants with event; N = number of participants in arm; NMA = network meta-analysis; NR = not reported; OCA = obeticholic acid; PBO = placebo; OR = odds ratio; RD = risk difference; RR = relative risk.
**Bold** indicates statistically significant results. Results of the IPD analyses could not be verified during the evaluation.

6.21 The RESPONSE trial met its primary efficacy endpoint, with a clinically meaningful and statistically significant difference in the percentage of participants in the seladelpar arm (61.7%) achieving the composite biochemical response compared with those in the placebo arm (20.0%); p<0.0001 based on percentage difference (Table 5). Regardless of whether biochemical response was defined per the RESPONSE, POISE or ELATIVE thresholds, there was a greater proportion of participants treated with seladelpar relative to placebo achieving a biochemical response at 12 months.

6.22 The Bucher indirect comparison showed comparable results for patients treated with seladelpar versus OCA. There were no statistically significant differences based on odds ratios (OR), relative risk (RR), or risk difference (RD). The results were similar

when the RESPONSE results were recalculated to fit the POISE trial threshold for biochemical response. The results were again similar when a Bayesian NMA was used for the comparison of seladelpar versus OCA.

6.23 The Bucher indirect comparison comparing seladelpar versus elafibranor achieved a statistically significant result using RR as the measure of association (RR = 0.23; 95% CI: 0.05, 0.99; p=0.048), but not OR (0.24; 95% CI: 0.05, 1.24; p=0.088) or RD (-0.05; 95% CI: -0.22, 0.12; p=0.565). When the RESPONSE results were recalculated to fit the ELATIVE trial threshold for biochemical response, there were no statistically significant differences based on OR, RR, or RD. The results of the anchored MAIC were consistent with the Bucher indirect comparison using the ELATIVE trial threshold for biochemical response.

6.24 Table 6 summarises the RESPONSE, POISE and ELATIVE whole trial results and indirect comparisons for the key secondary outcome of ALP normalisation.

**Table 6: Summary of the RESPONSE, POISE and ELATIVE whole trial results and indirect comparisons for ALP normalisation (ITT population).**

| Trial ID | Intervention n /N (%) | Placebo n/N (%) | Treatment effect | | |
|---|---|---|---|---|---|
| | | | OR [95% CI]; p-value | RR [95% CI]; p-value | RD [95% CI]; p-value |
| **Seladelpar vs OCA 5-10 mg** | | | | | |
| **Bucher ITC per individual trial thresholds** | | | | | |
| RESPONSE | 32/128 (25.0) | 0 | **44.12 [2.65, 733.27]** | **33.26 [2.07, 534.58]** | **0.25 [0.17, 0.33]** |
| POISE | 1/70 (1.4) | 0 | 3.17 [0.13, 79.2] | 3.13 [0.13, 75.49] | 0.01 [-0.02, 0.33] |
| Indirect estimate of effect adjusted for the common reference | | | 13.92 [0.20, 989.68]; 0.226 | 10.626 [0.16, 725.42]; 0.273 | **0.24 [0.05, 0.43]; 0.015** |
| **Bucher ITC per POISE threshold** | | | | | |
| RESPONSE | 33/128 (25.8) | 0 | **45.95 [2.77, 763.32]** | **34.28 [2.13, 550.68]** | **0.26 [0.18, 0.34]** |
| POISE | 1/70 (1.4) | 0 | 3.17 [0.13, 79.2] | 3.13 [0.13, 75.49] | 0.01 [-0.02, 0.05] |
| Indirect estimate of effect adjusted for the common reference | | | 14.50 [0.20, 1029.33]; 0.219 | 10.95 [0.16, 747.93]; 0.267 | **0.25 [0.16, 0.34]; < 0.001** |
| **Bayesian NMA per POISE threshold** | | | | | |
| Indirect estimate of effect adjusted for the common reference | | | NR | 16.62 [95% CrI: 0.04, 2512] | NR |
| **Seladelpar vs elafibranor** | | | | | |
| **Bucher ITC per individual trial thresholds** | | | | | |
| RESPONSE | 32/128 (25.0) | 0 | **44.12 [2.65, 733.27]** | **33.26 [2.07, 534.58]** | **0.25 [0.17, 0.33]** |
| ELATIVE | 16/108 (14.8) | 0 | **19.09 [1.12, 324.58]** | **16.35 [1, 267.38]** | **0.15 [0.08, 0.22]** |
| Indirect estimate of effect adjusted for the common reference | | | 0.1 [-0.01, 0.21]; 0.065 *2.31 [0.04, 125.23]; 0.681* | 2.03 [0.04, 104.55]; 0.724 | 2.31 [0.04, 125.23]; 0.681 *0.1 [-0.01, 0.21]; 0.065* |
| **Bucher ITC per ELATIVE threshold** | | | | | |
| RESPONSE | 23/128 (18.0) | 0 | **29.18 [1.74, 488.60]** | **24.05 [1.48, 389.70]** | **0.18 [0.11, 0.25]** |
| ELATIVE | 16/108 (14.8) | 0 | **19.09 [1.12, 324.58]** | **16.35 [1.00, 267.38]** | **0.15 [0.08, 0.22]** |
| Indirect estimate of effect adjusted for the common reference | | | 1.53 [0.03, 83.26]; 0.835 | 1.21 [0.04, 37.11]; 0.912 | 0.03 [-0.07, 0.13]; 0.553 |
| **Anchored MAIC (4 effect modifiers) per ELATIVE threshold (ESS=70)** | | | | | |
| Indirect estimate of effect adjusted for the common reference | | | 1.77 [0.03, 96.33] | 1.66 [0.03, 85.54] | 0.05 [-0.04, 0.15] |

Source: Tables 56 & 61, pp133 & 136 of the submission; Table 14, p26, Attachment 7 of the submission; Bucher indirect analysis spreadsheet_Seladepar and Seladelpar for PBC RevMan file, Attachment 7 of the submission. Italicised text (corrections to submission based on values from Bucher indirect analysis spreadsheet, Attachment 7 of the submission)added during the evaluation.

CI = confidence interval; CrI = credible interval; ESS = effective sample size; ITC = indirect treatment comparison; ITT = intention to treat; n = number of participants with event; N = number of participants in arm; NMA = network meta-analysis; NR = not reported; OCA = obeticholic acid; PBO = placebo; OR = odds ratio; RD = risk difference; RR = relative risk.

**Bold** indicates statistically significant results. *Results of the IPD analyses could not be verified during the evaluation.*

6.25 The RESPONSE trial met the key secondary endpoint of ALP normalisation, with a statistically significant absolute difference between seladelpar and placebo of 25% (95% CI: 18.3, 33.2; p <0.0001) (Table 6). Regardless of whether ALP normalisation was defined per the RESPONSE, POISE, or ELATIVE thresholds, there was a greater proportion of participants treated with seladelpar relative to placebo achieving ALP normalisation at 12 months.

6.26 The Bucher indirect comparison comparing seladelpar versus OCA achieved a statistically significant result using RD as the measure of association (RD = 0.24; 95% CI: 0.05, 0.43; p=0.015), but not OR (13.92; 95% CI: 0.20, 989.68; p=0.226) or RR

(10.63; 95% CI: 0.16, 725.42) p=0.273). Similar results were observed when the indirect comparison was conducted after the RESPONSE results were recalculated to fit the POISE trial threshold for ALP normalisation. The Bayesian NMA based on RR found no significant difference in ALP normalisation.

6.27 The Bucher ITC assessing ALP normalisation (as per the individual trial thresholds) showed comparable results for participants treated with seladelpar versus elafibranor (RD = 0.1; 95% CI: -0.01, 0.21; p=0.0065). Similar results were observed when the RESPONSE trial results were recalculated to fit the ELATIVE trial threshold for ALP normalisation, and when an anchored MAIC was used.

6.28 Table 7 summarises the RESPONSE, POISE and ELATIVE whole trial results and indirect comparisons for Pruritus NRS, PBC-40 itch, and 5-D Itch. Reductions in these measures indicate symptom improvement. The POISE trial did not assess Pruritus NRS. The submission did not present Bucher indirect comparisons for the patient-reported outcomes of PBC-40 itch domain, 5-D Itch, and Pruritus NRS. P-values were not presented for the Bayesian NMA results.

**Table 7: Summary of the RESPONSE, POISE and ELATIVE whole trial results and indirect comparisons for Pruritus NRS, PBC-40 itch, and 5-D Itch.**

| Trial ID | Treatment effect, Mean Difference (95% CI); p-value |
|---|---|
| **Seladelpar vs OCA 5-10 mg (ITT population)** | |
| **PBC-40 itch** | |
| RESPONSE (vs PBO) | -0.83 (-1.68, 0.02); 0.054 |
| Indirect estimate of effect vs OCA adjusted for the common reference – Bayesian NMA | -1.47 (-3.12, 0.17); NR |
| **5-D itch** | |
| RESPONSE (vs PBO) | **-2.3 (-3.4, -1.2); <0.0001** |
| Indirect estimate of effect vs OCA adjusted for the common reference – Bayesian NMA | **-3.51 (-5.80, -1.23); NR** |
| **Seladelpar vs elafibranor (MSPN population)** | |
| **Pruritus NRS[a]** | |
| RESPONSE (vs PBO) | **-1.8 (-3.0, -0.6); 0.004** |
| Indirect estimate of effect vs ELA adjusted for the common reference – Bayesian NMA | -1.01 (-2.76, 0.75); NR |
| **PBC-40 itch domain[b]** | |
| RESPONSE (vs PBO) | -1.51 (-3.25, 0.22); 0.085 |
| Indirect estimate of effect vs ELA adjusted for the common reference – Bayesian NMA | 0.87 (-1.64, 3.35); NR |
| **5-D itch[c]** | |
| RESPONSE (vs PBO) | **-3.5 (-5.5, -1.6); 0.0005** |
| Indirect estimate of effect vs ELA adjusted for the common reference – Bayesian NMA | -0.50 (-4.77, 3.63); NR |

Source: Tables 31, 33, 34, 57 & 62, pp97, 100, 102, 133 & 137 of the submission.

5-D = 5-dimension; CrI = credible interval; ELA = elafibranor; ITT = intention to treat; MSPN = moderate to severe pruritus; n = number of participants with event; N = number of participants in arm; NMA = network meta-analysis; NR = not reported; NRS = numeric rating scale; OCA = obeticholic acid; PBC = primary biliary cholangitis; PBO = placebo; OR = odds ratio; RD = risk difference; RR = relative risk.

[a] ELATIVE (Elafibranor: N=42, PBO: N=16); RESPONSE (Seladelpar: N=36, PBO: N=16)

[b] ELATIVE (Elafibranor: N=42, PBO: N=16); RESPONSE (Seladelpar: N=33, PBO: N=15)

[c] ELATIVE (Elafibranor: N=44, PBO: N=22); RESPONSE (Seladelpar: N=39, PBO: N=16)

**Bold** indicates statistically significant results. However, Pruritus NRS and 5-D itch score at 12 months were not adjusted for multiplicity in the RESPONSE trial

6.29 In the RESPONSE trial, there was a larger reduction in PBC-40 itch domain at 12 months for the seladelpar arm versus placebo in the ITT population and in the MSPN

population; however, the differences were not significant. The results of the Bayesian NMA found comparable results for seladelpar versus OCA (mean difference = -1.47; 95% Credible interval [CrI]: -3.12, 0.17) and the anchored MAIC of seladelpar versus elafibranor (mean difference = -0.87; 95% CrI: -1.64, 3.35).

6.30 In the RESPONSE trial, there was a larger, but not statistically significant, reduction in 5-D itch at 12 months for the seladelpar arm versus placebo in the ITT population and in the MSPN population. The results of the Bayesian NMA found that seladelpar significantly reduced 5-D itch compared to OCA (mean difference = -3.51, 95% CrI: -5.80, -1.23). Seladelpar had a greater reduction in 5-D itch compared to elafibranor; however, the difference was not significant (mean difference = -0.50; 95% CrI: -4.77, 3.63).

6.31 In the RESPONSE trial, there was a larger, but not statistically significant, reduction in Pruritus NRS at 12 months for the seladelpar arm versus placebo in the MSPN population. The results of the Bayesian NMA found comparable results for seladelpar versus elafibranor (mean difference = -1.01; 95% CrI -2.76, 0.75).

6.32 The RESPONSE trial did not collect quality of life data through a generic preference elicitation instrument such as the EuroQol 5-dimension questionnaire (EQ-5D). The submission mapped PBC-40 questionnaire data collected at baseline and Months 1, 3, 6, 9, and 12 to generate EQ-5D data for use in the economic evaluation.

6.33 Table 8 summarises the change from baseline in PBC-40 total score at 1, 3, 6, 9, and 12 months in the RESPONSE trial (ITT population). The PBC-40 QoL questionnaire is a disease-specific health-related QoL tool developed to specifically measure the psychometric profile of PBC participants. The questionnaire covers 6 domains relevant to PBC including cognitive, social, emotional function, fatigue, itch and other symptoms. Within each domain, every item is scored from 1 to 5 and the individual item scores are summed to give a total domain score. This outcome was not part of the clinical claim made by the submission. The POISE and ELATIVE trials did not report this outcome. This outcome was used to generate utility values for the economic model.

**Table 8: Results of change from baseline in PBC-40 total score at 1, 3, 6, 9, and 12 months in the RESPONSE trial (ITT population)**

| Trial ID | Seladelpar 10 mg | | | Placebo | | | LS Mean of difference, [95% CI], p-value |
|---|---|---|---|---|---|---|---|
| | Mean baseline (SD) | Mean end point (SD) | LS mean (SE) | Mean baseline (SD) | Mean end point (SD) | LS mean (SE) | |
| **ITT population[a]** | | | | | | | |
| 1 months | 89.9 (28.45) | 85.5 (28.34) | -5.62 (1.207) | 90.1 (29.02) | 83.8 (27.95) | -7.40 (1.619) | 1.78 (-1.98, 5.55); 0.3512 |
| 3 months | 91.5 (28.97) | 86.4 (29.59) | -5.85 (1.252) | 90.4 (29.24) | 83.8 (29.22) | -7.60 (1.728) | 1.75 (-2.26, 5.75); 0.3902 |
| 6 months | 89.0 (27.94) | 84.5 (27.31) | -5.57 (1.344) | 89.5 (29.40) | 86.5 (29.97) | -4.65 (1.884) | -0.92 (-5.30, 3.46); 0.6787 |
| 9 months | 89.8 (28.66) | 83.9 (29.49) | -6.97 (1.468) | 89.9 (30.15) | 84.9 (28.76) | -5.64 (2.039) | -1.33 (-6.11, 3.45); 0.5839 |
| 12 months | 87.4 (28.54) | 82.0 (28.84) | -5.85 (1.640) | 88.3 (28.78) | 83.7 (26.29) | -6.19 (2.229) | 0.33 (-4.98, 5.64); 0.9019 |

Source: Table 14.2.10.1.1 of the RESPONSE CSR.

CI = confidence interval; ITT = intention to treat; LS = least-squares; n = number of participants who had both a baseline value and a value at that timepoint; N = number of participants in arm; PBC-40 = primary biliary cholangitis 40 quality of life questionnaire; PBO = placebo; SD = standard deviation; SE = standard error; SEL = seladelpar.

[a] At baseline, SEL N = 128, PBO N = 65; at 1 month, SEL n = 118, PBO n = 65; at 3 months, SEL n = 121, PBO n = 59; at 6 months, SEL n = 113, PBO n = 53; at 9 months, SEL n = 112, PBO n = 55, at 12 months, SEL n = 94, PBO n = 51.

6.34 Mean baseline total scores for PBC-40 total score were generally comparable between the seladelpar and placebo arms of the RESPONSE trials. No significant differences were observed between treatments at any time point.

## *Comparative harms*

### Whole trial analyses

6.35 Table 9 presents key summary safety data reported across the RESPONSE, POISE and ELATIVE trials.

**Table 9: Summary of key adverse events in the randomised trials**

| Trial ID | Intervention n/N (%) | Placebo n/N (%) | OR [95% CI] | RR [95% CI] | RD [95% CI] |
|---|---|---|---|---|---|
| **RESPONSE (seladelpar 10 mg)** | | | | | |
| TEAE | 111/128 (86.7) | 55/65 (84.6) | 1.19 [0.51, 2.76] | 1.02 [0.91, 1.16] | 0.02 [-0.08, 0.13] |
| Serious TEAE | 9/128 (7.0) | 4/65 (6.2) | 1.15 [0.34, 3.90] | 1.14 [0.37, 3.57] | 0.01 [-0.06, 0.08] |
| Severe TEAE[a] | 14/128 (10.9) | 5/65 (7.7) | 1.47 [0.51, 4.29] | 1.42 [0.54, 3.78] | 0.03 [-0.05, 0.12] |
| Drug-related TEAE | 22/128 (17.2) | 8/65 (12.3) | 1.48 [0.62, 3.53] | 1.40 [0.66, 2.96] | 0.05 [-0.05, 0.15] |
| TEAE leading to discontinuation of study drug | 4/128 (3.1) | 3/65 (4.6) | 0.67 [0.14, 3.07] | 0.68 [0.16, 2.94] | -0.01 [-0.07, 0.04] |
| TEAE leading to study discontinuation | 3/128 (2.3) | 3/65 (4.6) | 0.50 [0.10, 2.53] | 0.51 [0.11, 2.45] | -0.02 [-0.08, 0.03] |
| Fatal TEAEs | 0 | 0 | NE | NE | 0.00 [-0.02, 0.02] |
| Pruritus TEAEs | 6/128 (4.7) | 10/65 (15.4) | 0.27 [0.09, 0.78] | 0.30 [0.12, 0.80] | -0.11 [-0.20, -0.01] |
| **POISE (OCA 5-10 mg)[b]** | | | | | |
| TEAEs | 65/70 (92.8) | 66/73 (90.4) | 1.38 [0.42, 4.57] | 1.03 [0.93, 1.13] | 0.02 [-0.07, 0.12] |
| Serious TEAE | 11/70 (15.7) | 3/73 (4.1) | 4.35 [1.16, 16.33] | 3.82 [1.11, 13.13] | 0.12 [0.02, 0.21] |
| Severe TEAE[c] | 22/70 (31.4) | 9/73 (12.3) | 3.26 [1.38, 7.71] | 2.55 [1.26, 5.15] | 0.19 [0.06, 0.32] |
| Drug-related TEAE | 42/70 (60.0) | 38/73 (52.1) | 1.38 [0.71, 2.68] | 1.15 [0.86, 1.54] | 0.08 [-0.08, 0.24] |
| TEAE leading to study discontinuation | 5/70 (7.1) | 2/73 (2.7) | 2.73 [0.51, 14.56] | 2.61 [0.52, 13.00] | 0.04 [-0.03, 0.12] |
| Deaths | 1/70 (1.4) | 0 | 3.17 [0.13, 79.20] | 3.13 [0.13, 75.49] | 0.01 [-0.02, 0.05] |
| Pruritus TEAEs | 39/70 (55.7) | 28/73 (38.3) | 2.02 [1.04, 3.94] | 1.45 [1.02, 2.08] | 0.17 [0.01, 0.33] |
| **ELATIVE (elafibranor 80 mg)[d]** | | | | | |
| TEAE | 104/108 (96.2) | 48/53 (90.6) | 2.71 [0.70, 10.54] | 1.06 [0.97, 1.17] | 0.06 [-0.03, 0.14] |
| Serious TEAE | 11/108 (10.2) | 7/53 (13.2) | 0.75 [0.27, 2.05] | 0.77 [0.32, 1.88] | -0.03 [-0.14, 0.08] |
| Severe TEAE[e] | 12/108 (11.1) | 6/53 (11.3) | 0.98 [0.35, 2.77] | 0.98 [0.39, 2.47] | -0.00 [-0.11, 0.10] |
| Drug-related TEAE | 42/108 (38.9) | 21/53 (39.6) | 0.97 [0.49, 1.90] | 0.98 [0.65, 1.48] | -0.01 [-0.17, 0.15] |
| TEAE leading to discontinuation of study drug | 11/108 (10.2) | 5/53 (9.4) | 1.09 [0.36, 3.31] | 1.08 [0.40, 2.95] | 0.01 [-0.09, 0.10] |
| Fatal TEAEs | 2/108 (1.9) | 0 | 2.51 [0.12, 53.25] | 2.48 [0.12, 50.70] | 0.02 [-0.02, 0.06] |
| Pruritus | 22/108 (20.3) | 14/53 (26.4) | 0.71 [0.33, 1.54] | 0.77 [0.43, 1.38] | -0.06 [-0.20, 0.08] |

Source: Tables 45, 46, 48, 49, 50, 51 & 52, pp114, 115, & 117- 120 of the submission; p162, POISE protocol; p208, ELATIVE protocol.
CI = confidence interval; n = number with an event; N = total participants in arm; NE = not estimable; OCA = obeticholic acid; OR = odds ratio; RD = risk difference; RR = relative risk; TEAE = treatment-emergent adverse event.
[a] The RESPONSE trial assessed severity according to NCI CTCAE Version 5.0 on a scale from Grade 1 to Grade 5, where Grade 3 was defined as severe or medically important but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
[b] The POISE trial did not report serious TEAEs or TEAEs leading to discontinuation of the study drug
[c] The POISE trial assessed severity on a scale from Grade 1 to Grade 3, where Grade 3 was Severe, causing an inability to carry out usual activities; the subject may experience intolerable discomfort or pain.
[d] The ELATIVE trial did not report TEAE leading to study discontinuation.
[e] The ELATIVE trial assessed severity on a 3-level scale from Mild to Severe, with severe events defined as events that interrupt the subject's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.
The statistical analysis of adverse events was not pre-planned, so statistically significant results are not bolded.

6.36 Overall, there were similar rates of TEAEs between the intervention and comparator arms of the RESPONSE, POISE, and ELATIVE trials, and similar rates across the trials (Table 9).

6.37 In the RESPONSE trial, the most common TEAE in both the seladelpar and placebo arms was COVID-19 (18.0% versus 15.4%, respectively). The types of adverse events were generally similar between arms. Participants in the seladelpar arm were more likely to experience headache (7.8% versus 3.1%) and abdominal pain (7.0% versus

1.5%), but less likely to experience pruritus (4.7% versus 15.4%; OR=0.27) and upper respiratory tract infections (0.8% versus 9.2%) in the seladelpar arm versus the placebo arm. The cost-utility model disutilities and costs associated with pruritus.

6.38 In the RESPONSE trial, a similar proportion of participants experienced serious TEAEs in the seladelpar and placebo arms. There was no single event that occurred in more than one participant in each arm. Despite this, the cost-utility model included adverse event disutilities and costs for serious TEAEs that occurred in ≥ 1 participant in the RESPONSE trial, stratified by concomitant UDCA use.

6.39 The submission nominated pruritus as an adverse event of interest. Pruritus was less frequent in the intervention arm compared to the placebo arm of the RESPONSE trial (4.7% versus 15.4%) and the ELATIVE trial (20.3% versus 26.4%) and more common in the intervention arm compared to the placebo arm of the POISE trial (55.7% versus 38.3%).

**Indirect comparisons**

6.40 Table 10 summarises the results of the indirect comparisons based on the proportion of participants experiencing any adverse event.

**Table 10: Summary of results of the indirect comparison for adverse events (any)**

| Trial ID | Treatment effect, OR (95% CI); p-value |
|---|---|
| **Seladelpar vs OCA 5-10 mg** | |
| **Bucher ITC** | |
| RESPONSE (vs PBO) | 1.19 [0.51, 2.76] |
| POISE (vs PBO) | 1.38 [0.42, 4.57] |
| Indirect estimate of effect vs OCA adjusted for the common reference | 0.86 [0.20, 3.72]; 0.843 |
| **Bayesian NMA** | |
| RESPONSE (vs PBO) | 1.18 [95% CrI: 0.47, 2.79] |
| POISE (vs PBO) | NR |
| Indirect estimate of effect vs OCA adjusted for the common reference | 0.83 [95% CrI: 0.17, 3.78] |
| **Seladelpar vs elafibranor** | |
| **Bucher ITC** | |
| RESPONSE (vs PBO) | 1.19 [0.51, 2.76] |
| ELATIVE (vs PBO) | 2.71 [0.7, 10.54] |
| Indirect estimate of effect vs ELA adjusted for the common reference | 0.44 [0.09, 2.17]; 0.313 |
| **Anchored MAIC** | |
| RESPONSE (vs PBO) | 0.99 [0.30, 3.28] |
| ELATIVE (vs PBO) | NR |
| Indirect estimate of effect vs ELA adjusted for the common reference | 0.37 [0.06, 2.24] |

Source: Tables 58 & 63, pp134 & 137 of the submission.

CI = confidence interval; CrI = credible interval; ELA = elafibranor; ITC = indirect treatment comparison; n = number of participants with event; N = number of participants in arm; MAIC = matched adjusted indirect comparison; NMA = network meta-analysis; NR = not reported; OCA = obeticholic acid; PBO = placebo; OR = odds ratio.

6.41 The Bucher indirect comparison demonstrated that seladelpar was associated with numerically lower odds of any adverse event compared to OCA, although this treatment effect was not statistically significant (OR = 0.86; 95% CI: 0.20, 3.72; p=0.843). A similar result was observed in the Bayesian NMA.

6.42 The Bucher indirect comparison demonstrated that seladelpar was associated with numerically lower odds of any adverse event compared to elafibranor, although this

treatment effect was not significant (OR = 0.44; 95% CI: 0.09, 2.17; p=0.313). A similar result was observed in the anchored MAIC.

6.43 Table 11 summarises the results of the indirect comparisons based on the proportion of participants experiencing pruritus adverse events.

**Table 11: Summary of results of the indirect comparison for pruritus adverse events**

| Comparison/Trial ID | Treatment effect, OR (95% CI); p-value |
|---|---|
| **Seladelpar vs OCA 5-10 mg** | |
| **Bucher ITC** | |
| RESPONSE (vs PBO) | 0.27 [0.09, 0.78] |
| POISE (vs PBO) | 2.02 [1.04, 3.94] |
| Indirect estimate of effect vs OCA adjusted for the common reference | 0.13 [0.04, 0.48]; 0.002 |
| **Bayesian NMA** | |
| RESPONSE (vs PBO) | 0.26 [95% CrI: 0.08, 0.77] |
| POISE (vs PBO) | NR |
| Indirect estimate of effect vs OCA adjusted for the common reference | 0.13 [95% CrI: 0.03, 0.45] |
| **Seladelpar vs elafibranor** | |
| **Bucher ITC** | |
| RESPONSE (vs PBO) | 0.27 [0.09, 0.78] |
| ELATIVE (vs PBO) | 0.71 [0.33, 1.54] |
| Indirect estimate of effect vs ELA adjusted for the common reference | 0.38 [0.10, 1.43]; 0.153 |
| **Anchored MAIC** | |
| RESPONSE (vs PBO) | 0.25 [0.05, 1.25] |
| ELATIVE (vs PBO) | NR |
| Indirect estimate of effect vs ELA adjusted for the common reference | 0.35 [0.06, 2.10] |

Source: Tables 59 & 64, pp134 & 138 of the submission.
CI = confidence interval; CrI = credible interval; ELA = elafibranor; ITC = indirect treatment comparison; n = number of participants with event; N = number of participants in arm; MAIC = matched adjusted indirect comparison; NMA = network meta-analysis; NR = not reported; OCA = obeticholic acid; PBO = placebo; OR = odds ratio.
The statistical analysis of adverse events was not pre-planned, so statistically significant results are not bolded

6.44 The Bucher indirect comparison demonstrated that seladelpar was associated with significantly lower odds of a pruritus-related adverse event compared to OCA (OR: 0.13; 95% CI: 0.04, 0.48; p=0.002). A similar result was observed in the Bayesian NMA.

6.45 The Bucher indirect comparison demonstrated that seladelpar was associated with numerically lower odds of a pruritus-related adverse event compared to elafibranor, although this treatment effect was not significant (OR = 0.38; 95% CI: 0.10, 1.43; p=0.153). A similar result was observed in the anchored MAIC.

## *Benefits/harms*

6.46 A summary of the comparative benefits and harms for seladelpar versus BSC is presented in Table 12.

**Table 12: Summary of comparative benefits and harms for seladelpar and OCA**

| Trial | Seladelpar, n/N | Placebo, n/N | RR (95% CI) | Event rate/100 patients[a] | | RD (95% CI) |
|---|---|---|---|---|---|---|
| | | | | Seladelpar | Placebo | |
| **Benefits** | | | | | | |
| **Biochemical response** | | | | | | |
| RESPONSE | 79/128 | 13/65 | 3.09 (1.86, 5.11) | 62 | 20 | 0.42 (0.29, 0.55) |
| **ALP normalisation** | | | | | | |
| RESPONSE | 32/128 | 0 | 33.26 (2.07, 534.58) | 25 | 0 | 0.25 (0.17, 0.33) |

| **Change from baseline in PBC-40 itch** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Seladelpar** | | | **Placebo** | | | **Mean difference[a] (95% CI)** |
| | **N** | **LS Mean Δ baseline PBC-40 itch** | **SE** | **N** | **LS Mean Δ baseline PBC-40 itch** | **SE** | **Direct comparison vs PBO** |
| RESPONSE | 94 | -1.31 | 0.264 | 51 | -0.48 | 0.361 | -0.83 (-1.68, 0.02) |

| **Change from baseline in 5-D itch: indirect comparison** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **N** | **LS Mean Δ baseline 5-D itch** | **SE** | **N** | **LS Mean Δ baseline 5-D itch** | **SE** | **Direct comparison vs PBO** |
| RESPONSE | 96 | -2.3 | 0.33 | 46 | 0.1 | 0.46 | **-2.3 (-3.4, -1.2)** |

| **Harms** | | | | | | |
|---|---|---|---|---|---|---|
| | **Seladelpar, n/N** | **Placebo, n/N** | **RR (95% CI)** | **Event rate/100 patients[a]** | | **RD (95% CI)** |
| | | | | **Seladelpar** | **Placebo** | |
| **Serious adverse events** | | | | | | |
| RESPONSE | 9/128 | 4/65 | 1.14 (0.37, 3.57) | 7 | 6 | 0.01 (-0.06, 0.08) |
| **Pruritus adverse events** | | | | | | |
| RESPONSE | 6/128 | 10/65 | **0.27 (0.09, 0.78)** | 5 | 15 | **-0.11 (-0.20, -0.01)** |

Source: Tables 29, 30, 33, 34, 35-38, 46, 49, 55-59, pp94, 96, 100, 101, 104-106, 115, 118, 132-134 of the submission; Attachment 7 of the submission.

ALP = alkaline phosphatase; CI = confidence interval; LS = least squares; n = number of participants with event; N = number of participants in arm; NR = not reported; OR = odds ratio; PBC = primary biliary cholangitis; PBO = placebo; RD = risk difference; RR = risk ratio; SE = standard error.

[a] Over the 12-month trial duration.

Bold text indicates statistically significant results. However, the statistical analysis of adverse events was not pre-planned, so results should be interpreted with caution.

6.47 On the basis of direct evidence presented by the submission, for every 100 patients treated with seladelpar in comparison with BSC over a duration of exposure of 12 months:

- Approximately 42 additional patients would achieve biochemical response.
- Approximately 25 additional patients would achieve ALP normalisation.
- Approximately one more patient would experience a serious adverse event.
- Approximately 11 fewer patients would experience pruritus (itching).

6.48 On the basis of direct evidence presented by the submission, the comparison of seladelpar and BSC resulted in:

- Approximately a 0.83 improvement in PBC-40 itch over a duration of exposure of 12 months. The submission did not indicate what difference in PBC-40 itch was considered to be clinically meaningful.
- Approximately a 2.30 improvement in 5-D itch over a duration of exposure of 12 months. The submission did not indicate what difference in 5-D itch was considered to be clinically meaningful.

### *Clinical claim*

6.49 The submission made clinical claims versus the 3 nominated comparators:

- The submission described seladelpar as superior in terms of efficacy compared with BSC and non-inferior in terms of safety compared to BSC.
- The submission described seladelpar as superior in terms of efficacy compared with OCA and superior in terms of safety with regards to pruritus compared to OCA.
- The submission described seladelpar as non-inferior in terms of efficacy compared with elafibranor and non-inferior in terms of safety compared to elafibranor.

6.50 The submission acknowledged that a claim of non-inferior safety versus BSC may be considered inappropriate given patients are being exposed to an additional treatment (i.e. seladelpar), and all treatments will have a toxicity profile of some description. The submission stated that any additional adverse events associated with seladelpar relative to placebo could not be detected within the clinical trials program and as such, could not be used to inform the cost-utility analysis.

6.51 The ESC considered that the claim that seladelpar was superior compared to BSC in terms of efficacy was adequately supported by the evidence presented. The ESC also considered that the claim of non-inferior safety compared to BSC was reasonable based on the evidence and the context provided in paragraph 6.50. Although additional treatment increases the risk of toxicity, the proportion of participants experiencing TEAEs, serious TEAEs, severe TEAEs, and TEAEs leading to dose interruption, dose reduction, drug discontinuation, or study withdrawal were similar in the seladelpar and placebo arms of the RESPONSE trial. Further, the types of adverse events were similar between arms (see paragraph 6.37 for discussion).

6.52 The evaluation considered the therapeutic conclusion presented in the submission versus OCA in terms of efficacy was not adequately supported because:

- There were differences across participants in the RESPONSE and POISE trials in terms of pruritus history, cirrhosis at baseline, baseline ALP and baseline TB (see paragraph 6.13 for discussion). The submission presented Bucher and Bayesian NMA indirect treatment comparisons; however, neither approach controlled for baseline differences in the participant populations.

- The indirect treatment comparison based on the primary outcome of biochemical response at 12 months was not statistically significant, regardless of the statistical approach (Bucher or Bayesian NMA) or ULN threshold applied.
- The indirect treatment comparison based on the key secondary outcome of ALP normalisation at 12 months was statistically significant using an RD, but not OR nor RR, regardless of the statistical approach (Bucher or Bayesian NMA) or ULN threshold applied.

On the balance of probabilities, the ESC considered that superiority compared to OCA was not adequately supported given there were no significant differences in the primary outcome (see Table 5) and limited significant differences in a secondary outcome (Table 6), and that non-inferior efficacy compared to OCA was a more reasonable conclusion.

6.53 The ESC considered that the claim that seladelpar was superior compared to OCA in terms of safety was not adequately supported. The ESC noted that neither the Bucher indirect comparison nor the Bayesian NMA reported statistically significant differences between seladelpar and OCA in terms of any adverse event. Overall, the ESC considered that seladelpar was likely non-inferior compared to OCA. However, the ESC, noting seladelpar patients reported symptom improvement in the PBC-40 itch and 5-D itch scores and that seladelpar was associated with significantly lower rates of pruritus-related adverse events, considered that seladelpar likely resulted in a significant reduction in pruritus compared to OCA.

6.54 The ESC considered that the claims that seladelpar was non-inferior compared to elafibranor in terms of efficacy and safety were reasonable noting:

- There were differences across participants in the RESPONSE and ELATIVE trials in terms of ALP, TB, AST, and GGT at baseline, and the proportion of participants with cirrhosis at baseline (see paragraph 6.13 for discussion). The submission identified age, ALP, TB, and cirrhosis at baseline as treatment effect modifiers for PBC. Although the submission presented Bucher indirect comparisons that did not control for baseline differences in the participant populations, it presented anchored MAICs for the primary and key secondary outcomes that adjusted for the 4 treatment effect modifiers.
- There was only one statistically significant difference between seladelpar and elafibranor based on the primary outcome of biochemical response (RR, when calculated using the individual trial thresholds). None of the other ITCs for biochemical response or any of the ITCS for the key secondary outcome of ALP response, regardless of the statistical approach (Bucher or MAIC) or ULN threshold applied demonstrated a statistically significant difference. When presented, the p-values were large.
- The indirect comparisons (Bayesian NMA) between seladelpar and elafibranor on the patient-reported outcomes favoured seladelpar for Pruritus NRS and 5-

D itch but favoured elafibranor for PBC-40 itch domain (Table 7). None of the differences were statistically significant.

- The indirect comparisons (Bucher and MAIC) did not identify significant differences between seladelpar and elafibranor in terms of any adverse events or pruritus TEAEs.

6.55 The PBAC considered that seladelpar was superior in terms of efficacy compared to BSC and non-inferior compared to OCA and elafibranor.

6.56 The PBAC considered that seladelpar had a different safety profile and was overall non-inferior in terms of safety compared to BSC, OCA and elafibranor, with notably fewer pruritus-related adverse events compared to BSC and OCA.

## *Economic analysis*

6.57 The submission presented cost utility analyses comparing seladelpar ± UDCA with BSC ± UDCA and OCA ± UDCA. Given that (i) the ESC considered that seladelpar was non-inferior compared to both OCA and elafibranor in terms of efficacy and safety, (ii) elafibranor was recommended by the PBAC in March 2025 on the basis of a cost-minimisation approach versus OCA (see paragraph 2.2) and (iii) elafibranor was not yet listed on the PBS, the ESC considered that a cost minimisation approach between seladelpar and OCA would be the most appropriate way forward. The ESC noted that in March 2025 the PBAC considered that a price premium for elafibranor would be reasonable given the potential reduction in PBC-related pruritus compared to OCA. The ESC considered that a similar approach could be applied to the cost minimisation between seladelpar and OCA.

**Cost utility analysis versus BSC (± UDCA) and OCA (± UDCA)**

6.58 The submission presented a Markov cohort model for the comparison of seladelpar ± UDCA versus BSC ± UDCA and versus OCA ± UDCA (Table 13).

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

| Component | Summary |
|---|---|
| Time horizon | 30 years. Same as the OCA PBAC submission and accepted by the PBAC (para 7.4, obeticholic acid PSD, Nov 2020 PBAC meeting). |
| Methods used to generate results | Markov cohort model. |
| Treatments | Intervention: Seladelpar (+/- UDCA)<br>Comparators: OCA (+/- UDCA)<br>BSC (+/- UDCA) |
| Health states | Similar structure and health states were used in the model presented in the OCA PBAC submissions (Table 7, obeticholic acid, PSD, November 2018 PBAC meeting) and the NICE elafibranor model (TA1016). |
| Cycle length | 1st cycle: 1 month<br>2nd cycle: 2 months<br>Subsequent cycles: 3 months<br>Length of 1st and 2nd cycles was aligned with the RESPONSE trial assessment visit interval. Subsequent cycle length was reasonable. |
| Age at initiation of second-line treatment | 56.7 years<br>Consistent with the RESPONSE trial. |
| % female patients | 94.82% |

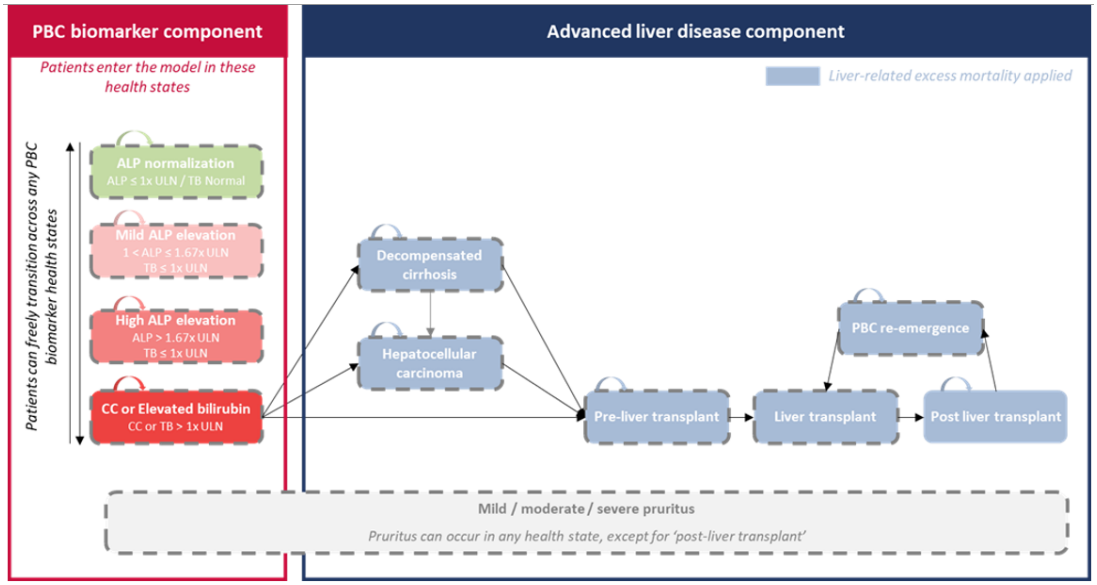
| Component | Summary |
|---|---|
| | Consistent with the RESPONSE trial. |
| Baseline distribution across biochemical health states | 0% ALP normalisation, 5.88% Mild ALP elevation, 71.66% high ALP elevation, CC or elevated bilirubin 22.46%.<br>Consistent with the RESPONSE trial. |
| Utility values | In line with PBAC guidance, trial data was used where available.<br>Utilities were reasonable except for the utility for post-liver transplant were given as 0.57 in NICE TA443, not 0.67 as in the submission. When 0.57 was used, the ICERs decreased by approximately [redacted]%. |
| Health state costs | Seladelpar drug costs were estimated based on the proposed placeholder price (i.e., $[redacted] per model cycle).<br>OCA costs were estimated based on the published prices for PBS items 12623J, 12630R, 12645M, 12631T, and 12640G (i.e., $11,546.77 per cycle).<br>UDCA costs were estimated based on PBS items 8448P / 11180K, weight-based dosing and a weight distribution based on the RESPONSE clinical trial. The monthly treatment cost was A181.26.<br>BSC costs were assumed to be $0.<br>Pruritus treatment costs were based on PBS item fees for relevant medicines and MBS item fees for relevant services ($53.69 for mild/moderate pruritus; $107.38 for severe pruritus per cycle).<br>Liver transplant costs were based on the cost weight for AR-DRG code H09Z (i.e., $185,012 per liver transplant). $11,480 per 3-monthly cycle being associated with the pre-liver transplant health state. $2,226 per 3-monthly cycle for being in post-liver transplant health state.<br>Background health state costs were based on health state-specific HCRU and unit costs based on MBS item fees and cost weights for relevant AR-DRG codes.<br>Adverse event costs associated with seladelpar, OCA, UDCA and/or BSC treatment were based on MBS item fees and cost weights for relevant AR-DRG codes. |
| Transition probabilities | Transition probabilities within the biomarker component of the model (i.e., ALP normalisation, Mild ALP elevation, high ALP elevation, and CC/elevated TB health states) were derived from the RESPONSE trial. Transition probabilities for OCA +/- UDCA were estimated relative to seladelpar +/- UDCA based on a hazard ratio obtained via an indirect treatment comparison. For transition probabilities beyond 12 months, it was assumed that the treatment benefit at 12 months was maintained and, hence, the 9-12 months transition probabilities were applied repeatedly for the remainder of the model time horizon. For UDCA/BSC, transition probabilities from the last observed cycle were carried forward and adjusted so that no further improvements could occur, but some worsening may be experienced.<br><br>For the model period of months 0-12, treatment discontinuation rates were derived from the relevant clinical trials. Discontinuation rates for seladelpar and OCA beyond month 12 were based on the ratio of Year 2 to Year 1 discontinuations in the ELATIVE trial.<br><br>The pruritus severity distribution for all treatments except OCA (seladelpar, UDCA, BSC) was derived from the RESPONSE trial population. For OCA, the pruritus severity distribution was based on the pruritus adverse event odds ratios from an indirect treatment comparison. The probability of pruritus beyond 12 months was assumed to stay constant at the probabilities as observed in the RESPONSE trial at month 12.<br><br>Transition probabilities within the advanced liver disease component of the model, including liver-related excess mortality, were based on the OCA PBAC submissions and NICE OCA appraisal and were the same across all treatment arms. Where estimated, calibrated values were used.<br>The submission assumed an annual probability of 2.6% for transition from post-liver transplant to PBC recurrence. However, this value should have been 23%, according to the source (NICE TA443 (OCA in PBC). When the correct value was used, the ICERs increased by approximately [redacted]%. |

| Component | Summary |
|---|---|
| | Background mortality was based on Australian life tables. |
| Outcomes | Life years gained, quality-adjusted life-years |
| Discount rate | 5% p.a.. |
| Software package | Microsoft Excel |

Source: Tables 71, 79, 80, pp151-153, 175, 178 of the submission. Comments in italics added during the evaluation.
ALP = alkaline phosphatase; AR-DRG = Australian Refined Diagnosis Related Group; BSC = best supportive care; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; HCRU = healthcare resource utilisation; MBS = Medicare Benefits Schedule; NICE = National Institute of Health and Care Excellence; OCA = obeticholic acid; p.a. = per annum; PBAC = Pharmaceutical Benefits Advisory Committee; PBC = primary biliary cholangitis; PBS = Pharmaceutical Benefits Scheme; QALYs = quality-adjusted life-years; TA = technology appraisal; TB = total bilirubin; UDCA = ursodeoxycholic acid.

6.59 The model diagram is given in Figure 1.

**Figure 1: Model structure**




Source: Figure 32, p168 of the submission
ALP = alkaline phosphatase; CC = compensated cirrhosis; PBC = primary biliary cholangitis; TB = total bilirubin; ULN = upper limit of normal

6.60 The model structure was divided into 2 core components: a PBC biomarker component (i.e., biochemical health states) and an advanced liver disease component. Health states in the PBC biomarker component captured the effects of treatment on key markers of disease status, while the advanced liver disease states reflected the clinical consequences of disease progression.

6.61 The health states for the current submission of seladelpar were the same as for the OCA model which has been previously assessed by the PBAC with the exception of an additional health state for the seladelpar model: ALP normalisation. The ALP normalisation state was considered appropriate for capturing the expected benefits of treatment.

6.62 Patient movement through the health states was based on the RESPONSE trial individual patient data evaluated at different time points, including at baseline, Month 1, Month 3, Month 6, Month 9, and Month 12.

6.63 Patients were assumed to discontinue seladelpar or OCA treatment upon progression into the advanced liver disease health states; however, it was assumed that all UDCA-tolerant patients would continue UDCA monotherapy and that all UDCA-intolerant patients would receive BSC in all health states except for post-liver transplant in line with clinical practice.

6.64 Pruritus was included within the economic model. Costs and disutilities were dependent on the severity of pruritus. Pruritus was modelled in all health states except for post-liver transplant.

6.65 The model time horizon was 30 years. This was long compared to the duration of follow-up, 1 year, in the RESPONSE trial. However, the time horizon was consistent with the OCA model accepted by the PBAC (paragraph 7.4, obeticholic acid, Public Summary Document (PSD), November 2020 PBAC meeting).

6.66 Given that the sample size of the UDCA-intolerant subgroup was very small (n=11 across the seladelpar and placebo arms in the RESPONSE trial), data for all participants, regardless of UDCA-tolerance, was used to inform transition probabilities for both the UDCA-tolerant and UDCA-intolerant subgroups in the model. This meant that the resulting ICERs for the UDCA-intolerant subgroup were uncertain.

6.67 The treatment effect for ALP normalisation was based on the Bayesian NMA comparison of seladelpar versus OCA, which indicated a relative risk of 16.62 and hazard ratio of 1/16.62 = 0.06 (Table 6). The submission did not justify the use of this treatment effect over the use of the treatment effects from the Bucher indirect treatment comparisons for ALP normalisation for seladelpar versus OCA.

6.68 For the treatment effect of seladelpar ± UDCA versus OCA ± UDCA, the economic model used the ALP normalisation rate, a secondary outcome from the RESPONSE trial, and the Toronto I criteria (ALP < 1.67×ULN), not the primary outcome from the RESPONSE trial, the rate of biochemical response. The treatment effect for ALP normalisation was significantly better for seladelpar ± UDCA compared to OCA ± UDCA, based on risk differences, whereas the treatment effect for the rate of biochemical response was not significantly better. Therefore, the treatment effect, and hence the ICERs for seladelpar ± UDCA versus OCA ± UDCA, may be biased in favour of seladelpar ± UDCA. It was not possible to assess the impact of this issue on the ICERs without major structural changes to the model. The Pre-Sub-Committee Response (PSCR) stated that both outcomes are valid and reliable surrogate endpoints which are crucial for predicting long-term clinical outcomes such as liver transplantation and mortality, but that ALP normalisation was a more stringent measure of response. The PSCR also states that biochemical response was developed specifically for inclusion in the POISE trial and there is less extensive long-term evidence modelling the relationship between biochemical response and clinical events.

6.69 Beyond month 12, which was the duration of the RESPONSE trial, it was assumed that the treatment benefit was maintained and, hence, the 9-12 month transition probabilities for seladelpar and OCA were applied repeatedly for the remainder of the

model time horizon. For UDCA/BSC, transition probabilities from the last observed cycle were carried forward and adjusted so that no further improvements could occur, but some worsening may be experienced. The ICERs were very sensitive to these assumptions. The PSCR stated that data from the open-label extension of the RESPONSE trial, the ASSURE trial, demonstrated that the benefits of treatment with seladelpar in terms of achieving biochemical response are sustained and even improved upon for up to 2 years and therefore, it was reasonable to assume that the distribution of health states at 9–12 months would remain stable.

6.70 Treatment discontinuation for seladelpar and OCA was assumed for all patients upon progression into the advanced liver disease health states (patients remained on UDCA/BSC treatment in all health states except for post-liver transplant). For the model period of months 0-12, treatment discontinuation rates were derived from the relevant clinical trials. Discontinuation rates for seladelpar and OCA beyond month 12 were calculated based on the ratio of Year 2 to Year 1 discontinuations in the ELATIVE trial.

6.71 Transition probabilities within the advanced liver disease component of the model, including liver-related excess mortality, were based on the OCA PBAC submissions and NICE OCA appraisal and were the same across all treatment arms.

6.72 Excess liver-related mortality risk was considered for the advanced liver disease health states (i.e., DCC, HCC, pre-liver transplant, liver transplant, post-liver transplant, and PBC re-emergence health states). Transition probabilities to liver-related death were sourced from the NICE appraisal for OCA (NICE TA443).

6.73 The utilities for the liver disease health states were taken from the NICE TA443 OCA submission. The economic model included an option to apply age-related utility decrements. However, these were not included in the base case analysis.

6.74 For the purposes of generating a base case result, the submission used a placeholder DPMQ of $ for seladelpar. As noted in paragraph 3.2, this approach deliberately overestimated the ICER, making the uncertainty in the ICER more difficult to assess.

6.75 Key model drivers are given in Table 14. For simplicity, ICERs for UDCA-tolerant patients only are presented. ICERs were similar for UDCA-intolerant patients.

**Table 14: Key drivers of the model**

| Description | Method/Value | Impact<br>Base case for UDCA-tolerant vs UDCA: $[redacted][1]/QALY gained,<br>vs OCA + UDCA: $[redacted][2]/ QALY gained |
|---|---|---|
| Extrapolation | Distribution of patients across biochemical health states over the 30-year time horizon of the model. Transition probabilities for the first 12 months were derived from the RESPONSE trial. After 12-months it was assumed that the treatment benefit at 12 months was maintained with the transition probabilities from 9-12 months applied repeatedly. For BSC/UDCA patients, no further improvement in health state was allowed. | Very high, favours seladelpar.<br>Use of alternative approach in which some improvements in biochemical states in the BSC/UDCA arm were allowed increased the ICER vs UDCA to $[redacted][3]/QALY gained and vs OCA+UDCA to $[redacted][3]/QALY gained. |
| Treatment effect | For the treatment effect of seladelpar ± UDCA with OCA ± UDCA, the economic model used the ALP normalisation rate, a secondary outcome from the RESPONSE trial, and the Toronto I criteria (ALP<1.67×ULN), not the primary outcome from the RESPONSE trial, the rate of biochemical response. The treatment effect for ALP normalisation was significantly better for seladelpar ± UDCA compared to OCA ± UDCA, based on risk differences, whereas the treatment effect for the rate of biochemical response was not significantly better. | Potentially high impact, favours seladelpar. Not possible to quantify impact without major structural changes to the model. |
| Utilities | The economic model included an option to apply age-related utility decrements. However, these were not included in the base case analysis. | Moderate impact, favours seladelpar. Use of age-related utility decrements increased the ICER vs UDCA to $[redacted][1]/QALY gained, and the ICER vs OCA+UDCA increased to $[redacted][2]/QALY gained |

Source: pp181-182 of the submission, worksheet "settings" of economic model.
ALP = alkaline phosphatase, BSC = best supportive care, ICER = incremental cost-effectiveness ratio, OCA = obeticholic acid, QALY = quality-adjusted life-year, UDCA = ursodeoxycholic acid, ULN = upper limit of normal.
*The redacted values correspond to the following ranges:*
[1] *$155,000 to < $255,000*
[2] *$455,000 to < $555,000*
[3] *$555,000 to < $655,000*

6.76 The results of the stepped economic evaluation are given in Table 15. The ICERs decreased substantially when costs and outcomes were modelled over the 30-year time horizon.

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

| Step | Description | Cost | Outcome | Horizon | Comparison | Incr. cost ($) | Incr. outcome | ICER |
|---|---|---|---|---|---|---|---|---|
| 1 | Trial-based analysis | Seladelpar costs only | Patient who achieved ALP normalisation | 12 months | | [redacted] | 0.2807 | [redacted][1] |
| 2 | Modelled analysis | Seladelpar and UDCA costs only | Patient who achieved ALP normalisation (without half-cycle correction) | 12 months | Seladelpar + UDCA vs UDCA | | 0.2824 | [redacted][1] |
| | | | | | Seladelpar vs BSC | | 0.2824 | [redacted][1] |
| 3 | Introduce OCA as comparator | Seladelpar, UDCA and OCA costs only | Patient who achieved ALP normalisation (without half-cycle correction) | 12 months | Seladelpar + UDCA vs OCA + UDCA | | 0.2582 | [redacted][2] |
| | | | | | Seladelpar vs OCA | | 0.2582 | [redacted][2] |
| 4 | Transform to QALYs | Seladelpar, UDCA and OCA costs only | QALYs | 12 months | Seladelpar + UDCA vs UDCA | | 0.0030 | [redacted][3] |
| | | | | | Seladelpar + UDCA vs OCA + UDCA | | 0.0060 | [redacted][3] |
| | | | | | Seladelpar vs BSC | | 0.2070 | [redacted][4] |
| | | | | | Seladelpar vs OCA | | 0.0090 | [redacted][3] |
| 5 | Introduce AE impacts; introduce background health state costs | Seladelpar, UDCA, OCA, AE, and background health state costs | QALYs | 12 months | Seladelpar + UDCA vs UDCA | | 0.0030 | [redacted][3] |
| | | | | | Seladelpar + UDCA vs OCA + UDCA | | 0.0060 | [redacted][3] |
| | | | | | Seladelpar vs BSC | | 0.2070 | [redacted][4] |
| | | | | | Seladelpar vs OCA | | 0.0090 | [redacted][3] |
| 6 | Extrapolate to 30-year time horizon | Seladelpar, UDCA, OCA, AE, and background health state costs | QALYs | 30 years | Seladelpar + UDCA vs UDCA | | 2.767 | [redacted][1] |
| | | | | | Seladelpar + UDCA vs OCA + UDCA | | 0.327 | [redacted][5] |
| | | | | | Seladelpar vs BSC | | 2.984 | [redacted][1] |
| | | | | | Seladelpar vs OCA | | 0.339 | [redacted][5] |

Source: Table 116, p220 of the submission.

AE = adverse event; ALP = alkaline phosphatase; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; incr. = incremental; OCA = obeticholic acid; QALYs = quality-adjusted life-years; UDCA = ursodeoxycholic acid.

*The redacted values correspond to the following ranges:*

[1] *$155,000 to < $255,000*

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

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

[4] *$255,000 to < $355,000*

[5] *$455,000 to < $555,000*

**Cost minimisation approach versus elafibranor**

6.77 The submission presented a cost-minimisation approach between seladelpar and elafibranor.

6.78 The equi-effective doses were estimated as:

seladelpar 10 mg daily = elafibranor 80 mg daily.

6.79 The equi-effective doses were taken from the RESPONSE trial for seladelpar (which was consistent with the draft seladelpar TGA Product Information) and the ELATIVE trial for elafibranor (consistent with the elafibranor Product Information).

6.80 The submission proposed that the price of seladelpar could be set so that the total daily cost of seladelpar and elafibranor is equal. The submission proposed no cost offsets for administration or adverse events (e.g. pruritus).

## *Drug cost/patient/year*

6.81 The drug cost per patient for seladelpar versus OCA, using the published price of OCA, is presented in Table 16.

**Table 16: Drug cost per patient for seladelpar versus OCA using the published price of OCA**

| | Seladelpar | | | OCA | | |
|---|---|---|---|---|---|---|
| | **Trial dose and duration** | **Economic Model** | **Financial estimates** | **Trial dose and duration** | **Economic Model** | **Financial estimates** |
| Dose | 10 mg/day | | | 5 mg/day (6 months); titrated to 10 mg/day if required | | 5 - 10 mg/day |
| Compliance rate | 92.19% | Year 1: 92.19%<br>Years 2+ 97.81% | Month 0-6: 100%<br>Month 7-12: 93.98%<br>Years 2+: 97.81% | 88.9% | Year 1:88.9%,<br>Years 2+: 97.81% | Not stated |
| Mean duration | 1 year | 15.785 years | Not stated | 1 year | 14.695 years | Not stated |
| Cost/patient/ month | $[redacted][a] | $[redacted][b]<br>In Month 1 | $[redacted][b] | $3,422[c] | $3,849[d]<br>In Month 1 | $3,849[d] |
| Cost/patient/ year | $[redacted] | Year 1:$[redacted][e]<br>Year 2:$[redacted][f] | Year 1:$[redacted][g]<br>Years 2+:$[redacted][h] | $41,060 | Year 1[e]: $44,281<br>Year 2+[f]: $39,690 | $46,187 |

Source: Complied during the evaluation from p26, p185 of the submission, pp246-247 of the submission, worksheet "clinical" of the economic model.

NR = not reported, OCA = obeticholic acid.

[a] = $[redacted] * (365.25/12) / 30 * 92.19% as DPMQ is $[redacted] per 30 days.

[b] = $[redacted] * (365.25/12) / 30.

[c] = $3,793.60 * (365.25/12) / 30 * 88.9% as DPMQ is $3,793.60 per 30 days.

[d] = $3,739.60 * (365.25/12) / 30.

[e] in CUA model, sum cells MP18:MP22, sheet engine (4) for seladelpar and sheet engine (6) for OCA.

[f] in CUA model, sum cells MP23:MP26, sheet engine (4) for seladelpar and sheet engine (6) for OCA.

[g] = $[redacted] * 7 + $[redacted] * 5.13 * 93.98%

[h] = $[redacted] * 12.13 * 97.81%

6.82 In the economic model, seladelpar and OCA costs per cycle were equal to the monthly cost of treatment, multiplied by the proportion of participants in the PBC biomarker component of the model (i.e., not dead or with advanced liver disease) and remaining on treatment. The estimated annual treatment costs therefore declined each modelled year.

6.83 In Year 1, the total cost per patient per year with seladelpar was $[redacted] in the economic model and $[redacted] in the financial estimates. The difference was because patients in the economic model were excluded from the treatment cost calculation upon death or disease progression, which was not accounted for in the financial estimates. Further, the economic model and financial estimates applied different compliance rates.

## *Estimated PBS usage & financial implications*

6.84 This submission was not considered by DUSC.

6.85 The submission used a mixed market share and epidemiological approach. The budget impact model used data from the DUSC Secretariat to estimate the proportion of UDCA use for PBC, incorporated UDCA intolerance rates from the RESPONSE trial, and used published literature to estimate inadequate UDCA response—together determining the proportion of patients eligible under the proposed PBS criteria.

6.86 The ESC advised that seladelpar would be expected to displace OCA and elafibranor (if PBS listed).

6.87 Table 17 outlines the key inputs in the financial estimates.

**Table 17: Key inputs for financial estimates**

| Data | Value applied and source | Comment |
|---|---|---|
| **Eligible population** | | |
| Prevalent patients who were treated with UDCA | 14,030 in Yr 1, increasing to 15,489 in Yr 6<br>Estimated from past data provided by the DUSC Secretariat. | The increase from Yr 1 to Yr 6, at 2.0% p.a., was not justified. |
| Proportion of patients on UDCA treatment who are being treated for PBC | 60%. Assumption | This assumption was uncertain, as it implied that 40% of the UDCA prescriptions for PBC were off label, a notably high proportion for a medicine with an Authority Required listing. |
| Proportion of PBC patients who are intolerant to UDCA treatment | 6.2%. The RESPONSE trial | Invernizzi (2017)[5] indicated that 3 to 5% of PBC patients were intolerant to UDCA. |
| Proportion of PBC patients on UDCA treatment > 1 year | 23.44%. Data provided by the DUSC Secretariat | - |
| Proportion of PBC patients on UDCA treatment > 1 year and who are UDCA-intolerant or have an incomplete response to UDCA | 40%. A literature search by the submission. | This was uncertain and not adequately justified. Assuming that 40% of PBC patients had an inadequate response to UDCA treatment may have overestimated the eligible population, as previous studies have reported a range of 30% to 40%, with 40% representing the upper bound. The submission also did not provide adequate justification for counting the UDCA-intolerant patients as part of the cohort treated with UDCA for >1 year. |
| **Treatment utilisation** | | |

[5] Invernizzi et al. (2017). Primary Biliary Cholangitis: advances in management and treatment of the disease. Digestive and Liver Disease, 49(8), 841-846, DOI: https://doi.org/10.1016/j.dld.2017.05.001.

| Data | Value applied and source | Comment |
|---|---|---|
| Uptake rate | Yr 1 = [redacted]% and growing by [redacted]% each year.<br>Assumption. | This was uncertain and not adequately justified. However, seladelpar was superior in efficacy compared to BSC, which may justify a higher uptake rate. This parameter is dependent upon the future availability of elafibranor for PBC. |
| Discontinuation rate of seladelpar for any reason (e.g., adverse events) | 7.81% in Yr 1 and 2.19% in the subsequent years<br>The ELATIVE trial and applied to the RESPONSE trial discontinuation rate | This was uncertain. The submission stated that the annual discontinuation rate for seladelpar was 7.81% in Year 1. However, it does not specify when the discontinuation occurred—whether it happened within the first 6 months, before the 6-month mark, or between 6 and 12 months.<br>In addition, combining elafibranor and seladelpar data presented uncertainty, as there were differences between the ELATIVE and RESPONSE trial populations. |
| Scripts (initial and continuing) | Initiation: [redacted][1] scripts<br>Continuation (1st year after initiation): [redacted][1]<br>Continuation (2nd year after initiation): [redacted][1]<br>Using the mean compliance of 97.8% from the RESPONSE trial and a 3.91% (7.81%/2) discontinuation rate. | These values were uncertain. The model's initial script count ([redacted][1]) and discontinuation rate used (to calculate continuing scripts) were not adequately supported or justified, leading to uncertainty. |
| Total scripts dispensed | [redacted][2] in Yr 1, increasing to [redacted][3] in Yr 6.<br>Submission calculation using [redacted] scripts (for initiating patients) and the RESPONSE trial discontinuation rate | The use of [redacted] scripts for initiating patients was uncertain due to inconsistencies with the proposed restrictions. The calculation was uncertain due to a potential double-counting of patient discontinuations. |
| **Costs** | | |
| Seladelpar | $[redacted]<br>Placeholder price: DPMQ | - |
| OCA | $3,793.60<br>Published DPMQ | - |

Source: Table 127, p237 of the submission, Table 129, p238 of the submission, Table 130, p239 of the submission, Table 131, p330 of the submission, Table 133, p240 of the submission, Table 134, p242 of the submission, Table 136, p244 of the submission, Table 137, p245 of the submission, Table 139, p246 of the submission, Table 140, p246 of the submission, Table 141, p247 of the submission, Table 142, p247 of the submission and Table 143, p248 of the submission.

BSC = Best supportive care; CSR = clinical study report; DUSC= Drug Utilisation Sub-Committee; DPMQ = Dispensed Price for Maximum Quantity; No.= number; OCA = Obeticholic acid; PBAC = Pharmaceutical Benefits Advisory Committee; PBC=Primary Biliary Cholangitis; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; Yr = year; UDCA = Ursodeoxycholic acid.

[a] Pharmaceutical Benefits: Fees, Patient Contributions and Safety Net Thresholds. Available from: https://www.pbs.gov.au/info/healthpro/explanatory-notes/front/fee.

*The redacted values correspond to the following ranges:*

[1] *<500*

[2] *20,000 to < 30,000*

[3] *30,000 to < 40,000*

6.88 Table 18 presents the estimated use and financial implications, using the placeholder price of seladelpar and published price of OCA.

**Table 18: Estimated use and financial implications**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|---|---|---|---|---|---|
| **Estimated extent of use** | | | | | | |
| Number of patients treated | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] |
| Number of scripts dispensed[a] | [redacted][2] | [redacted][2] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] |
| **Estimated financial implications of seladelpar** | | | | | | |
| Cost to PBS/RPBS less copayments | [redacted][4] | [redacted][4] | [redacted][4] | [redacted][4] | [redacted][4] | [redacted][4] |
| Estimated financial implications for OCA | | | | | | |
| Cost to PBS/RPBS less copayments | [redacted][5] | [redacted][5] | [redacted][5] | [redacted][5] | [redacted][5] | [redacted][5] |
| **Net financial implications** | | | | | | |
| **Net cost to PBS/RPBS** | [redacted][4] | [redacted][4] | [redacted][4] | [redacted][4] | [redacted][4] | [redacted][4] |
| Net cost to MBS | [redacted] | | | | | |
| Net cost to PBS/RPBS/MBS [b] | [redacted][4] | [redacted][4] | [redacted][4] | [redacted][4] | [redacted][4] | [redacted][4] |

Source: Table 145, p250 of the submission, Table 148, p252 of the submission; sheet '5. Impact – net' of the seladelpar BIM. Compiled during the evaluation from the workbook Seladelpar BIM.xlsx, sheets 'Seladelpar BIM', '4a. Scripts-affected' and ' '4b. Impact – affected (pub)' and Compiled during the evaluation Seladelpar BIM.xlsx, sheet 'Seladelpar BIM'.

OCA = Obeticholic acid; MBS= Medicare Benefits Schedule; PBS= Pharmaceutical Benefits Scheme; RPBS= Repatriation Pharmaceutical Benefits Scheme.

[a] Number of scripts per year as estimated by the submission.

[b] Values based on the PBAC Excel workbook, 5. Impact -net. These values differ very marginally from the submission 'Seladelpar BIM' worksheet. Calculation from the 'Seladelpar BIM' worksheet was presented in the seladelpar submission.

*The redacted values correspond to the following ranges:*

*[1] 500 to < 5,000*

*[2] 20,000 to < 30,000*

*[3] 30,000 to < 40,000*

*[4] $100 million to < $200 million*

*[5] net cost saving*

6.89 The total cost to the PBS/RPBS of listing seladelpar was estimated to be $100 million to < $200 million in Year 6, and a total of $800 million to < $900 million in the first 6 years of listing (using the placeholder price of seladelpar).

6.90 The ESC noted that many parameter inputs were not justified and uncertain, for example, the proportion of patients on UDCA treatment who are being treated for PBC, the proportion of PBC patients on UDCA treatment > 1 year with an incomplete response to UDCA, assumed uptake rate for seladelpar, the discontinuation rates, and the number of scripts used were inconsistent with the proposed restrictions.

6.91 The estimated number of seladelpar scripts per year was uncertain due to a potential double-counting of patient discontinuations. The submission applied a 7.81% discontinuation rate in the first year (and 2.19% in subsequent years) to estimate the eligible patient population for seladelpar. However, it again applied the 7.81% discontinuation rate for seladelpar when calculating the annual number of scripts, which may lead to an underestimation of treatment use.

6.92 The ESC considered that the financial impact of listing seladelpar would be reduced compared to the submission estimates when the price of seladelpar was cost-minimised to OCA, in a similar manner to elafibranor.

6.93 The ESC considered that there would be three populations who would be treated with seladelpar: (i) prevalent patients who are intolerant of OCA; (ii) prevalent patients who

are currently receiving OCA who may switch to seladelpar; and (iii) incident patients who require second-line treatment in addition to UDCA or are intolerant of UDCA.

### *Financial Management – Risk Sharing Arrangements*

6.94 The submission indicated a willingness to discuss an appropriately formulated and structured risk sharing arrangement.

6.95 In the March 2021 OCA submission, the PBAC considered that the estimated ICER was acceptable when considered in conjunction with the estimated financial impact and proposed risk-sharing arrangement (paragraph 6.1, obeticholic acid, PSD, March 2021 PBAC meeting).

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

## 7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for the listing of seladelpar for the treatment of primary biliary cholangitis (PBC). The PBAC was of a mind to recommend seladelpar, pending advice from the TGA Delegate. The PBAC considered that seladelpar was non-inferior in terms of effectiveness and safety compared to obeticholic acid (OCA) and therefore, considered that a cost-minimisation approach versus OCA was appropriate. The PBAC also considered that seladelpar was non-inferior in terms of comparative effectiveness and safety to the near market comparator, elafibranor. The PBAC considered that a price premium for seladelpar over OCA, consistent with what was recommended for elafibranor in March 2025, would be reasonable given the potential reduction in PBC-related pruritus compared to OCA. The PBAC considered that seladelpar should join the risk sharing arrangement (RSA) for OCA.

7.2 The PBAC acknowledged the input from the Liver Foundation supporting the submission. The PBAC also noted the input provided during the Sponsor hearing, which highlighted the need for alternative treatments for patients who do not respond to first-line treatment with ursodeoxycholic acid (UDCA). The PBAC noted the severity of impairment before effective medication was received, as articulated from the patient perspective, and the individual's positive experience from the seladelpar trial (see paragraph 6.1).

7.3 The PBAC considered that seladelpar, as an add-on to UDCA, would be used as an alternative to OCA in the second line setting for patients that had failed to achieve an adequate response after at least 12 months treatment with UDCA monotherapy. The PBAC considered that most seladelpar use would be in combination with UDCA, but noted that for those patients' intolerant to UDCA, seladelpar would likely be used as monotherapy. The PBAC also considered that seladelpar should be available for use in the third line setting for patients who have an inadequate response to, or are intolerant of, OCA (and elafibranor if PBS listed), noting that there was minimal clinical evidence in this population.

7.4 The PBAC considered that an Authority Required – immediate assessment (telephone/online) listing for initiation and an Authority required (Streamlined) listing for continuing supply, as was recommended for elafibranor, would be appropriate. The PBAC, noting that consistency with the wording proposed for elafibranor at the March 2025 meeting would be appropriate, agreed with other suggestions for the restriction, including:

- The Administrative Advice should exclude use in patients with sclerosing cholangitis only (i.e. cholelithiasis can be deleted);
- A criterion should be added to each restriction excluding concomitant use with the alternative agent; and
- The initial restriction should prevent use in patients who have severe liver disease or who are immunocompromised

7.5 The PBAC considered that the nomination of OCA as the main comparator was reasonable. The PBAC also considered the nominations of best supportive care (BSC), as a comparator for patients who are intolerant to OCA, and of elafibranor, as a near market comparator, were reasonable.

7.6 The PBAC noted that the submission was based on indirect treatment comparisons between seladelpar (data from the RESPONSE trial, N = 193) and OCA (data from the POISE trial, N = 144) and elafibranor (data from the ELATIVE trial, N = 161), with placebo as the common comparator. The PBAC noted the transitivity issues between the trials outlined in paragraphs 6.11 to 6.14, however considered that this approach was reasonable.

7.7 The PBAC noted that although the primary outcome in all three trials was cholestasis or biochemical response, defined as achieving an alkaline phosphatase (ALP) < 1.67 x the upper limit of normal (ULN), a decrease in ALP of ≥ 15% and total bilirubin (TB) ≤ ULN, the ULN thresholds differed between the trials (see Table 4). Thus, the submission presented indirect comparisons based on recalculated response rates using individual patient data from the REPONSE trial and the thresholds defined in the POISE and ELATIVE trials.

7.8 The PBAC noted that compared to placebo, seladelpar was associated with a significantly higher proportion of patients achieving cholestasis response (61.7% of seladelpar patients versus 20.0% of placebo patients; RD = 0.42; 95% CI: 0.29, 0.55) and ALP normalisation (25.0% of seladelpar patients versus 0% of placebo patients; RD = 0.25; 95% CI: 0.17, 0.33) at 12 months (see Table 5 and Table 6).

7.9 The PBAC noted that the submission presented indirect treatment comparisons, with outcome measures of odds ratio, relative risk and risk difference, comparing seladelpar with OCA and elafibranor for cholestasis response and ALP normalisation at 12 months/52 weeks. The PBAC noted that for the majority of the comparisons, there were no statistically significant differences between seladelpar and OCA and elafibranor (see Table 5 and Table 6).

7.10 The PBAC noted that the submission also presented Bayesian network analyses for the comparisons between seladelpar and OCA and anchored matched adjusted indirect comparisons (MAICs) for the comparisons between seladelpar and elafibranor. No statistically significant differences in cholestasis response or ALP normalisation were observed (seeTable 5 and Table 6).

7.11 Overall, the PBAC considered that seladelpar was superior in terms of efficacy compared to BSC and non-inferior compared to both OCA and elafibranor.

7.12 The PBAC noted that there were no statistically significant differences in the ITCs between seladelpar and OCA and seladelpar and elafibranor in terms of the outcome, any adverse event. Overall, the PBAC considered that seladelpar was non-inferior in terms of safety compared to BSC, OCA and elafibranor.

7.13 The PBAC also noted that patients treated with seladelpar reported symptom improvement in the PBC-40 itch and 5-D itch scores and significantly lower rates of PBC-related pruritus compared to patients treated with OCA. The PBAC acknowledged that pruritus is a significant issue for patients with PBC.

7.14 The PBAC noted that the submission presented cost utility analyses comparing seladelpar ± UDCA with BSC ± UDCA and OCA ± UDCA. Although the PBAC considered that seladelpar was superior in terms of efficacy compared to BSC, it was noted that the resultant incremental cost effectiveness ratio (ICER) was uncertain (see paragraph 6.66). In addition, the use of placeholder price in the CUA deliberately overestimated the ICER and made the overall uncertainty difficult to assess. Given that the PBAC considered that seladelpar was non-inferior compared to both OCA in terms of efficacy and safety, the PBAC considered that a cost-minimisation approach versus OCA, based on daily drug costs only, would be appropriate. Noting the significant effects of pruritus for PBC patients, the PBAC considered that if seladelpar was associated with a reduction in pruritus this could improve treatment adherence and persistence. The PBAC considered that a price premium could be applied to seladelpar in accordance with the PBAC Guidelines, September 2016 v5.0, which allow a price advantage over the comparator on the basis of reduced costs offsets, which in this case would be reduced costs associated with the management of pruritus.

7.15 The PBAC considered that the equi-effective doses were:

Seladelpar 10 mg once daily = OCA 5 mg or 10 mg once daily

7.16 The PBAC considered that for the purpose of Section 101(3B) of the *National Health Act 1953*, that seladelpar was an alternative therapy to elafibranor and does not provide a significant improvement in efficacy or a reduction in toxicity. The PBAC advised that therefore, the price of seladelpar should not be higher than the price of elafibranor, should it be listed on the PBS, for PBC. The equi-effective doses were:

Seladelpar 10 mg once daily = Elafibranor 80 mg once daily

7.17 The PBAC considered that there would be three populations who would be treated

with seladelpar: (i) prevalent patients who are intolerant of OCA; (ii) prevalent patients who are currently receiving OCA who may switch to seladelpar; and (iii) incident patients who require-second line treatment in addition to UDCA or an intolerant of UDCA.

7.18 The PBAC noted that there were a number of uncertainties with the proposed financial estimates (see paragraphs 6.90 and 6.91). However, the PBAC considered that the financial impact of listing seladelpar would be reduced compared to the submission estimates when the price of seladelpar was cost-minimised to OCA.

7.19 The PBAC noted that there is an RSA in place for OCA and considered that seladelpar should join the OCA RSA, with no increase to the current expenditure caps.

**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.

**December 2025 Addendum to the July 2025 PBAC Public Summary Document:**

# 4.01 SELADELPAR, Capsule 10 mg, Livdelzi®, Gilead Sciences Pty Ltd

## 10 Purpose

10.1 In July 2025, the PBAC was of a mind to recommend seladelpar for the treatment of primary biliary cholangitis (PBC), pending advice from the TGA Delegate. The Sponsor has provided the TGA Delegate's Overview and also proposed further amendments to the restriction.

## 11 Background

11.1 The TGA Delegate proposed to approve the registration of seladelpar, pending advice from the Advisory Committee for Medicines (ACM), for the following indication:

> 'For the treatment of primary biliary cholangitis (PBC), in adults in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA.'

## 12 Requested listing

12.1 The deferral response has proposed amendments to the previously considered PBS restriction:

- Authority level: The response stated that an Authority Required (STREAMLINED) was appropriate for the initial and grandfather listings. The corresponding listings for obeticholic acid (OCA) and elafibranor are Authority Required (telephone/online) for the initial and grandfather listings and Authority Required (STREAMLINED) for the continuing treatment phase.
- Immunocompromised patients: The initial and grandfather restrictions for OCA and elafibranor prevent use in patients who have severe liver disease or who are immunocompromised. The deferral response requests removal of 'or who are immunocompromised' as (i) the draft TGA Product Information (PI) for seladelpar does not exclude immunocompromised patients; (ii) immunocompromised patients were not broadly excluded from the RESPONSE trial; (iii) seladelpar does not increase the risk of infections; and (iv) seladelpar has a different mechanism of action compared to OCA that regulates bile acid metabolism, reduces inflammation, and has anti-inflammatory and antifibrotic

effects which actually supports its role in treating immunocompromised patients with PBC. It was noted that the PI for elafibranor also does not exclude immunocompromised patients.

- Hepatic decompensation and failure: The deferral response requested that the Caution that states "Hepatic decompensation and failure, in some cases fatal, have been reported in post-marketing reports in patients with moderate to severe hepatic impairment when dosed incorrectly" be removed. The response stated that this only applies to OCA as it reflects the black box warning in its TGA PI. The draft PI for seladelpar states 'Monitor patients with cirrhosis for evidence of decompensation. Consider discontinuing if the patient progresses to moderate or severe hepatic impairment (Child-Pugh B or C)'. The PI for elafibranor states 'Use is not recommended in patients who have or develop decompensated cirrhosis (e.g. ascites, variceal bleeding, hepatic encephalopathy)'.
- Moderate-to-severe pruritus: At the July 2025 meeting, the PBAC noted that patients treated with seladelpar reported symptom improvement in the PBC-40 itch and 5-D itch scores and significantly lower rates of PBC-related pruritus compared to patients treated with OCA. In response to this, the response proposed adding a clinical criterion allowing patients who have been treated with UDCA for at least 52 weeks and continue to experience moderate-to-severe pruritus (despite achieving a biochemical response) to access seladelpar. The response stated that this would apply to a small subset of patients, as the majority of these patients would already be eligible for seladelpar (i.e. under ALP or total bilirubin measures).

12.2 The proposed amendments are presented in strikethrough and italics below.

| **MEDICINAL PRODUCT**<br>**medicinal product pack** | **Max. qty packs** | **Max. qty units** | **№. of Rpts** | **Available brands** |
|---|---|---|---|---|
| SELADELPAR | | | | |
| seladelpar 10 mg capsule, 30 | 1 | 30 | 5 | Livdelzi |
| | | | | |
| Restriction Summary [1] / Treatment of Concept: [1A] | | | | |
| **Category / Program:** ☒ GENERAL - General Schedule (Code GE) | | | | |
| **Prescriber type:** ☒ Medical Practitioners | | | | |
| **Restriction type:** ☒ Authority Required: ~~Telephone/Online~~ *Streamlined [new code]* | | | | |
| **Administrative Advice:**<br>Not for use in the treatment of sclerosing cholangitis | | | | |
| **Administrative Advice:**<br>No increase in the maximum quantity or number of units may be authorised. | | | | |
| **Administrative Advice:**<br>No increase in the maximum number of repeats may be authorised. | | | | |
| **Administrative Advice:**<br>Special Pricing Arrangements apply. | | | | |
| **Indication:** Primary biliary cholangitis (previously known as Primary biliary cirrhosis) | | | | |
| **Treatment Phase:** Initial treatment | | | | |

| |
|---|
| **Treatment criteria:** |
| Must be treated by a prescriber who is either: (i) a gastroenterologist, (ii) a hepatologist; |
| **OR** |
| Must be treated by a medical practitioner who has consulted at least one of the above mentioned specialist types |
| **AND** |
| **Treatment criteria:** |
| Patient must be undergoing concurrent treatment with ursodeoxycholic acid |
| **OR** |
| Patient must be undergoing treatment with this drug as monotherapy because treatment with ursodeoxycholic acid is not tolerated/contraindicated |
| **AND** |
| **Treatment criteria:** |
| Patient must not be undergoing concurrent treatment with either of: (i) obeticholic acid (ii) elafibrinor |
| **Clinical criteria:** |
| Patient must have experienced an inadequate response to ursodeoxycholic acid, despite treatment with ursodeoxycholic acid for at least 52 weeks at a therapeutic dose, prior to initiating treatment with this drug; |
| **OR** |
| Patient must have experienced an intolerance/contraindication to ursodeoxycholic acid of a severity requiring permanent treatment discontinuation, prior to initiating treatment with this drug |
| **AND** |
| **Clinical criteria:** |
| Patient must not have ~~each of (i)~~ severe liver disease~~, (ii) immunocompromised~~ |
| **AND** |
| **Clinical criteria:** |
| Patient must have an alkaline phosphatase (ALP) level of at least 1.67 times the upper limit of normal (ULN) *prior to initiating treatment with this drug,* having accounted for each of: (i) age, (ii) gender, (iii) laboratory to laboratory variances in the definition of 'normal', despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks; |
| **OR** |
| Patient must have a total bilirubin level between 1 to 2 times the ULN *prior to initiating treatment with this drug*, despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks; |
| ***OR*** |
| *Patient must have moderate to severe pruritus despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks;* |
| **OR** |
| Patient must have abnormal readings of at least one of: (i) alkaline phosphatase (ii) total bilirubin, or moderate-to-severe pruritus, in the presence of an intolerance/contraindication of a severity requiring treatment discontinuation with ursodeoxycholic acid |
| **OR** |
| *Patient must have experienced an intolerance to either of (i) obeticholic acid (ii) elafibrinor, of a severity requiring treatment discontinuation, prior to initiating treatment with this drug;* |
| **OR** |
| *Patient must have inadequately responded to treatment with (i) obeticholic acid (ii) elafibrinor, prior to initiating treatment with this drug* |
| **Population criteria:** |
| Patient must be at least 18 years of age |
| **Prescribing Instructions:**<br>Document and retain in the patient's medical records the qualifying baseline laboratory reading for the purpose of assessing response to treatment under the 'Continuing treatment' restriction. |
| **Prescribing Instructions:**<br>Moderate-to-severe pruritus is defined moderate or severe pruritus via the pruritus numeric rating scale |

| |
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| **Administrative Advice:**<br>Laboratory readings requested in this authority application must be no older than 52 weeks, *prior to starting either of (i) obeticholic acid (ii) elafibranor (iii) seladelpar, whichever is used first.* |
| ~~**Caution:**~~<br>~~Hepatic decompensation and failure, in some cases fatal, have been reported in post-marketing reports in patients with moderate to severe hepatic impairment when doses incorrectly.~~ |
| |
| Restriction Summary [12138] / Treatment of Concept: [12138] |
| **Category / Program:** ☒ GENERAL - General Schedule (Code GE) |
| **Prescriber type:** ☒ Medical Practitioners ☒ *Nurse Practitioners* |
| **Restriction type:** ☒ Authority Required: STREAMLINED |
| **Indication:** Primary biliary cholangitis (previously known as Primary biliary cirrhosis) |
| **Treatment Phase:** Continuing treatment |
| **Treatment criteria:** |
| Must be treated by a prescriber who is either: (i) a gastroenterologist, (ii) a hepatologist; |
| **OR** |
| Must be treated by an eligible practitioner type who has consulted at least one of the above mentioned specialist types |
| **AND** |
| **Treatment criteria:** |
| Patient must be undergoing continuing PBS-subsidised treatment with this drug, with treatment having commenced through one of: (i) the 'Initial treatment' listing, (ii) 'Grandfather' arrangements, (iii) 'Switching treatment' listing |
| **AND** |
| **Treatment criteria:** |
| Patient must be undergoing concurrent treatment with ursodeoxycholic acid |
| **OR** |
| Patient must be undergoing treatment with this drug as monotherapy because combination treatment with ursodeoxycholic acid is not tolerated/contraindicated |
| ***AND*** |
| **Treatment criteria:** |
| Patient must not be undergoing concurrent treatment with either of: (i) obeticholic acid (ii)elafibranor |
| **Clinical criteria:** |
| Patient must have achieved an adequate response to this drug, defined as having at least one of: (i) an alkaline phosphate (ALP) level less than 1.67 times the upper limit of normal (ULN), (ii) a reduction in the ALP reading of at least 15% compared to the baseline level provided with the initial authority application, (iii) a total bilirubin level within the normal reference range; or a reduction in pruritus to no or mild pruritus |
| **Prescribing Instructions:**<br>The improvement in the qualifying laboratory reading(s) has/have been documented in the patient's medical records. |
| **Administrative Advice:**<br>Laboratory readings requested in this authority application must be no older than 52 weeks. |
| ~~**Caution:**~~<br>~~Hepatic decompensation and failure, in some cases fatal, have been reported in post-marketing reports in patients with moderate to severe hepatic impairment when doses incorrectly.~~ |
| |
| **Restriction Summary [NEW] / Treatment of Concept: [NEW]** |
| **Category / Program:** ☒ GENERAL - General Schedule (Code GE) |
| **Prescriber type:** ☒ Medical Practitioners ☒ *Nurse Practitioners* |
| **Restriction type:** ☒ Authority Required: ~~Telephone/Online~~ *STREAMLINED* |

| |
|---|
| **Administrative Advice:**<br>Not for use in the treatment of sclerosing cholangitis |
| **Administrative Advice:**<br>**Continuing Therapy Only:**<br>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners. |
| **Administrative Advice:**<br>No increase in the maximum quantity or number of units may be authorised. |
| **Administrative Advice:**<br>No increase in the maximum number of repeats may be authorised. |
| **Administrative Advice:**<br>Special Pricing Arrangements apply. |
| |
| **Indication:** Primary biliary cholangitis (previously known as Primary biliary cirrhosis) |
| **Treatment Phase:** Transitioning from non-PBS to PBS subsidised supply - Grandfather arrangements |
| ***Clinical criteria:*** |
| Patient must have received treatment with this drug for this PBS indication prior to [Date] |
| **Treatment criteria:** |
| Must be treated by a prescriber who is either: (i) a gastroenterologist, (ii) a hepatologist; |
| **OR** |
| Must be treated by an eligible practitioner type who has consulted at least one of the above mentioned specialist types |
| **AND** |
| **Treatment criteria:** |
| Patient must be undergoing concurrent treatment with ursodeoxycholic acid |
| **OR** |
| Patient must be undergoing treatment with this drug as monotherapy because combination treatment with ursodeoxycholic acid is not tolerated/contraindicated |
| ***AND*** |
| **Treatment criteria:** |
| Patient must not be undergoing concurrent treatment with either of: (i) obeticholic acid (ii) elafibranor |
| **AND** |
| **Clinical criteria:** |
| Patient must have experienced an inadequate response to ursodeoxycholic acid, despite treatment with ursodeoxycholic acid for at least 52 weeks at a therapeutic dose, prior to initiating treatment with this drug; |
| **OR** |
| Patient must have experienced an intolerance/contraindication to ursodeoxycholic acid of a severity requiring permanent treatment discontinuation, prior to initiating treatment with this drug |
| **AND** |
| **Clinical criteria:** |
| Patient must not have ~~each of (i)~~ severe liver disease~~, (ii) immunocompromised~~ |
| **AND** |
| **Clinical criteria:** |
| Patient must have had, prior to initiating treatment with this drug, an alkaline phosphatase (ALP) level of at least 1.67 times the upper limit of normal (ULN) having accounted for each of: (i) age, (ii) gender, (iii) laboratory to laboratory variances in the definition of 'normal', despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks; |
| **OR** |
| Patient must have had, prior to initiating treatment with this drug, a total bilirubin level between 1 to 2 times the ULN, despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks; |

| |
|---|
| ***OR*** |
| *Patient must have had, prior to initiating treatment with this drug, moderate to severe pruritus despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks;* |
| **OR** |
| Patient must have had, prior to initiating treatment with this drug, abnormal readings of at least one of: (i) alkaline phosphatase (ii) total bilirubin, or moderate-to-severe pruritus in the presence of an intolerance/contraindication of a severity requiring treatment discontinuation with ursodeoxycholic acid |
| **OR** |
| *Patient must have experienced an intolerance to either of (i) obeticholic acid (ii) elafibrinor, of a severity requiring treatment discontinuation, prior to initiating treatment with this drug;* |
| **OR** |
| *Patient must have inadequately responded to treatment with (i) obeticholic acid (ii) elafibrinor, prior to initiating treatment with this drug* |
| **Population criteria:** |
| Patient must be at least 18 years of age |
| **Prescribing Instructions:**<br>Document and retain in the patient's medical records the qualifying baseline laboratory reading for the purpose of assessing response to treatment under the 'Continuing treatment' restriction. |
| **Prescribing Instructions:**<br>Moderate-to-severe pruritus is defined moderate or severe pruritus via the pruritus numeric rating scale |
| **Administrative Advice:**<br>Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria. |
| **Administrative Advice:**<br>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria. |
| ~~**Caution:**~~<br>~~Hepatic decompensation and failure, in some cases fatal, have been reported in post-marketing reports in patients with moderate to severe hepatic impairment when doses incorrectly.~~ |

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

# 13 PBAC Outcome

13.1 The PBAC recommended the listing of seladelpar for the treatment of primary biliary cholangitis (PBC). The PBAC noted that the TGA Delegate was supportive of registering seladelpar for the following indication: 'For the treatment of PBC, in adults in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA.'

13.2 The PBAC considered that the restriction for seladelpar should:

- remain as an Authority Required (telephone/online) listing for the initial and grandfather supply, in line with the corresponding listings for obeticholic acid (OCA) and elafibranor. The PBAC considered that an Authority Required (STREAMLINED) listing was appropriate for continuing supply;
- remove the criterion in the initial and grandfather supply restrictions that prevents use in immunocompromised patients as these patients are not excluded in the draft TGA Product Information (PI). The PBAC noted that the TGA approved PI for elafibranor also does not exclude use in

immunocompromised patients and this change should flow on to the current elafibranor listings.

- remove the caution that states "Hepatic decompensation and failure, in some cases fatal, have been reported in post-marketing reports in patients with moderate to severe hepatic impairment when dosed incorrectly" as this warning only applies to OCA. The PBAC noted that this change should flow on to the current elafibranor listings.
- not allow patients who have been treated with UDCA for at least 52 weeks and have achieved a biochemical response, but who continue to experience moderate-to-severe pruritus, to access seladelpar as there were no clinical data to support this request.
- allow nurse prescribing for continuing supply of seladelpar, which aligned with the restrictions for OCA and elafibranor; and
- allow patients who have experienced an intolerance and/or inadequate response to either OCA or elafibranor to initiate treatment with seladelpar. The PBAC considered that patients should be able to access all three agents and noted that flow on changes would be required to the current OCA and elafibranor listings.
- remove the criterion that the total bilirubin (TB) level for patients should be 'between 1 to 2 times' above the ULN. There were differences between the trials in terms of how ULN was defined with respect to TB and a bilirubin level of greater than 2 times above the ULN should not preclude therapy. The PBAC noted that flow on changes would be required to the current OCA and elafibranor initial/grandfather listings.

13.3 The PBAC reiterated its previous consideration that the cost minimisation approach outlined in paragraph 7.14 was reasonable and the financial implications of listing seladelpar on the PBS would be minimal. The PBAC advised that seladelpar should be included in the existing risk sharing arrangement for OCA and elafibranor with no increase in expenditure caps (see paragraph 7.14).

13.4 Aligning with OCA and elafibranor, the PBAC advised that continuing supply of seladelpar is suitable for prescribing by nurse practitioners.

13.5 The PBAC advised that seladelpar should not be exempt from the Early Supply rule.

13.6 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because seladelpar is not expected to provide a substantial and clinically relevant improvement in efficacy over OCA and not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

13.7 The PBAC recommended that seladelpar should not be treated as interchangeable with any other drugs.

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

**Outcome:**
Recommended

# 14 Recommended listing

14.1 Add new medicinal product:

**Initial/Grandfather**

| MEDICINAL PRODUCT medicinal product pack | PBS item code | Max. qty packs | Max. qty units | №. of Rpts | Available brands |
|---|---|---|---|---|---|
| SELADELPAR | | | | | |
| seladelpar 10 mg capsule, 30 | NEW | 1 | 30 | 5 | Livdelzi |
| | | | | | |

| | | |
|---|---|---|
| Restriction Summary [1] / Treatment of Concept: [1A] | | |
| **Concept ID** (for internal Dept. use) | | **Category / Program:** ☒ GENERAL - General Schedule (Code GE) |
| | | **Prescriber type:** ☒ Medical Practitioners |
| | | **Restriction type:** ☒ Authority Required: telephone/online |
| Prescribing rule level | | **Administrative Advice:** Not for use in the treatment of sclerosing cholangitis |
| | | **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 888 333. |
| | | **Indication:** Primary biliary cholangitis (previously known as Primary biliary cirrhosis) |
| | | **Treatment Phase:** Initial treatment |
| | | **Treatment criteria:** |
| | | Must be treated by a prescriber who is either: (i) a gastroenterologist, (ii) a hepatologist; |
| | | **OR** |
| | | Must be treated by a medical practitioner who has consulted at least one of the above mentioned specialist types |
| | | **AND** |
| | | **Treatment criteria:** |
| | | Patient must be undergoing concurrent treatment with ursodeoxycholic acid; |
| | | **OR** |
| | | Patient must be undergoing treatment with this drug as monotherapy because treatment with ursodeoxycholic acid is not tolerated/contraindicated |
| | | **AND** |
| | | **Treatment criteria:** |
| | | Patient must not be undergoing concurrent treatment with either of: (i) obeticholic acid (ii) elafibrinor |
| | | **Clinical criteria:** |

| | |
|---|---|
| | Patient must have experienced an inadequate response to ursodeoxycholic acid, despite treatment with ursodeoxycholic acid for at least 52 weeks at a therapeutic dose, prior to initiating treatment with this drug; |
| | **OR** |
| | Patient must have experienced an intolerance/contraindication to ursodeoxycholic acid of a severity requiring permanent treatment discontinuation, prior to initiating treatment with this drug |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must not have severe liver disease |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have an alkaline phosphatase (ALP) level of at least 1.67 times the upper limit of normal (ULN) prior to initiating treatment with this drug, having accounted for each of: (i) age, (ii) gender, (iii) laboratory to laboratory variances in the definition of 'normal', despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks; |
| | **OR** |
| | Patient must have a total bilirubin level that is above the ULN prior to initiating treatment with this drug, despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks; |
| | **OR** |
| | Patient must have abnormal readings of at least one of: (i) alkaline phosphatase (ii) total bilirubin, in the presence of an intolerance/contraindication of a severity requiring treatment discontinuation with ursodeoxycholic acid |
| | **OR** |
| | Patient must have experienced an intolerance to one of (i) obeticholic acid (ii) elafibrinor, of a severity requiring treatment discontinuation, prior to initiating treatment with this drug; |
| | **OR** |
| | Patient must have inadequately responded to treatment with either of (i) obeticholic acid (ii) elafibrinor, prior to initiating treatment with this drug |
| | **Population criteria:** |
| | Patient must be at least 18 years of age |
| | **Prescribing Instructions:**<br>Document and retain in the patient's medical records the qualifying baseline laboratory reading for the purpose of assessing response to treatment under the 'Continuing treatment' restriction. |
| | **Administrative Advice:**<br>Laboratory readings requested in this authority application must be no older than 52 weeks, prior to starting either of (i) obeticholic acid (ii) elafibranor (iii) seladelpar, whichever is used first. |
| | |
| **Restriction Summary [2] / Treatment of Concept: [2A]** | |
| **Concept ID** (for internal Dept. use) | **Category / Program:** ☒ GENERAL - General Schedule (Code GE) |
| | **Prescriber type:** ☒ Medical Practitioners ☒ Nurse Practitioners |
| | **Restriction type:** ☒ Authority Required: telephone/online |

| | | |
|---|---|---|
| Prescribing rule level | | **Administrative Advice:**<br>Not for use in the treatment of sclerosing cholangitis |
| | | **Administrative Advice:**<br>**Continuing Therapy Only:**<br>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners. |
| | | **Administrative Advice:**<br>No increase in the maximum quantity or number of units may be authorised. |

| | | |
|---|---|---|
| | | **Administrative Advice:**<br>No increase in the maximum number of repeats may be authorised. |
| | | **Administrative Advice:**<br>Special Pricing Arrangements apply. |
| | | **Administrative Advice:**<br>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 888 33 |
| | | **Indication:** Primary biliary cholangitis (previously known as Primary biliary cirrhosis) |
| | | **Treatment Phase:** Transitioning from non-PBS to PBS subsidised supply - Grandfather arrangements |
| | | **Clinical criteria:** |
| | | Patient must have received treatment with this drug for this PBS indication prior to [Date] |
| | | **Treatment criteria:** |
| | | Must be treated by a prescriber who is either: (i) a gastroenterologist, (ii) a hepatologist; |
| | | **OR** |
| | | Must be treated by an eligible practitioner type who has consulted at least one of the above mentioned specialist types |
| | | **AND** |
| | | **Treatment criteria:** |
| | | Patient must be undergoing concurrent treatment with ursodeoxycholic acid |
| | | **OR** |
| | | Patient must be undergoing treatment with this drug as monotherapy because treatment with ursodeoxycholic acid is not tolerated/contraindicated |
| | | ***AND*** |
| | | **Treatment criteria:** |
| | | Patient must not be undergoing concurrent treatment with either of: (i) obeticholic acid (ii)elafibranor |
| | | **AND** |
| | | **Clinical criteria:** |
| | | Patient must have experienced an inadequate response to ursodeoxycholic acid, despite treatment with ursodeoxycholic acid for at least 52 weeks at a therapeutic dose, prior to initiating treatment with this drug; |
| | | **OR** |
| | | Patient must have experienced an intolerance/contraindication to ursodeoxycholic acid of a severity requiring permanent treatment discontinuation, prior to initiating treatment with this drug |
| | | **AND** |
| | | **Clinical criteria:** |
| | | Patient must not have severe liver disease |
| | | **AND** |
| | | **Clinical criteria:** |
| | | Patient must have had, prior to initiating treatment with this drug, an alkaline phosphatase (ALP) level of at least 1.67 times the upper limit of normal (ULN) having accounted for each of: (i) age, (ii) gender, (iii) laboratory to laboratory variances in the definition of 'normal', despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks; |
| | | **OR** |
| | | Patient must have had, prior to initiating treatment with this drug, a total bilirubin level above the ULN, despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks; |
| | | **OR** |
| | | Patient must have had, prior to initiating treatment with this drug, abnormal readings of at least one of: (i) alkaline phosphatase (ii) total bilirubin, in the presence of an intolerance/contraindication of a severity requiring treatment discontinuation with ursodeoxycholic acid |

| | |
|---|---|
| | **OR** |
| | Patient must have experienced an intolerance to either of (i) obeticholic acid (ii) elafibrinor, of a severity requiring treatment discontinuation, prior to initiating treatment with this drug; |
| | **OR** |
| | Patient must have inadequately responded to treatment with (i) obeticholic acid (ii) elafibrinor, prior to initiating treatment with this drug |
| | **Population criteria:** |
| | Patient must be at least 18 years of age |
| | **Prescribing Instructions:**<br>Document and retain in the patient's medical records the qualifying baseline laboratory reading for the purpose of assessing response to treatment under the 'Continuing treatment' restriction. |
| | **Administrative Advice:**<br>Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria. |
| | **Administrative Advice:**<br>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria. |

**Continuing treatment:**

| MEDICINAL PRODUCT<br>medicinal product pack | PBS item code | Max. qty packs | Max. qty units | №. of Rpts | Available brands |
|---|---|---|---|---|---|
| SELADELPAR | | | | | |
| seladelpar 10 mg capsule, 30 | NEW | 1 | 30 | 5 | Livdelzi |

| | | |
|---|---|---|
| **Restriction Summary [3] / Treatment of Concept: [3A]** | | |
| **Concept ID** (for internal Dept. use) | | **Category / Program:** ☒ GENERAL - General Schedule (Code GE) |
| | | **Prescriber type:** ☒ Medical Practitioners ☒ Nurse Practitioners |
| | | **Restriction type:** ☒ Authority Required: STREAMLINED |
| Prescribing rule level | | **Administrative Advice:**<br>Not for use in the treatment of sclerosing cholangitis |
| | | **Administrative Advice:**<br>No increase in the maximum quantity or number of units may be authorised. |
| | | **Administrative Advice:**<br>No increase in the maximum number of repeats may be authorised. |
| | | **Administrative Advice:**<br>Special Pricing Arrangements apply. |
| | | |
| **Concept ID** (for internal Dept. use) | | **Category / Program:** ☒ GENERAL - General Schedule (Code GE) |
| | | **Prescriber type:** ☒ Medical Practitioners ☒ Nurse Practitioners |
| | | **Restriction type:** ☒ Authority Required: STREAMLINED |
| | | **Indication:** Primary biliary cholangitis (previously known as Primary biliary cirrhosis) |
| | | **Treatment Phase:** Continuing treatment |
| | | **Treatment criteria:** |
| | | Must be treated by a prescriber who is either: (i) a gastroenterologist, (ii) a hepatologist; |
| | | **OR** |
| | | Must be treated by an eligible practitioner type who has consulted at least one of the above mentioned specialist types |
| | | **AND** |
| | | **Treatment criteria:** |

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| | Patient must be undergoing continuing PBS-subsidised treatment with this drug, with treatment having commenced through one of: (i) the 'Initial treatment' listing, (ii) 'Grandfather' arrangements |
| | **AND** |
| | **Treatment criteria:** |
| | Patient must be undergoing concurrent treatment with ursodeoxycholic acid; |
| | **OR** |
| | Patient must be undergoing treatment with this drug as monotherapy because treatment with ursodeoxycholic acid is not tolerated/contraindicated |
| | **AND** |
| | **Treatment criteria:** |
| | Patient must not be undergoing concurrent treatment with either of: (i) obeticholic acid (ii)elafibranor |
| | **Clinical criteria:** |
| | Patient must have achieved an adequate response to this drug, defined as having at least one of: (i) an alkaline phosphate (ALP) level less than 1.67 times the upper limit of normal (ULN), (ii) a reduction in the ALP reading of at least 15% compared to the baseline level provided with the initial authority application, (iii) a total bilirubin level within the normal reference range. |
| | **Prescribing Instructions:**<br>The improvement in the qualifying laboratory reading(s) has/have been documented in the patient's medical records. |
| | **Administrative Advice:**<br>Laboratory readings requested in this authority application must be no older than 52 weeks. |

**Flow on changes to other listings**

14.2 Amend the existing obeticholic acid restrictions as follows:

- Update concept in OCA to exclude concomitant treatment with seladelpar:
  - 12640G / obeticholic acid 10 mg tablet, 30 (continuing treatment)
  - 12630R / obeticholic acid 5 mg tablet, 30 (continuing treatment)
  - 12623J / obeticholic acid 5 mg tablet, 30 (initial treatment)

| | |
|---|---|
| | ***Treatment criteria:*** |
| | *Patient must not be undergoing concurrent treatment with either of: (i) seladelpar (ii) elafibrinor* |

- Update concept 34108/34109 (addition of seladelpar) to be flowed on to OCA only for PBS items codes:
  - 12623J / obeticholic acid 5 mg tablet, 30 (initial treatment)

| | |
|---|---|
| | **Clinical criteria:** |
| | Patient must have experienced an intolerance to *either of: (i)* elafibranor *(ii) seladelpar* of a severity requiring treatment discontinuation, prior to initiating treatment with this drug; or |
| | Patient must have inadequately responded to treatment with *either of: (i)* elafibranor *(ii) seladelpar*, prior to initiating treatment with this drug |

14.3 Amend the existing elafibranor restrictions as follows:

- Update concept 33894/33893 (excluding concomitant treatment with seladelpar/OCA) to be flowed on to elafibranor only for PBS item codes:
  - 15084X / elafibranor 80 mg tablet, 30 (grandfather treatment)
  - 15089E / elafibranor 80 mg tablet, 30 (continuing treatment)

- 15107D/ elafibranor 80 mg tablet, 30 (initial treatment)

| | |
|---|---|
| | ***Treatment criteria:*** |
| | *Patient must not be undergoing concurrent treatment with either of: (i) seladelpar (ii) obeticholic acid* |

- Update concept 34053/34174 (addition of seladelpar) to be flowed on to elafibrinor only for PBS item codes:
  - 15084X / elafibranor 80 mg tablet, 30 (grandfather treatment)
  - 15107D/ elafibranor 80 mg tablet, 30 (initial treatment)

| | |
|---|---|
| | **Clinical criteria:** |
| | Patient must have experienced an intolerance to *either of: (i)* obeticholic acid *(ii) seladelpar* of a severity requiring treatment discontinuation, prior to initiating treatment with this drug; or |
| | Patient must have inadequately responded to treatment with *either of: (i)* obeticholic acid *(ii) seladelpar*, prior to initiating treatment with this drug |

- Update concept 27508/27507 (preventing use in immunocompromised patients) to be flowed on to elafibrinor only for PBS item codes:
  - 15084X / elafibranor 80 mg tablet, 30 (grandfather treatment)
  - 15107D/ elafibranor 80 mg tablet, 30 (initial treatment)

| | |
|---|---|
| | **Clinical criteria:** |
| | Patient must not have~~/be each of: (i)~~ severe liver disease~~, (ii) immunocompromised~~ |

- Remove concept 27499 (hepatic decomposition and failure caution) to be flowed on to elafibrinor only for PBS item codes:
  - 15084X / elafibranor 80 mg tablet, 30 (grandfather treatment)
  - 15107D/ elafibranor 80 mg tablet, 30 (initial treatment)
  - 15089E/ elafibrinor 80mg tablet, 30 (continuing treatment)

| | |
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| | ~~**Caution:**~~<br>~~Hepatic decompensation and failure, in some cases fatal, have been reported in post-marketing reports in patients with moderate to severe hepatic impairment when dosed incorrectly.~~ |

- Update concept 34502/34055 (removal of the reference to total bilirubin levels between 1 to 2 times above the ULN) to be flowed on to elafibrinor and OCA for PBS item codes:
  - 12623J / obeticholic acid 5 mg tablet, 30 (initial treatment)
  - 15107D/ elafibranor 80 mg tablet, 30 (initial treatment)

| | |
|---|---|
| | **Clinical criteria:** |
| | Patient must have a total bilirubin level ~~between 1 to 2 times~~ *that is above* the ULN prior to initiating treatment with this drug, despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks; or |

- Update concept 34101/27530 (removal of the reference to total bilirubin levels between 1 to 2 times above the ULN) to be flowed on to elafibrinor PBS item code:
  - 15084X/ elafibranor 80 mg tablet, 30 (grandfather treatment)

| | |
|---|---|
| ~~*34101*~~ *NEW* | **Clinical criteria:** |

| | |
|---|---|
| ~~*27530*~~ *NEW* | Patient must have had, prior to initiating treatment with this drug, a total bilirubin level *that was above* ~~between 1 to 2 times~~ the ULN, despite treatment with ursodeoxycholic acid for at least 52 cumulative weeks; or |

# 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.