5.06 ELAFIBRANOR, Tablet 80 mg, Iqirvo®, Ipsen Pty Ltd.

1 Purpose of submission

1.1 The Category 1 submission requested Authority required (STREAMLINED) listing for elafibranor for the treatment of primary biliary cholangitis (PBC).

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus obeticholic acid (OCA). Table 1 summarises the components of the overall 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 diagnosed with PBC with elevated levels of alkaline phosphatase and bilirubin, with an inadequate response to UDCA or intolerance to UDCA.
Intervention	Elafibranor 80mg tablet once daily.
Comparator	1. OCA 5-10 mg tablet once daily. 2. In OCA non-responders or patients intolerant to OCA: a. For UDCA inadequate responders, UDCA 12-16 mg/kg body weight/day + placebo. b. For UDCA intolerant patients, placebo.
Outcomes	• The primary end point was a biochemical response (defined by an ALP level of <1.67 times the upper limit of the normal range, with a reduction of ≥15% from baseline, and normal total bilirubin levels) at week 52. • Key secondary end points were normalisation of ALP at week 52 and a change in pruritus intensity from baseline through week 52 and through week 24, assessed with the use of the WI-NRS among patients with moderate-to-severe pruritus (defined as a WI-NRS score of ≥4 at baseline). • Adverse events.
Clinical claim	Elafibranor is non-inferior in terms of effectiveness compared with OCA. Elafibranor is superior in terms of safety compared with OCA.

Source: Table 1-1, p13 of the submission.
ALP= alkaline phosphatase; OCA= obeticholic acid; PBC= primary biliary cholangitis; UDCA= ursodeoxycholic acid; WI-NRS= Worst Itch Numeric Rating Scale.

2 Background

Registration status

2.1 The submission was made under the Therapeutic Goods Administration (TGA)/Pharmaceutical Benefits Advisory Committee (PBAC) Parallel Process. Elafibranor is being considered by the TGA for "the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA".

2.2 At the time of the PBAC consideration, the TGA's Advisory Committee on Medicines (ACM) minutes were available, in addition to the Clinical Evaluation Report and Delegate's Overview.

2.3 The Delegate's Overview requested ACM advice regarding the proposal to include elafibranor monotherapy in adults unable to tolerate UDCA in the indication, as there was only a small subset of patients in the ELATIVE trial (6 in the elafibranor arm and 2 in the placebo arm) who received monotherapy. The ACM considered that the full indication, including monotherapy, had a positive benefit-risk profile.

2.4 Elafibranor was approved for the treatment of PBC by the United States Food and Drug Administration (FDA) in June 2024 (accelerated approval), by the European Medicines Agency (EMA) in September 2024 (conditional marketing authorisation), and in the United Kingdom by the Medicines and Healthcare products Regulatory Agency (MHRA) in October 2024. The FDA and EMA approvals were conditional on conducting a variety of clinical trials and post-market studies, including: CLIN-60190-454 (ELFIDENCE), a randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of elafibranor in adults with PBC.[1,2]

- According to the FDA, efficacy must be demonstrated using a composite endpoint of all-cause mortality, liver transplant, hepatic decompensation, change in Model for End-Stage Liver Disease 3.0 (MELD) score to ≥ 15 in subjects with baseline MELD score ≤ 12, and development of hepatocellular carcinoma. The ELFIDENCE trial completion was stated in the submission to be May 2029.
- According to the EMA, the marketing authorisation holder shall conduct and submit the final results of the phase III randomised, parallel-arm, double-blind, placebo-controlled, 2-arm trial (ELFIDENCE) to evaluate the efficacy and safety of elafibranor on long-term clinical outcomes in adults with PBC.

Previous PBAC consideration

2.5 The PBAC has not previously considered elafibranor for the treatment of PBC.

2.6 The PBAC has previously considered OCA, which was recommended for the treatment of PBC in March 2021.

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

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[1] US Food and Drug Administration (6 October 2024) NDA 218860. Available: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/218860Orig1s000ltr.pdf

[2] European Medicines Agency (2024) Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 22-25 July 2024, Available: https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-22-25-july-2024, and European Medicines Agency (2024) Annex I: Summary of Product Characteristics, Available: https://www.ema.europa.eu/en/documents/product-information/iqirvo-epar-product-information_en.pdf

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№. of Rpts	Available brands
ELAFIBRANOR					
Elafibranor, 80mg tablet, 30	Published: $6,262.60 Effective: $[redacted]	1	30	5	Iqirvo

Category / Program: General Schedule
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required (STREAMLINED)
Indication: Primary biliary cholangitis (previously known as Primary biliary cirrhosis)
Treatment Phase: Initial
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 to ursodeoxycholic acid of a severity requiring permanent treatment discontinuation, prior to initiating treatment with this drug,
AND
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; and
Patient must have a total bilirubin level no more than 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.
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
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.
Population criteria:
Patient must be aged 18 years or over.
Prescribing Instructions: 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.

Category / Program: General Schedule
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required (STREAMLINED)
Indication: Primary biliary cholangitis (previously known as Primary biliary cirrhosis)
Treatment Phase: Continuing
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
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
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.
Prescribing Instructions: The improvement in the qualifying laboratory reading(s) must be documented in the patient's medical records.

Category / Program: General Schedule
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required (STREAMLINED)
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 1 XXXXXXX 202X
AND
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 to ursodeoxycholic acid of a severity requiring permanent treatment discontinuation, prior to initiating treatment with this drug,
AND
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; and
Patient must have had, prior to initiating treatment with this drug a total bilirubin level no more than 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.
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
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.
AND

Patient must not be undergoing concurrent treatment with obeticholic acid, but treatment may replace obeticholic acid where it is not tolerated, or an inadequate response is achieved.
Population criteria:
Patient must be aged 18 years or over.
Prescribing Instructions: 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.
Notes:
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.
This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

3.1 The requested PBS restriction positioned elafibranor as a second-line treatment following UDCA. The submission requested that, whilst elafibranor has not been specifically studied in a third line setting, elafibranor should be available on the PBS for patients who have failed treatment with OCA, either due to inadequate response or intolerance, given the absence of alternative treatment options. The clinical benefits in OCA non-responders (third line) were uncertain, as only 8.1% of patients (n=13) in the ELATIVE trial had previously received treatment with OCA.

3.2 The ESC and DUSC considered that the proposed PBS restriction for elafibranor should be consistent with that recommended for OCA and therefore suggested that:

- the requested Authority Required (STREAMLINED) initial and grandfather restriction for elafibranor should be revised to an Authority Required (telephone/online) restriction.
- the continuing restriction for elafibranor should allow prescribing by nurse practitioners.
- although the initial and grandfather restrictions proposed for elafibranor had different clinical criteria compared to OCA in terms of requiring alkaline phosphatase (ALP) **and** total bilirubin (TB) levels to be met, rather than ALP **or** TB levels to be met, which aligned with the eligibility criteria of the ELATIVE trial, it was reasonable for the restrictions to state 'or'.
- although the initial and grandfather restrictions for elafibranor had different clinical criteria compared to OCA in terms of requiring a TB level **no more than 2 times** the upper limit of normal (ULN), despite treatment with UDCA for at least 52 cumulative weeks, rather than **between 1 to 2 times**, which aligned with the eligibility criteria of the ELATIVE trial, the restrictions should state 'between 1 to 2 times'.
- the initial and grandfather restrictions for elafibranor should include the clinical criterion: Patient must not have/be each of: (i) severe liver disease, and (ii) immunocompromised.
- the continuing restriction for elafibranor should include the clinical criterion: Patient must have achieved an adequate response to this drug, defined as having

at least one of: (i) an ALP level less than 1.67 times the 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 TB level within the normal reference range. The Pre-Sub-Committee Response (PSCR) noted that there is significant intra-patient variability in blood tests for liver disease and that there were concerns regarding the reliability of these to assess response but, overall, was amenable to including the continuation criteria as proposed.

3.3 Further, the ESC considered that the restrictions for elafibranor should specifically exclude concomitant therapy with OCA. Similarly, if elafibranor is recommended by the PBAC, flow-on changes to the OCA restriction would be required to preclude concomitant therapy with elafibranor.

3.4 The requested PBS restriction was broader than the clinical evidence presented by the submission. In particular, the ELATIVE trial excluded patients with a history or presence of other concomitant liver disease, or clinically significant hepatic decompensation. The ESC and DUSC considered that the restriction should include a Caution precluding the use of elafibranor in patients with a history of these conditions.

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

4 Population and disease

4.1 PBC is a rare, progressive, chronic autoimmune disease of the liver characterised by the slow destruction of small intrahepatic bile ducts. This prevents the flow of bile and other toxins to the intestine, causing them to build up in the liver in a process known as cholestasis, which leads to scarring of the liver (fibrosis) and eventually can progress to cirrhosis, liver failure and death.

4.2 Patients who are symptomatic at diagnosis most commonly present with pruritus (itching) and fatigue (29 to 69% and 25 to 76% of patients with PBC, respectively).[3,4,5] Patients develop symptoms of liver disease and may accumulate comorbidities as their disease progresses, including osteoporosis, rheumatoid arthritis, thyroid disorders and autoimmune disorders.[6,7,8] Progression of PBC can lead to:

[3] Jung et al. 2012. 'Prognostic indicators in primary biliary cirrhosis: significance of revised IAHG (International Autoimmune Hepatitis Group) score', *Clin Mol Hepatol,* 18: 375-82.
[4] Milovanovic et al. 2020. 'Quality of Life in Patients with Primary Biliary Cholangitis: A Single-Center Experience in Serbia', *Dig Dis,* 38: 515-21.
[5] Oeda et al. 2018. 'Prevalence of pruritus in patients with chronic liver disease: A multicenter study', *Hepatol Res,* 48: E252-e62.
[6] Hirschfield et al. 2021b. 'A consensus integrated care pathway for patients with primary biliary cholangitis: a guideline-based approach to clinical care of patients', *Expert Rev Gastroenterol Hepatol,* 15: 929-39.
[7] Parés et al. 'Primary biliary cholangitis in Spain. Results of a Delphi study of epidemiology, diagnosis, follow-up and treatment', *Rev Esp Enferm Dig,* 110: 641-49.
[8] Liu et al. 'Clinical Characteristics and Prognosis of Concomitant Primary Biliary Cholangitis and Autoimmune Diseases: A Retrospective Study', *Can J Gastroenterol Hepatol,* 2021: 5557814.

- Liver cirrhosis: Up to 15% of patients treated with UDCA developed cirrhosis-associated complications within 15 years.[9,10] Overall 5-year survival and transplant-free survival is lower in people with cirrhosis versus those without cirrhosis (80% vs 93%; p=0.003 and 80% vs 93%; p=0.002, respectively).[11]
- Hepatocellular carcinoma (HCC): A 2020 meta-analysis of 29 cohort studies reported the incidence of HCC in patients with cirrhotic PBC as 15.7 per 1,000 patient-years (n=22,615), compared with 2.68 per 1,000 patient-years in patients with non-cirrhotic PBC.[12] Overall 5-year survival is lower in people with HCC versus PBC only (71.6% vs 91.5%; p=0.003 and 80% vs 93%; p=0.002, respectively).[13]

4.3 The submission noted a recent Australian study estimated the prevalence of PBC at 189.0 per million.[14] This equates to 5,035 patients in Australia. In the financial estimates of the submission, it was estimated that 5,695 patients were receiving UDCA for PBC in Australia. The ESC noted that there was likely to be some off-label usage of UDCA for other cholestatic liver function disorders.

4.4 The first-line recommended treatment is UDCA 13 to 15 mg/day. OCA is second-line therapy, either as monotherapy in UDCA intolerant patients or in combination with UDCA in patients who have not experienced an adequate clinical response after 12 months of UDCA monotherapy. The submission proposed that elafibranor will be used as an alternative to OCA for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, as monotherapy in adults unable to tolerate UDCA, or as a therapeutic alternative for patients treated unsuccessfully with OCA with or without UDCA.

4.5 Elafibranor is a first-in-class, selective activator ligand of peroxisome proliferator-activated receptor alfa (PPARα) and peroxisome proliferator-activated receptor delta (PPARδ) (anatomical therapeutic chemical (ATC) classification code: A05AX06).

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

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[9] Laschtowitz et al. 2020. 'Diagnosis and treatment of primary biliary cholangitis', *United European Gastroenterol J,* 8: 667-74.

10 Harms et al. 2018. 'Major Hepatic Complications in Ursodeoxycholic Acid-Treated Patients With Primary Biliary Cholangitis: Risk Factors and Time Trends in Incidence and Outcome', *Am J Gastroenterol,* 113: 254-64

[11] Axley et al. 2018. 'Patients with stage 3 compared to stage 4 liver fibrosis have lower frequency of and longer time to liver disease complications', *PLoS One,* 13: e0197117.

[12] Natarajan et al. 2021. 'Incidence of Hepatocellular Carcinoma in Primary Biliary Cholangitis: A Systematic Review and Meta-Analysis', *Dig Dis Sci,* 66: 2439-51.

[13] Rong et al. 2015. 'Incidence and risk factors for hepatocellular carcinoma in primary biliary cirrhosis', *Clin Rev Allergy Immunol,* 48: 132-41.

[14] French et al. 2020. 'Increasing prevalence of primary biliary cholangitis in Victoria, Australia', *J Gastroenterol Hepatol,* 35: 673-79.

5 Comparator

5.1 The submission nominated OCA (+ UDCA) as the main comparator, as OCA is the only second-line therapy for patients with PBC approved in Australia and funded on the PBS. OCA was PBS listed on 1 September 2021.

5.2 The submission noted that in October 2023, the European Committee for Medicinal Products for Human Use (CHMP) considered that the COBALT trial (study 747-302) had failed to demonstrate the clinical benefit of OCA across the spectrum of patients with PBC and considered the request to switch to full marketing authorisation not acceptable. In June 2024 the EMA recommended revoking conditional market authorisation for OCA as the clinical benefits had not been confirmed and thus the benefits of OCA did not outweigh its risks.[15]

5.3 The submission also noted that in September 2024 an FDA advisory panel[16] voted 10 to 1 against market authorisation for OCA, citing concerns about the lack of available data to verify the benefits of OCA on clinical outcomes and as it did not have a favourable benefit-risk assessment for use as a second-line treatment. In particular, the panellists noted that the COBALT trial (study 747-302) did not meet its primary endpoint, there was a higher rate of liver transplants in the OCA arm versus placebo arm and panellists were concerned about safety signals related to hepatotoxicity and decompensation.[17]

5.4 The COBALT trial (study 747-302) was a phase IIIb/IV, double-blinded, randomised controlled trial (RCT) comparing OCA 5-10 mg to placebo. The planned sample size was 428 patients[18]; however, the trial was terminated early as it "was not feasible to continue the study as designed owing to the impossibility of conducting a placebo-controlled randomised trial of long-term outcomes in the setting of commercially available therapies" (N=334).[19] The primary composite endpoint was time to all-cause mortality, liver transplant, MELD score ≥ 15, uncontrolled ascites, or hospitalisation

[15] EMA (2024) EMA recommends revoking conditional marketing authorisation for Ocaliva. Available: https://www.ema.europa.eu/en/news/ema-recommends-revoking-conditional-marketing-authorisation-ocaliva

[16] The FDA currently has a box warning for OCA regarding: hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, have been reported with OCA treatment in PBC patients with either compensated or decompensated cirrhosis; OCA is contraindicated in PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension; and permanently discontinue OCA in patients who develop laboratory or clinical evidence of hepatic decompensation, have compensated cirrhosis and develop evidence of portal hypertension, or experience clinically significant hepatic adverse reactions while on treatment.

[17] FDA (2024) Food and Drug Administration, Center for Drug Evaluation and Research, Final Summary Minutes of the Gastrointestinal Drugs Advisory Committee Meeting, September 12 2024

[18] National Institute of Health (2024) Phase 4 Study of Obeticholic Acid Evaluating Clinical Outcomes in Patients with Primary Biliary Cholangitis (COBALT). Available: https://clinicaltrials.gov/study/NCT02308111

[19] Kowdley et al. (2024) COBALT: A Confirmatory Trial of Obeticholic Acid in Primary Biliary Cholangitis with Placebo and External Controls. Am J Gastroenterol. 2024 Aug 14. doi: 10.14309/ajg.0000000000003029.

for hepatic decompensation. There was no statistically significant difference in the primary endpoint (hazard ratio (HR) = 1.01; 95% confidence interval (CI): 0.68, 1.51).[20] Compared to placebo, more patients died in the OCA arm (8.3% vs 6.6%), more patients received liver transplants (11.9% vs 10.8%), more patients experienced pruritus (78.6% vs 51.2%) and upper abdominal pain (14.9% vs 7.2%), but there were a similar rate of serious adverse events (SAEs; 31.5% vs 31.9%).[21]It was noted that the COBALT trial was confounded by unblinding and cross-over, and that a re-analysis of the COBALT trial data, accounting for crossover, remained favourable to OCA.

5.5 The submission proposed additional comparators in OCA non-responders or patients who are intolerant to OCA:

- For OCA inadequate responders: UDCA + placebo (UDCA monotherapy).
- For OCA intolerant patients: placebo (or no treatment).

5.6 The ESC considered that OCA was a relevant comparator. Noting that elafibranor may also be used in the third line setting by OCA non-responders or patients intolerant to OCA, the ESC considered that UDCA monotherapy or no treatment are also relevant comparators in the third line setting.

5.7 The submission identified seladelpar, a selective PPARδ agonist and saroglitazar, a PPARα/γ agonist, as near-market comparators. No clinical comparisons of elafibranor to seladelpar or saroglitazar were presented.

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 available pharmacological interventions in PBC, describing current practice, the place in therapy for elafibranor and how the drug would be used in practice. The clinician noted that up to 40% of patients will not respond or have intolerances to UDCA. At present the only option for these patients is OCA. The clinician noted that uptake of OCA in these patients has been low and stated that this may be because OCA increases pruritus and is associated with other adverse events such as hypertension. The clinician noted that the PBS listing of elafibranor would provide another treatment option for these patients and help prevent patients progressing to more severe disease. The PBAC considered that the hearing was informative.

[20] Up to 7 years follow-up.

[21] Kowdley et al. (2024) COBALT: A Confirmatory Trial of Obeticholic Acid in Primary Biliary Cholangitis with Placebo and External Controls. Am J Gastroenterol. 2024 Aug 14. doi: 10.14309/ajg.0000000000003029.

Consumer comments

6.2 The PBAC noted and welcomed the input from an individual (1) and an organisation (1) via the Consumer Comments facility on the PBS website. The comment supported the listing of elafibranor on the PBS.

6.3 The PBAC noted the advice received from the Liver Foundation which described PBC and its symptoms. The Liver Foundation noted the impact of PBC on quality of life and highlighted the impact of pruritis and fatigue on patients. The Liver Foundation supported the listing of elafibranor on the PBS.

Clinical trials

6.4 No head-to-head trials comparing elafibranor and OCA were identified.

6.5 The submission was based on one RCT, the ELATIVE trial (N=161), comparing:

- Elafibranor + UDCA versus placebo + UDCA in patients with PBC and an inadequate response to UDCA (elafibranor 80 mg: N=102; placebo: N=51), or
- Elafibranor versus placebo in patients with PBC and an intolerance to UDCA (elafibranor 80 mg: N=6; placebo: N=2).

6.6 The submission was also based on one RCT, the POISE trial (N=217 enrolled, 216 randomised), comparing:

- OCA + UDCA versus placebo + UDCA in patients with PBC and an inadequate response to UDCA (OCA 5-10 mg titration: N=65; OCA 10 mg: N=67; placebo: N=68), or
- OCA versus placebo in patients with PBC and an intolerance to UDCA (OCA 5-10 mg titration: N=5; OCA 10 mg: N=6; placebo: N=5).

6.7 The POISE trial was previously considered by the PBAC in the submissions for OCA.

6.8 The submission conducted pairwise indirect comparisons of elafibranor compared to OCA with placebo as the common comparator.

6.9 The submission did not present the results of the COBALT trial for OCA (see paragraph 5.4), as there were no comparable outcomes available for an indirect treatment comparison with elafibranor. However, recruitment is currently underway for the ELFIDENCE trial. The ELFIDENCE trial, like the COBALT trial, is a RCT comparing elafibranor 80 mg to placebo in patients with PBC.[22] The primary endpoint is event-free survival (adjudicated disease progression or death, defined as a composite endpoint of all-cause mortality, liver transplant, hepatic decompensation, change in MELD score to ≥ 15 in patients with a baseline MELD score ≤ 12, and development of

[22] National Institute of Health (2024) A Long-Term Study of Elafibranor in Adult Participants With Primary Biliary Cholangitis (ELFIDENCE). Available: https://clinicaltrials.gov/study/NCT06016842

hepatocellular carcinoma).[23] The expected completion date for the ELFIDENCE trial is May 2029, with the final trial report expected in May 2030.

6.10 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ELATIVE Study NCT04526665 EUCTR2019-004941-34-BE GFT505B-319-1	Clinical Study Report: A double-blind, randomized, placebo-controlled study and open-label long term extension to evaluate the efficacy and safety of elafibranor 80 mg in patients with primary biliary cholangitis with inadequate response or intolerance to ursodeoxycholic acid. Data cut-off date: 01 June 2023. CSR (Double-blind Period): 31 August 2023.	2023
	Kowdley KV, Bowlus CL, Levy C, et al. ELATIVE Study Investigators' Group; ELATIVE Study Investigators' Group. Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis.	*NEJM* 2024; 390(9):795-805
	Bowlus, CL, Kowdley, KV, Levy C, et al. Efficacy and safety of elafibranor in primary biliary cholangitis: results from the ELATIVE™ double-blind, randomized, placebo-controlled phase 3 trial.	*Hepatology* 2024;79:e40-e42.
	Bowlus, C; Kowdley, K; Levy C. et al. 5007 | Efficacy and safety of elafibranor in primary biliary cholangitis: Results from the ELATIVE™ double-blind, randomized, placebo-controlled phase 3 trial 2023.	AASLD 2023
	Bowlus CL, Levy C, Akarca U, et al. LBP-006 - Efficacy of elafibranor in primary biliary cholangitis: results from the variable double-blind period of ELATIVE®, a randomised, placebo-controlled phase III trial.	EASL International Liver Congress, 2024.
	Kremer AE, Levy C, Mayo MJ, et al. LBP-028 - Effect of elafibranor on pruritus in primary biliary cholangitis: symptom severity and quality of life measurements from the phase III ELATIVE® trial.	EASL International Liver Congress, 2024.
	Mayo MJ, Pedersen M, Tonev D, et al. THU-105 - Improvement in lipid profiles with elafibranor treatment in primary biliary cholangitis during the phase III Elative® trial.	EASL International Liver Congress, 2024.
	Sonderup M, Calvaruso V, Antunes N, et al. OS-016 - Elafibranor efficacy in primary biliary cholangitis according to biochemical response criteria in the phase III ELATIVE® trial.	EASL International Liver Congress, 2024.
POISE NCT01473524	Nevens F, Andreone P, Mazzella G, et al. POISE Study Group. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis.	*NEJM* 2016; 375(7):631-43.
	Andreone P, Floreani A, Invernizzi P, et al. Durable response in the markers of cholestasis through 24 months of open-label extension with obeticholic acid in Italian patients with primary biliary cholangitis.	*Digestive and liver disease* 2017;49:e21.

[23] This differs from the conditions of the FDA accelerated approval, where efficacy must be demonstrated using a composite endpoint of all-cause mortality, liver transplant, hepatic decompensation, change in Model for End-Stage Liver Disease (MELD) 3.0 to ≥15 in patients with baseline MELD ≤12, and development of HCC. US Food and Drug Administration (6 October 2024) NDA 218860.
Available: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/218860Orig1s000ltr.pdf

Trial ID	Protocol title/ Publication title	Publication citation
	Andreone P, Floreani A, Invernizzi P, et al. Durable response in the markers of cholestasis through 36 months of open-label extension with obeticholic acid in Italian patients with primary biliary cholangitis.	*Digestive and liver disease* 2018;50:26.
	Bowlus C, Trauner M, Liberman A, et al. Long-Term Efficacy and Safety of Obeticholic Acid in Patients with PBC from POISE Grouped by Risk of Disease Progression.	*Zeitschrift fur Gastroenterologie* 2021;59(1):e14-e15.
	Bowlus CL, Pockros PJ, Kremer AE, et al. Three years of Obeticholic Acid (OCA) Therapy Results in Histological Improvements in Patients with Primary Biliary Cholangitis: further Analysis of the POISE Biopsy Substudy.	*Zeitschrift fur Gastroenterologie* 2019;57:e9.
	Bowlus CL, Pockros PJ, Kremer AE, et al. Long-Term Obeticholic Acid Therapy Improves Histological Endpoints in Patients With Primary Biliary Cholangitis.	*Clinical gastroenterology and hepatology* 2020;18:1170-1178.e6.
	Bowlus CL, Trauner M, Liberman A, et al. Long-term efficacy and safety of obeticholic acid in patients with PBC from the POISE trial grouped biochemically by risk of disease progression.	*Digestive and Liver Disease* 2021;53(Supplement 1): S18.
	Carbone M, Harms MH, Lammers WJ, et al. Clinical application of the GLOBE and United Kingdom-primary biliary cholangitis risk scores in a trial cohort of patients with primary biliary cholangitis.	*Hepatology Communications* 2018;2:683-692.
	Floreani A, Bowlus CL, Trauner M, et al. Long-Term Efficacy And Safety Of Obeticholic Acid In Patients With PBC From The Poise Trial Grouped Biochemically By Risk Of Disease Progression.	*Digestive and Liver Disease* 2021;53(Supplement 3):S109.
	Halilbasic E, Hofer H, Munda P, et al. Durable response in the markers of cholestasis through 18 months of open-label extension with obeticholic acid in Austrian and German patients with primary biliary cholangitis.	*Zeitschrift fur Gastroenterologie* 2017;55.
	Halilbasic E, Zoller H, Munda P, et al. Durable response in the markers of cholestasis through 36 months of open-label extension with obeticholic acid in Austrian and German patients with primary biliary cholangitis.	*Zeitschrift fur Gastroenterologie* 2018;56:e47.
	Hirschfield G, Carbone M, Jones D, et al. Durability of obeticholic acid response in PBC patients who did not achieve poise trial criteria.	*Gut* 2021;70(SUPPL 1): A13.
	Jones D, Carbone M, Mells G, et al. Predicted risk of end stage liver disease utilizing the UK-PBC risk score in PBC patients.	*Gut* 2021;70(SUPPL 1): A153-A154.
	Pares A, Shiffman M, Vargas V, et al. Reduction and stabilization of bilirubin with obeticholic acid treatment in patients with primary biliary cholangitis.	*Liver International* 2020;40:1121-1129.
	Trauner M, Nevens F, Shiffman ML, et al. Long-term efficacy and safety of obeticholic acid for patients with primary biliary cholangitis: 3-year results of an international open-label extension study.	*The Lancet. Gastroenterology & hepatology* 2019;4:445-453.

Trial ID	Protocol title/ Publication title	Publication citation
	Bonder A, Wheeler D, Nair R, et al. Effect Of Obeticholic Acid On Prognostic Thresholds Of Gamma-Glutamyl Transferase And Alkaline Phosphatase Levels: Sub-Analysis Of The Phase 3 Poise Trial In Primary Biliary Cholangitis.	*Hepatology* 2023;78:S2047-S2048.

Source: Table 2-3 and Table 2-4, pp62-64 of the submission.

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

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
ELA + UDCA vs UDCA+ placebo for UDCA inadequate responders or ELA vs placebo for UDCA intolerant						
ELATIVE	161	R, DB [a] 52-104 weeks	Low/ Moderate	Aged 18-75 years, PBC, ALP ≥ 1.67 x ULN and TB ≤ 2 x ULN. Excluded if they had clinically significant hepatic decompensation.	Primary: Cholestasis response[b] Key secondary: ALP normalisation[c], change in PBC WI-NRS score[d] in patients with baseline PBC Worst Itch NRS score ≥4. Other secondary: Change in ALP, ALP response rates, 5-D Itch Scale[e], PBC-40[f], EQ-5D-5L VAS. Exploratory: PBC-40 Itch Domain score. Safety: TEAEs, AESIs, and discontinuations.	Patient-level data on ALP and TB, drug exposure days, all-cause discontinuations, PBC-40 itch domain, TEAEs
OCA + UDCA vs UDCA+ placebo for UDCA inadequate responders or OCA vs placebo for UDCA intolerant						
POISE	217	R, DB [g] 12 mths	Moderate	Aged ≥18 years, PBC, ALP ≥ 1.67 x ULN or TB < 2 x ULN. Excluded if they had clinically significant hepatic decompensation, or severe pruritus requiring current or prior systemic treatment	Cholestasis response[b] Secondary: ALP normalisation[c]; change in ALP, ALP response rates, 5-D Itch Scale[e]; PBC-40[f]. Exploratory: PBC-40 Itch Domain score. Safety: TEAEs, AESIs, and discontinuations.	Indirect comparison of cholestasis response, all-cause discontinuations, pruritus TEAEs and PBC-40 Itch Domain

Source: Compiled during the evaluation based on pp65-81 of the submission.

AESI: adverse events of special interest; ALP= Alkaline phosphatase; DB = double blind; ELA= elafibranor; OCA = obeticholic acid; PBC= Primary biliary cholangitis; R = randomised; TB= total bilirubin; TEAE= Treatment-emergent adverse event; UDCA= Ursodeoxycholic acid; ULN= Upper limit of normal; WI-NRS= Worst Itch Numeric Rating Scale.

[a] Stratified by baseline ALP and total bilirubin (ALP >3 x ULN or TB >ULN); and WI-NRS ≥4 (averaged over the 14 days preceding baseline)

[b] Achieving ALP <1.67 x ULN and TB ≤ULN and ALP decrease of ≥15%.

[c] ALP ≤ULN.

[d] The PBC WI-NRS asks patients to rate their worst itch over the past 24 hours on a scale ranging from zero (no itch) to 10 (worst itch imaginable).

[e] The 5-D Itch Scale comprises of five domains, each accounting for five points: duration, degree, direction, disability and distribution. Scores can range from five (no pruritus) to 25 (most severe pruritus).

[f] The PBC-40 comprises of 40 questions that evaluate patients' experience across 6 domains: fatigue, emotional impact, social impact, cognitive function, general symptoms and itch. Each question is scored from 1 to 5 (5-point Likert Scale), then summed to give a total domain score. High scores represent high impact, and low scores low impact of PBC on quality of life.

[g] Stratified by Paris 1 risk criteria (ALP ≥ 3 x ULN or AST ≥ 2 x ULN or bilirubin > ULN); and the use or non-use of UDCA prior to the POISE trial.

6.12 The ESC considered that the ELATIVE trial had a low risk of bias for the primary endpoint (cholestasis response) and first secondary endpoint (ALP normalisation) as they were analysed using the intent-to-treat population. However, the ESC considered that there was a moderate risk of bias for the secondary endpoints regarding pruritus

(e.g. PBC Worst Itch Numerical Rating Scale (WI-NRS) score, 5-D Itch Scale score, and PBC-40 Itch Domain score) as:

- these endpoints were analysed using the Pruritus Intent-to-treat (ITT) analysis set (patients with baseline PBC WI-NRS score ≥4). The results were not generalisable to the whole ITT or PBC population due to the exclusion of patients with PBC WI-NRS score <4.
- pruritus scores for patients who stopped the study treatment prematurely or took a rescue therapy for pruritus prior to Week 52 assessment were considered as missing. The data was analysed using a Mixed Model for Repeated Measures (MMRM) and missing values were assumed to be missing at random. The treatment effect may be overestimated as these patients may have had worse pruritus scores as they discontinued, or took rescue therapy due to severe pruritus, thus were not missing at random.

6.13 The PBAC previously considered the 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).

6.14 The ESC noted that there were differences across the ELATIVE and POISE trials, which affected the assumption of transitivity, including:

- the POISE trial required for patients to have an ALP level or a TB level to meet a threshold, while the ELATIVE trial required both ALP and TB to meet the threshold.
- the POISE trial excluded patients with severe pruritus, while the ELATIVE trial did not exclude these patients.
- patients in the elafibranor arm were less likely to receive concomitant medication during the trial for pruritus compared to patients in the placebo arm in the ELATIVE trial (13.0% vs 22.6%). In contrast, patients in the OCA 5-10 mg arm and the OCA 10 mg arm were more likely to receive concomitant medication during the trial for pruritus compared to the placebo arm in the POISE trial (15.7% vs 19.2% vs 9.6%). The lower use of concomitant medication for pruritus in the placebo arm in the POISE trial compared to the ELATIVE trial may reflect that the POISE trial excluded patients with severe pruritus.
- there was a slightly higher discontinuation rate in the POISE trial (OCA 5-10 mg: 9.9%; OCA 10 mg: 12.3%; placebo: 4.1%) compared to the ELATIVE trial (elafibranor: 8.3%; placebo: 7.5%).

6.15 The key primary outcome was the same in the ELATIVE and POISE trials, with cholestasis response being assessed as achieving ALP < 1.67 x ULN, a decrease in ALP of ≥ 15% and TB ≤ ULN. Arguments in support of this surrogate outcome included:

- Complications associated with PBC progression such as cirrhosis and liver failure take a long time to develop and clinical trials of novel PBC therapies would require a prolonged follow-up period to demonstrate a reduction in these outcomes. It is

also difficult to recruit a large enough study population of patients with advanced PBC (i.e. the patients most likely to experience these complications) to provide sufficient statistical power for a clinical trial, as PBC is a rare disease.

- The PBAC had previously considered that the use of biochemical markers to monitor disease progression in PBC had been validated, with European Association for the Study of the Liver (EASL) Guidelines indicating that levels of ALP and total bilirubin correlate with disease severity and progression to fibrosis and cirrhosis (paragraph 6.13, obeticholic acid, PSD, November 2018 PBAC meeting). The ESC noted that the relationship of these surrogate endpoints to disease progression and patient outcomes was uncertain given the results of the COBALT trial; however, the ESC did consider that there could be other potential causes for the COBALT trial results (see paragraph 6.16).
- The FDA: 1) granted accelerated approval for OCA based on a significant reduction in ALP and bilirubin levels demonstrated in the POISE trial in 2016;[24] and 2) granted elafibranor a Breakthrough Therapy Designation based on surrogate endpoint data from the Phase II Elafibranor Trial in PBC, with Orphan Drug Designation granted by the FDA and EMA soon after. The FDA granted accelerated approval for elafibranor, conditional on efficacy being demonstrated using a composite endpoint of all-cause mortality, liver transplant, hepatic decompensation, change in MELD score to ≥ 15 in patients with baseline MELD score ≤ 12, and development of HCC.[25]
- Lammers et al. (2014), in a meta-analysis of studies involving 4,845 patients primarily treated with UDCA across North America and Europe, found that ALP and bilirubin were strongly associated with clinical outcomes. Levels of both ALP and bilirubin, measured at study enrolment and each year for five years, were strongly associated with clinical outcomes, with combined assessment of both ALP and bilirubin levels being the strongest predictor of transplant-free survival duration.

6.16 A surrogate marker's correlation with disease progression does not necessarily mean that a medicine affecting the surrogate marker will affect disease progression. The PBAC guidelines consider a multi-trial meta-regression or a randomised trial to be the strongest evidence of a relationship between a surrogate endpoint and a clinical outcome (PBAC Guidelines v5.0, Appendix 5). The COBALT trial found a significantly larger decrease in ALP in the OCA arm (-156.4 U/L; standard error (SE) = 14.93; N = 98) than in the placebo arm (-113.1 U/L; SE = 14.6; p = 0.0394[26]; N = 102) and a non-significant smaller increase in TB in the OCA arm (0.30 mg/DL; SE = 0.141; N = 97) than

[24] US FDA (2016) 'FDA approves Ocaliva for rare, chronic liver disease'. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-ocaliva-rare-chronic-liver-disease
[25] US FDA (6 October 2024) NDA 218860, Accelerated Approval. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/218860Orig1s000ltr.pdf
[26] Calculated during the evaluation.

in the placebo arm (0.63 mg/DL; SE = 0.138;p = 0.0960[27]; N = 101) at 24 months, but the COBALT trial did not find a decrease in the primary composite endpoint (HR = 1.01; 95% CI: 0.68, 1.51).[28,29] Consequently, cholestasis response and ALP may not be adequate surrogates for disease progression in PBC. On the other hand, the COBALT trial was confounded by unblinding and cross-over, especially in the placebo arm, which may have had an effect on the results. Using real-world evidence has been suggested as a potential solution.[30] The observational HEROES PBC study (NCT05292872, Study 747-405) found that OCA significantly improved clinical outcomes[31]; however, the FDA advisory panel considered the analysis methodologically flawed.[32]

6.17 The ESC, noting that the submission claimed that elafibranor was non-inferior compared to OCA in terms of effectiveness, considered that the lack of proposed minimum clinically important differences (MCIDs) and defined non-inferiority margins was inappropriate.

6.18 The submission also did not define what would be a clinically meaningful change in the surrogate endpoints or patient-relevant outcomes; however, according to the published literature:

- Vernon et al (2021) used anchor-based methods to confirm what would be a clinically meaningful change in the WI-NRS using phase III trial patients. A change of ≥ 3 points in the WI-NRS was considered clinically meaningful.[33]
- Kraft et al (2023) pooled data from phase III clinical trials and estimated that a change of ≥ 5 points in the 5-D Itch Scale was considered clinically meaningful.[34]

6.19 The clinical significance of changes in the exploratory outcome of PBC-40 Itch domain was unknown.

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[27] Calculated during the evaluation.

[28] National Institute of Health (2024) Phase 4 Study of Obeticholic Acid Evaluating Clinical Outcomes in Patients with Primary Biliary Cholangitis (COBALT). Available: https://clinicaltrials.gov/study/NCT02308111

[29] Kowdley et al. (2024) COBALT: A Confirmatory Trial of Obeticholic Acid in Primary Biliary Cholangitis with Placebo and External Controls. *Am J Gastroenterol.* 2024 Aug 14.

[30] Jones et al. (2024) Primary biliary cholangitis drug evaluation and regulatory approval: Where do we go from here?. Hepatology 80(5):p 1291-1300.

[31] Brookhart et al. (2024) Hepatic real-world outcomes with obeticholic acid in primary biliary cholangitis (HEROES): A trial emulation study design. Hepatology.

[32] FDA (2024) Food and Drug Administration, Center for Drug Evaluation and Research, Final Summary Minutes of the Gastrointestinal Drugs Advisory Committee Meeting, September 13 2024

[33] Vernon et al. (2021) Psychometric validation and meaningful change thresholds of the Worst Itching Intensity Numerical Rating Scale for assessing itch in patients with chronic kidney disease-associated pruritus. *J Patient Rep Outcomes.* 5: 134.

[34] Kraft et al (2023) Clinically meaningful improvement in quality of life accompanies itch relief in patients with chronic kidney disease associated pruritus. *Nephrology Dialysis Transplantation*, Volume 38, Issue Supplement_1

Comparative effectiveness

6.20 Table 4 presents the primary endpoint (cholestasis response) and key secondary endpoint (ALP normalisation) at 52 weeks in the ELATIVE trial (ITT analysis set).

Table 4: Results of primary endpoint (cholestasis response) and key secondary endpoint (ALP normalisation) at 52 weeks in the ELATIVE and POISE trials (ITT)

	Elafibranor n/N (%)	Placebo n/N (%)	Unadjusted RR (95% CI)	Unadjusted RD (95% CI)	OR (95% CI)	Cochran-Mantel-Haenszel test p-value
Cholestasis response [a]	55/108 (50.9)	2/53 (3.8)	13.5 (3.4, 53.2)	47.2% (36.4, 57.9)	**37.6 (7.6, 302.2)**	**<0.0001**
ALP normalisation [b]	16/108 (14.8)	0	-	14.8% (8.1, 21.5)	∞ **(2.8, ∞)**	**0.002**

Source: Figure 2-7 and Figure 2-8, p87-88 of the submission.
Bold indicates statistical significance.
ALP= alkaline phosphatase; CI= confidence interval; ITT= Intent-to-treat; OR = odds ratio; RD = risk difference; RR= relative risk; ULN=upper limit of normal.
[a] ALP < 1.67x ULN, total bilirubin ≤ ULN, and ALP decrease of ≥ 15% from baseline.
[b] ALP ≤ ULN

6.21 In the ELATIVE trial, the proportion of patients with cholestasis response was significantly higher in the elafibranor arm (50.9%) than the placebo arm (3.8%) at Week 52 (odds ratio (OR) = 37.6; 95% CI: 7.6, 302.2).

6.22 In the ELATIVE trial, the proportion of patients achieving ALP normalisation was significantly higher in the elafibranor arm (14.8%) than the placebo arm (0%) at Week 52 (p<0.002); however, the ESC noted that the overall incidence ALP normalisation in the elafibranor arm was low (14.8%).

6.23 It was uncertain whether cholestasis response and ALP normalisation would translate to benefits in patient-relevant or clinically relevant outcomes.

6.24 Table 5 presents the key secondary (change in PBC WI-NRS score at 24 and 52 weeks), other secondary (change in 5-D Itch Scale score at 52 weeks) and exploratory endpoints (PBC-40 itch domain at 52 weeks) from the ELATIVE trial (Pruritus ITT analysis set and ITT analysis set).

Table 5: Key secondary, other secondary and exploratory endpoints of change in pruritus in the ELATIVE trial

Trial ID	Elafibranor			Placebo			LS Mean difference (95% CI)	P-value
	Mean baseline (SD)	Mean end point (SD)	LS mean change (95% CI)	Mean baseline (SD)	Mean end point (SD)	LS mean change (95% CI)		
Key secondary endpoints								
Change in PBC WI-NRS score[a] from baseline to week 24 (Pruritus ITT analysis set) [b]	6.2 (1.5)	NR	-1.6 (-2.2, -1.0)	6.3 (1.2)	NR	-1.3 (-2.2, -0.3)	-0.3 (-1.5, 0.8)	0.552[c]
N analysed	44	37	37	22	16	16	-	-
Change in PBC WI-NRS score from baseline to week 52 (Pruritus ITT analysis set) [b]	6.2 (1.5)	NR	-1.9 (-2.6, -1.3)	6.3 (1.2)	NR	-1.1 (-2.1, -0.2)	-0.8 (-2.0. 0.4)	0.197[c]
N analysed	44	32	32	22	12	12	-	-
Other secondary endpoints								
Change in 5-D Itch Scale score[d] from baseline to week 52 (Pruritus ITT analysis set)	15.7 (4.2)	11.2 (4.6)	-4.2 (-5.6, -2.9)	15.2 (3.6)	14.5 (6.1)	-1.2 (-3.3, 0.9)	-3.0 (-5.5, -0.5)	Nominal p-value: 0.0199[c]
N analysed	43	42	42	21	17	16	-	-
Change in 5-D Itch Scale score[d] from baseline to week 52 or month 12 (ITT)	11.8 (4.6)	9.9 (3.8)	-1.9 (-2.6, -1.3)	11.9 (4.4)	11.3 (5.0)	-0.6 (-1.6, 0.3)	-1.3 (-2.4, -0.2)	Nominal p-value: 0.0238[c]
N analysed	107	95	95	52	47	46	-	-
Exploratory endpoints								
Change in PBC-40 Itch Domain score[e] from baseline to week 52 (Pruritus ITT analysis set)	8.5 (3.3)	6.0 (3.7)	-2.5 (-3.4, -1.6)	8.1 (3.7)	8.4 (4.5)	-0.1 (-1.6, 1.3)	-2.3 (-4.0, -0.7).	**0.0070**
N analysed	43	42	42	21	19	16	-	-
Change in PBC-40 Itch Domain score[e] from baseline to week 52 or month 12 (ITT)	5.8 (3.6)	4.3 (3.4)	-1.4 (-1.8, -0.9)	5.3 (3.7)	5.2 (4.2)	-0.2 (-0.9, 0.5)	-1.2 (-2.0, -0.3).	**0.0065**
N analysed	107	95	NR	52	49	NR	-	-

Source: Figure 2-9, pp88-89, Figure 2-12 and Figure 2-13, pp93-94, Table 2-26 and Table 2-27 pp116-117 of the submission, Table 15, p85, Table 21, p101, p104, of ELATIVE CSR (gft505b3191 csr body-final.pdf), Table 12.2.6.25.1, p724, Table 14.2.6.28.1, p760, Table 14.2.6.28.2, p808, Table 14.2.6.38.1, p1074 and Table 14.2.6.38.2, p1231 of ELATIVE CSR appendices (gft505b-319-1-14-tfg.pdf).

CI= Confidence interval; ELA= Elafibranor; ITT= Intent-to-treat; LS= Least squares; NR= Not reported; OCA= Obeticholic acid; PBC= Primary biliary cholangitis; SD= Standard deviation; UDCA= Ursodeoxycholic acid; WI-NRS= Worst itch numeric rating scale.

Bold indicates statistical significance

[a] The PBC WI-NRS asks patients to rate their worst itch over the past 24 hours on a scale ranging from zero (no itch) to 10 (worst itch imaginable).

[b] Treatment effect through Week 52 is the average of WI-NRS changes from baseline for the six 4-week periods, treatment effect through Week 24 is the average of WI-NRS changes from baseline for the 13 4-week periods.

[c] Mixed Model for repeated measures.

[d] The 5-D Itch Scale comprises of five domains, each accounting for five points: duration, degree, direction, disability and distribution. Scores can range from five (no pruritus) to 25 (most severe pruritus).

[e] The PBC-40 comprises of 40 questions that evaluate patients' experience across 6 domains: fatigue, emotional impact, social impact, cognitive function, general symptoms and itch. Each question is scored from 1 to 5 (5-point Likert Scale), then summed to give a total domain score. High scores represent high impact, and low scores low impact of PBC on quality of life.

6.25 A key secondary endpoint of the ELATIVE trial was the change from baseline to Week 24 and Week 52 in the PBC WI-NRS score only in patients with baseline PBC WI-NRS score ≥4 (Pruritus ITT analysis set). The change in the WI-NRS score from baseline through Week 52 demonstrated a trend towards greater reduction in pruritus with elafibranor compared with placebo but it did not differ significantly (-1.9 vs -1.1; LSM difference = -0.8; 95% CI: -2.0, 0.4; p=0.1970). The difference in WI-NRS was not

statistically significant and did not meet the threshold of being clinically significant (≥ 3 points).[35] Furthermore, the treatment effect may be overestimated as patients with missing data may have had a worse PBC WI-NRS score as they discontinued or took rescue therapy due to severe pruritus and thus were not missing at random. Finally, these results were not generalisable to the whole PBC population due to the exclusion of patients with PBC WI-NRS score <4.

6.26 The ELATIVE trial also reported the change from baseline in the 5-D Itch Scale score as a secondary endpoint and PBC-40 Itch Domain score as an exploratory endpoint (Pruritus ITT analysis set and ITT analysis set):

- The change in the 5-D Itch Scale score from baseline through Week 52 demonstrated a statistically significant reduction in pruritus with elafibranor compared with placebo (-4.2 vs -1.2; LSM difference = -3.0; 95% CI: -5.5, -0.5; p=0.0199). This improvement was also supported by similar results in the ITT analysis set. The difference was smaller in the ITT analysis set and neither met the threshold of being clinically significant (≥ 5 points).[36]
- The change in the PBC-40 Itch Domain score from baseline through Week 52 demonstrated a statistically significant reduction in pruritus with elafibranor compared with placebo (-2.5 vs -0.1; LSM difference = -2.3; 95% CI: -4.0, -0.7; p=0.0070). This improvement was also supported by similar results in the ITT analysis set. This was an exploratory analysis, the difference was smaller in the ITT analysis set, and it was unclear whether the difference was clinically significant as there was no MCID stated.

Quality of life

6.27 The submission did not present the overall PBC-40 and EQ-5D-5L visual analogue scale (VAS) results collected during the ELATIVE trial. These were extracted from the CSR and presented in Table 6.

[35] Vernon et al. (2021) Psychometric validation and meaningful change thresholds of the Worst Itching Intensity Numerical Rating Scale for assessing itch in patients with chronic kidney disease-associated pruritus. *J Patient Rep Outcomes.* 5: 134.

[36] Kraft et al (2023) Clinically meaningful improvement in quality of life accompanies itch relief in patients with chronic kidney disease associated pruritus. *Nephrology Dialysis Transplantation,* Volume 38, Issue Supplement_1

Table 6: Results of quality-of-life outcomes across the trials

	ELA			Placebo			LS Mean difference (95% CI)	P-value
	Baseline, mean (SD)	End point, mean (SD)	LS mean change (95% CI)	Baseline, mean (SD)	End point, mean (SD)	LS mean change (95% CI)		
EQ-5D-5L VAS (ITT)								
ELATIVE	68.1 (19.5)	71.2 (16.9)	2.5 (0.0, 4.9)	71.8 (18.9)	73.8 (16.3)	1.6 (-1.9, 5.0)	0.9 (-3.3, 5.1)	0.6720
N analysed	106	95	94	52	47	46	-	-
PBC-40								
ELATIVE	15.4 (5.7)	15.5 (5.1)	0.1 (3.5)[a]	15.6 (5.2)	14.4 (5.4)	-1.0 (3.7)[a]	NR	NR
N analysed	107	95	95	52	49	48	-	-

Source: Compiled during the evaluation based on Table 24, p104 of ELATIVE CSR (gft505b3191 csr body-final.pdf) and Table 14.2.6.38.1 of ELATIVE CSR appendices (gft505b-319-1-14-tfg.pdf).
CI = confidence interval; ELA = elafibranor; EQ-5D-5L VAS= EuroQol 5-Dimension, 5-Level Visual Analog Scale; ITT= Intent to treat; LS = Least squares; SD = standard deviation.
[a] Means, not LS means.

6.28 Elafibranor did not demonstrate any significant abatement in symptoms as measured by the PBC-40 questionnaire or the EQ-5D-5L VAS.

Indirect comparisons of the efficacy endpoints

6.29 The submission conducted pairwise indirect comparisons of elafibranor compared to OCA with placebo as the common comparator for the following efficacy endpoints analysed using the ITT population:

- Cholestasis response, defined by ALP ≤1.67 x ULN, ALP decreased by ≥ 15%, and TB ≤ULN at 52 weeks (binary endpoint).
- Change from baseline in ALP levels (U/L) at 52 weeks (continuous endpoint).
- ALP normalisation, defined by ALP ≤1.0 x ULN at 52 weeks (binary endpoint).

6.30 The Bucher method was used. The submission conducted the indirect comparisons using odd ratios for dichotomous variables, and mean differences for continuous variables. The submission should have conducted the indirect comparisons using least squares means for continuous variables, which would have controlled for other covariates that may have affected the outcomes.

6.31 Table 7 and Table 8 presents the results of the indirect comparisons.

Table 7: Summary of results of the indirect comparisons regarding cholestasis response and ALP normalisation (ITT)

Comparison	Trial ID	Treatment, n with event/N (%)	Placebo, n with event/N (%)	Treatment effect, OR (95%CI)
Cholestasis response at 52 weeks/12 months [a]				
ELA vs placebo	ELATIVE	55/108 (50.93)	2/53 (3.77)	**37.6 (7.6, 302.2)**
OCA 5-10mg vs placebo	POISE	32.20/70 (46)[b] 32/70 (46)[c]	7.30/73 (10)[b] 7/73 (10)[c]	**9.1 (3.6, 23.2)**
OCA 10mg vs placebo	POISE	34.31/73 (47)[b] 34/73 (47)[c]	7.30/73 (10)[b] 7/73 (10)[c]	**9.4 (3.7, 23.9)**
Indirect estimate of effect adjusted for the common reference				
ELA vs OCA 5-10mg	–	–	–	3.45 (0.62, 19.19) 4.13 (0.52, 32.54)[d]
ELA vs OCA 10mg	–	–	–	3.32 (0.6, 18.39) 4.00 (0.51, 31.52)[d]
ALP normalisation at 52 weeks/12 months [e]				
ELA vs placebo	ELATIVE	16/108 (14.8)	0	**∞ (2.8, ∞)**
OCA 5-10mg vs placebo	POISE	1/70 (1.4)	0	NR
OCA 10mg vs placebo	POISE	5/73 (6.8)	0	NR
Indirect estimate of effect adjusted for the common reference				
ELA vs OCA 5-10mg	–	–	–	8.71 (0.10, 734.86)
ELA vs OCA 10mg	–	–	–	1.72 (0.03, 100.96)

Source: Table 2-23, Figure 2-23, Table 2-25 and Figure 2-25 p113, p115, and p87-88 of the submission, Table 5 in Obeticholic Acid, PSD, July 2019 PBAC meeting, Figure S4, Supplementary Appendix of Nevens et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. N Engl J Med 2016;375:631-43.

ALP= alkaline phosphatase; ELA = elafibranor; ITT = intent-to-treat; NR = not reported; OCA= obeticholic acid; OR= odds ratio; TB= total bilirubin; ULN= upper limit of normal.

Bold indicates statistically significant results.

[a] ALP ≤1.67xULN, TB ≤ULN, and ALP reduction ≥15%.

[b] The submission estimated the number of patients experiencing the outcomes from the POISE trial from the rate of occurrence reported by Nevens et al. 2016.

[c] Table 5 in Obeticholic acid, PSD, July 2019 PBAC meeting.

[d] Estimated using reported ORs during the evaluation.

[e] ALP ≤ ULN

Table 8: Results of the indirect comparison for mean change in ALP (U/L) from baseline at 12 months (ITT)

Trial	Change from baseline in ALP (U/L) LSM (SE)			LSM (95% CI)
	ELA	Placebo	OCA	
ELATIVE, mean (SE)	N=94 -117.7 (10.0)	N=47 -8.8 (13.3)	-	**-111.7 (-142.0, -81.3)**
ELATIVE, LSM (SE)	-117.0 (NR)	-5.3 (NR)	-	
POISE (OCA 5-10mg), mean (SE)	-	N=70 -7.7 (10.5)	N=64 -103.5 (10.9)	**-98.1 (SE=13.1)**
POISE (OCA 5-10mg), LSM (SE)	-	N=70 -14.4 (14.7)	N=64 -112.5 (14.4)	
POISE (OCA 10mg), mean (SE)	-	N=70 -7.7 (10.5)	N=62 -117.7 (9.3)	**-115.5 (SE=13.2)**
POISE (OCA 10mg), LSM (SE)	-	N=70 -14.4 (14.7)	N=62 -129.9 (14.6)	
Indirect comparison, ELA vs OCA 5-10 mg (95% CI)				MD = -13.10 (-57.14, 30.94)
Indirect comparison, ELA vs OCA 10 mg (95% CI)				MD = 1.10 (-41.54, 43.74)

Source: Table 2-15, p92, Table 2-24 and Figure 2-24, p114 and p89, Table 2-17, p99 of the submission.
ALP= alkaline phosphatase; CI = confidence interval; ELA = elafibranor; ITT = intent-to-treat; LSM = least square mean; OCA= obeticholic acid; SE = standard error; MD = mean difference; U/L= units per litre.
Bold indicates statistically significant results; *italics* indicates added during the evaluation.

6.32 Elafibranor resulted in numerically more patients experiencing cholestasis response compared to OCA 5-10 mg (OR = 3.45; 95% CI: 0.62, 19.19) and OCA 10 mg (OR = 3.32; 95% CI: 0.6, 18.39), and numerically more patients experiencing ALP normalisation compared to OCA 5-10 mg (OR = 8.71; 95% CI: 0.10, 734.86) and OCA 10 mg (OR = 1.72; 95% CI: 0.03, 100.96). Elafibranor also resulted in a numerically greater reduction in ALP compared with OCA 5-10 mg (mean difference = -13.10; 95% CI: -57.14, 30.94) and a smaller decrease compared with OCA 10 mg (mean difference = 1.10; 95% CI: -41.54, 43.74). However, none of the differences were statistically significant.

6.33 These results were uncertain as the submission did not propose any MCIDs nor define non-inferiority margins, the sample sizes in the ELATIVE trial (N=161) and the POISE trial (N=217) were small, which reduced the statistical power to detect differences across the treatment arms and there were differences across the ELATIVE and POISE trials that affected the assumption of transitivity (see paragraph 6.14).

Comparative harms

6.34 Table 9 presents the key safety outcomes reported in the ELATIVE trial.

Table 9: Summary of key adverse events reported in the ELATIVE trial (Safety analysis set)

	ELA 80mg n with event/N (%)	Placebo n with event/N (%)	EAIR difference estimate (95% CI)
TEAEs	104/108 (96.3)	48/53 (90.6)	0.957 (-0.853; 2.766)
TEAEs related to study medication	42/108 (38.9)	21/53 (39.6)	-0.020 (-0.282; 0.242)
AESIs[a]	32/108 (29.6)	14/53 (26.4)	0.016 (-0.141; 0.173)
Serious TEAEs	11/108 (10.2)	7/53 (13.2)	-0.031 (-0.130; 0.068)
Serious TEAEs related to study medication	3/108 (2.8)	1/53 (1.9)	0.006 (-0.033; 0.046)
TEAEs leading to treatment discontinuation	11/108 (10.2)	5/53 (9.4)	0.002 (-0.084; 0.088)
Serious TEAEs related to study medication leading to treatment discontinuation	2/108 (1.9)	1/53 (1.9)	-0.001 (-0.038; 0.036)
Severe AEs	12/108 (11.1)	6/53 (11.3)	-
Fatal AE	2/108 (1.9)	0	-

Source: Table 2-18, p102 of the submission; Table 2-19, p103 of the submission, and Table 33, p128 of ELATIVE CSR (gft505b3191 csr body-final.pdf).

AE=adverse event; AESI= adverse event of special interest; CI= Confidence interval; EAIR= exposure-adjusted incidence rates (patients per patient-years); ELA = Elafibranor N = total patients in the treatment arm; RR = relative risk; TEAE= treatment emergent adverse event.

[a] The most frequently reported AESI in both treatment arms was weight gain of >5% from baseline, which was reported for 25 (23.1%) patients in the elafibranor arm and 11 (20.8%) patients in the placebo arm.

6.35 Treatment-related treatment-emergent adverse events (TEAEs) were reported for 38.9% of patients in the elafibranor arm and 39.6% of patients in the placebo arm. Serious TEAEs were reported for 10.2% of patients in the elafibranor arm and 13.2% of patients in the placebo arm. The serious TEAEs for 2.8% of patients in the elafibranor arm and 1.9% of patients in the placebo arm were considered to be related to study treatment. Two patients experienced serious TEAEs that led to death; both patients were in the elafibranor arm and were considered unrelated to study treatment.

6.36 The TEAEs were mostly gastrointestinal in nature, including vomiting (11.1% versus 1.9%; exposure-adjusted incidence rate (EAIR) difference = 0.077; 95% CI: 0.015, 0.139), diarrhoea (11.1% versus 9.4%), nausea (11.1% versus 5.7%), constipation (8.3% versus 1.9%), abdominal pain upper (7.4% versus 5.7%), and gastroesophageal reflux disease (6.5% versus 1.9%).

Indirect comparisons of the pruritus and safety endpoints

6.37 The submission conducted pairwise indirect comparisons of elafibranor compared to OCA with placebo as the common comparator for the following safety endpoints:

- Change from baseline in pruritus according to the 5-D Itch Scale score questionnaire at 52 weeks (continuous endpoint).
- Change from baseline in pruritus according to the 5-D Itch Scale score questionnaire using the earliest reported data after commencement of treatment (week 2 and week 4 data for the POISE and ELATIVE trials, respectively; continuous endpoint).
- Change from baseline in pruritus according to the PBC-40 Itch domain score using the earliest reported data after commencement of treatment (week 2 and week 4 data for the POISE and ELATIVE trials, respectively; continuous endpoint).

- Change from baseline in pruritus according to the PBC-40 Itch domain score at 52 weeks (continuous endpoint).
- Occurrence of pruritus of any severity as a TEAE within 52 weeks (binary outcome).
- Discontinuation due to pruritus within 52 weeks (binary outcome).
- Change from baseline in high-density lipoprotein (HDL) cholesterol at 52 weeks (continuous endpoint).

6.38 The submission did not conduct an indirect comparison of the change in PBC WI-NRS score from baseline through Week 24 and Week 52 in patients with baseline PBC WI-NRS score ≥ 4 as this endpoint was not reported by the POISE trial. This was a key secondary outcome of the ELATIVE trial.

6.39 The submission also did not conduct an indirect comparison of vomiting, which was higher with elafibranor versus placebo in the ELATIVE trial. The POISE trial did not publicly report the incidence of vomiting.

6.40 The indirect comparisons were conducted on both the ITT analysis set and the Pruritus ITT analysis set.

6.41 Table 10 and Table 11 present the results of the indirect comparisons for the safety endpoints.

Table 10: Results of the indirect comparison for mean change in pruritus from baseline at 52 weeks/12 months

Trial	Treatment			LSM (95% CI)
	ELA	Placebo	OCA	
Change from baseline at 52 weeks/12 months in pruritus (5-D Itch Scale) (ITT)				
ELATIVE, mean (SE)	N=95 -2.1 (0.41)	N=48 -0.9 (0.43)	-	-1.3 (-2.4, -0.2)
ELATIVE, LSM (SE)	N=95 -1.9 (0.33)	N=46 -0.6 (0.48)	-	
POISE (OCA 5-10mg), mean (SE)[a]	-	N=73 0.5 (0.75)	N=70 1.7 (0.74)	NR
POISE (OCA 5-10mg), LSM (SE)[a]	-	N=73 0.5 (0.75)	N=70 1.7 (0.74)	NR
POISE (OCA 10mg), mean (SE)[a]	-	N=73 0.5 (0.75)	N=73 1.4 (0.74)	NR
POISE (OCA 10mg), LSM (SE)[a]	-	N=73 0.5 (0.75)	N=73 1.4 (0.74)	NR
Indirect comparison, ELA vs OCA 5-10mg (95% CI)				MD = -2.37 (-4.75, 0.01)
Indirect comparison, ELA vs OCA 10mg (95% CI)				MD = -2.06 (-4.43, 0.31)
Indirect comparison, ELA vs OCA 5-10mg (95% CI), LSM				**MD = -2.47 (-4.84, -0.10)** [b]
Indirect comparison, ELA vs OCA 10mg (95% CI), LSM				MD = -2.16 (-4.52, 0.20) [b]
Change from baseline in pruritus (PBC-40 Itch domain) LSM (SE) (ITT)				
ELATIVE, mean (SE)	N=95 -1.6 (0.28)	N=48 -0.2 (0.32)	-	-1.2 (-2.0, -0.3)
ELATIVE, LSM (SE)	N=95 -1.4 (0.23)	N=46 -0.2 (0.36)	-	
POISE (OCA 5-10mg), mean (SE)[a]	-	N=73 0.8 (0.47)	N=70 1.3 (0.44)	NR
POISE (OCA 5-10mg), LSM (SE)[a]		N=73 0.8 (0.47)	N=70 1.3 (0.44)	NR
POISE (OCA 10mg), mean (SE)[a]	-	N=73 0.8 (0.47)	N=73 1.5 (0.47)	NR
POISE (OCA 10mg), LSM (SE)[a]		N=73 0.8 (0.47)	N=73 1.5 (0.47)	NR
Indirect comparison, ELA vs OCA 5-10mg (95% CI), mean				**MD = -1.87 (-3.38, -0.36)**
Indirect comparison, ELA vs OCA 10mg (95% CI), mean				**MD = -2.03 (-3.57, -0.49)**
Indirect comparison, ELA vs OCA 5-10mg (95% CI), LSM				**MD = -1.67 (-3.18, -0.16)** [a]
Indirect comparison, ELA vs OCA 10mg (95% CI), LSM				**MD = -1.83 (-3.37, -0.29)** [a]

Source: Table 2-26 to 2-27, Figure 2-26 to 2-27 pp116-17 of the submission, Table 5, Table 8, Figure 8 and Figure 11, p20-24 of 'Ipsen FIECON Elafibranor Bucher technical report_v2.0_FINAL_17Apr2024', and Table 12.2.6.25.1, p724, Table 14.2.6.28.1, p760 of ELATIVE CSR appendices (gft505b-319-1-14-tfg.pdf).

CI = confidence interval; ELA = elafibranor; LSM = least square mean; OCA= obeticholic acid; SE = standard error; MD = mean difference; **Bold** indicates statistical significance. Italicised text indicates information added during the evaluation.

[a] Based on Figure S8, Supplementary Appendix of Nevens et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. N Engl J Med 2016;375:631-43. *Unable to be verified.*

[b] Presented in Table 8, Figure 8 and Figure 11, p20-24 of 'Ipsen FIECON Elafibranor Bucher technical report_v2.0_FINAL_17Apr2024'.

Table 11: Summary of results of the indirect comparison for occurrence of pruritus TEAE and discontinuation due to pruritus within 52 weeks/12 months

Trial type or estimate	Trial ID	Treatment, n with event/N (%)	Placebo, n with event/N (%)	Treatment effect (OR)
Occurrence of pruritus TEAE of any severity within 12 months				
ELA vs placebo	ELATIVE	22/108 (20.4)	14/53 (26.4)	NR
OCA 5-10mg vs placebo	POISE	39/70 (55.7)	28/73 (38.4)	NR
OCA 10mg vs placebo	POISE	50/73 (68.5)	28/73 (38.4)	NR
Indirect estimate of effect adjusted for the common reference				
ELA vs OCA 5-10mg	–	–	–	**0.35 (0.13, 0.98)**
ELA vs OCA 10mg	–	–	–	**0.20 (0.07, 0.57)**
Discontinuations due to pruritus within 12 months				
ELA vs placebo	ELATIVE	1/108 (0.9)	1/53 (1.9)	NR
OCA 5-10mg vs placebo	POISE	1/70 (1.4)	0	NR
OCA 10mg vs placebo	POISE	7/73 (9.6)	0	NR
Indirect estimate of effect adjusted for the common reference				
ELA vs OCA 5-10mg	–	–	–	0.23 (0.00, 18.85)
ELA vs OCA 10mg	–	–	–	0.03 (0.00, 1.74)

Source: Table 2-28 to 2-29, Figure 2-28 to 2-29, pp118-9 of the submission.
ELA = elafibranor; OCA= obeticholic acid; N= total patients in the treatment arm; OR= odds ratio; TEAE= treatment emergent adverse events; **Bold** indicates statistically significant results.

6.42 Elafibranor resulted in a greater reduction in the 5-D Itch Scale and the PBC Itch Domain Score compared with OCA 5-10 mg and OCA 10 mg. Elafibranor also resulted in fewer patients experiencing pruritus TEAEs compared to OCA 5-10 mg and OCA 10 mg and discontinuations due to pruritus compared to OCA 5-10 mg and OCA 10 mg. The submission claimed that statistically significant differences were observed between elafibranor and OCA for mean change in pruritus (PBC-40 Itch Domain) from baseline at 12 months and occurrence of pruritus TEAE of any severity within 12 months. The submission noted that statistically significant differences between elafibranor and OCA could not be concluded for the analyses of mean change in pruritus (5-D Itch Scale) at 12 months and odds of discontinuation due to pruritus.

6.43 These results were uncertain as there were differences across the ELATIVE and POISE trials that affected the assumption of transitivity; in particular, the POISE trial excluded patients with severe pruritus (see paragraph 6.14) and the occurrence of pruritus TEAEs in the placebo arm were lower in the ELATIVE trial. Furthermore, the analysis of the PBC-40 Itch Domain score was an exploratory analysis. It was also unclear whether the difference in the PBC-40 Itch Domain was clinically significant.

6.44 Table 12 presents the results of the indirect comparison for mean change in high density lipoprotein (HDL) cholesterol (mg/dL).

Table 12: Results of the indirect comparison for mean change in HDL cholesterol (mg/dL) from baseline at 12 months (ITT)

Trial	Change from baseline in HDL cholesterol LSM (SE)			LSM (95% CI)
	ELA	Placebo	OCA	
ELATIVE	N=95 0.4 (1.4)	N=47 -2.2 (2.3)	-	1.55 (-0.36, 6.6504)
POISE (OCA 5-10mg)	-	N=73 -2.7 (2.3)	N=70 -13.3 (3.2)	NR
POISE (OCA 10mg)	-	N=73 -2.7 (2.3)	N=73 -9.2 (2.7)	NR
Indirect comparison, ELA vs OCA 5-10mg (95% CI)				**MD = 13.16 (3.86, 22.45)**
Indirect comparison, ELA vs OCA 10mg (95% CI)				**MD = 9.07 (0.42, 17.72)**

Source: Table 2-27 and Figure 2-27, p117 of the submission and p631, Table 14.2.6.18 of ELATIVE CSR appendices (gft505b-319-1-14-tfg.pdf). Estimates for the POISE study were unable to be verified.
CI = confidence interval; ELA = elafibranor; HDL= high density lipoprotein; LSM = least square mean; MD = mean difference; NR=Not reported; OCA= obeticholic acid; SE = standard error; **Bold** indicates statistically significant results

6.45 Elafibranor resulted in a greater increase in HDL cholesterol compared with OCA 5-10 mg (0.34 mmol/L) and OCA 10 mg (0.23 mmol/L). The submission also claimed that statistically significant differences were observed between elafibranor and OCA for mean change from baseline in HDL cholesterol at 12 months.

6.46 The economic model applied the results of an indirect comparison of all-cause discontinuations. This comparison was not presented by the submission.

Benefits/harms

6.47 A summary of the pruritus safety outcomes for elafibranor versus OCA is presented in Table 13. The ESC noted that pruritus is a symptom of PBC. The benefits portion of the table was not presented as the submission made a claim of non-inferior efficacy.

Table 13: Summary of comparative benefits and harms for elafibranor and OCA

Harms								
Occurrence of pruritus TEAE of any severity within 12 months								
	ELA, n/N	**PBO, n/N**	**OCA 5-10 mg, n/N**	**OR (95% CI)**	**Event rate/100 patients[a]**			**RD (95% CI)**
					ELA	**PBO**	**OCA 5-10 mg**	
ELATIVE	22/108	14/53	-	NR	20.4	26.4	-	-6.0
POISE	-	28/73	39/70	NR	-	38.4	55.7	17.3
Indirect comparison: ELATIVE vs POISE				0.35 (0.13, 0.98)	-			-23.3
Occurrence of pruritus TEAE of any severity within 12 months								
	ELA, n/N	**PBO, n/N**	**OCA 10 mg, n/N**	**OR (95% CI)**	**Event rate/100 patients[a]**			**RD (95% CI)**
					ELA n/N	**PBO n/N**	**OCA 10 mg n/N**	
ELATIVE	22/108	14/53	-	NR	20.4	26.4	-	-6.0
POISE	-	28/73	50/73	NR	-	38.4	68.5	30.1
Indirect comparison: ELATIVE vs POISE				0.20 (0.07, 0.57)	-			-36.1
Change from baseline at 52 weeks/12 months in pruritus (PBC Itch Domain)								
	Active treatment group			**PBO**			**Indirect comparison: MD[a] ELA vs OCA 5-10 mg (95% CI)**	
	N	**Mean Δ**	**SE**	**N**	**Mean Δ**	**SE**	**-**	
ELATIVE	95	-1.6	0.28	48	-0.2	0.32	-1.87 (-3.38, -0.36)	
POISE	70	1.3	0.44	73	0.8	0.47		
Change from baseline at 52 weeks/12 months in pruritus (PBC Itch Domain)								
	Active treatment group			**PBO**			**Indirect comparison: MD[a] ELA vs OCA 10 mg (95% CI)**	
	N	**Mean Δ**	**SE**	**N**	**Mean Δ**	**SE**	**-**	
ELATIVE	95	-1.6	0.28	48	-0.2	0.32	-2.03 (-3.57, -0.49)	
POISE	73	1.5	0.47	73	0.8	0.47		

Source: Table 2-27 - 2-28 and Figure 2-27 - 2-28, pp117-8 of the submission.
ELA = elafibranor; MD = Mean difference; OCA = obeticholic acid; PBO = placebo; RD = risk difference; OR = odds ratio; SE=Standard error
a Duration of follow-up: ELATIVE = 52 weeks; POISE = 12 months.

6.48 The ESC noted that, although there were some differences in terms of pruritus events between elafibranor and OCA, the clinical significance of these differences and their relevance to the management of PBC was unclear, particularly as pruritus is a symptom of PBC.

Clinical claim

6.49 The submission described elafibranor as non-inferior in terms of effectiveness compared to OCA. This claim was based on an indirect comparison of surrogate endpoints (cholestasis response, ALP normalisation, and change in ALP). The ESC considered that the clinical claim of non-inferior effectiveness was appropriate, noting that:

- the submission did not propose any MCIDs nor define non-inferiority margins.

- the sample sizes in the ELATIVE trial (N=161) and the POISE trial (N=217) were small, which reduced the statistical power to detect differences between the treatments.
- there were differences across the ELATIVE and POISE trials that affected the assumption of transitivity (see paragraph 6.14).

6.50 It was also unclear whether cholestasis response or ALP were adequate surrogates for disease progression (see paragraph 6.16).

6.51 The submission described elafibranor as superior in terms of safety compared to OCA. This claim was based on indirect comparisons of pruritus endpoints (PBC-40 Itch Domain, pruritus TEAE) and HDL. The ESC considered that the clinical claim regarding superior safety was not adequately supported by the data presented in the submission. Noting the uncertainties below, the ESC considered that elafibranor was non-inferior compared to OCA:

- The indirect comparisons did not find significant differences between elafibranor and OCA for other pruritus endpoints (e.g. 5-D Itch Scale, discontinuations due to pruritus). Furthermore, the analysis of the PBC-40 Itch Domain score was an exploratory analysis. The pre-PBAC response stated that the pruritus endpoints had limited statistical power given they were secondary outcomes.
- It was unclear whether the difference in the PBC-40 Itch Domain was clinically significant. The pre-PBAC response stated that the PBC-40 Itch Domain is disease specific and the only validated instrument for PBC which include an itch domain.
- There were differences across the ELATIVE and POISE trials that affected the assumption of transitivity. In particular, the POISE trial excluded patients with severe pruritus (see paragraph 6.14) and the occurrence of pruritus TEAEs in the respective placebo arms were lower in the ELATIVE trial than the POISE trial.
- The ELATIVE trial had a moderate risk of bias for the secondary endpoints regarding pruritus, especially as missing values were assumed to be missing at random. The treatment effect may be overestimated as patients with missing data may have had worse pruritus scores as they discontinued or took rescue therapy due to severe pruritus, and thus were not missing at random.
- The PBAC previously considered the unblinding due to the occurrence of pruritus introduced a moderate potential for bias in the POISE trial (paragraph 6.9, obeticholic acid, PSD, November 2018 PBAC meeting).
- The change in the WI-NRS score from baseline through Week 24 and Week 52, a key secondary outcome in the ELATIVE trial, did not differ significantly between elafibranor and placebo (-1.9 versus -1.1; LSM difference = -0.8; 95% CI: -2.0, 0.4; p=0.1970). The difference did not meet the threshold of being clinically significant

(≥ 3 points).[37] An indirect comparison was not conducted on the WI-NRS score as this endpoint was not reported by the POISE trial.

6.52 The ESC considered that it may have been reasonable to conclude that elafibranor does not exacerbate pruritus compared to OCA.

6.53 The PBAC considered that the claim of non-inferior comparative effectiveness between elafibranor and OCA was reasonable.

6.54 The PBAC considered that the claim that elafibranor was superior compared to OCA in terms of safety was not adequately supported by the data. The PBAC considered that overall, a claim of non-inferior safety was reasonable, although acknowledged that elafibranor is likely associated with less pruritus.

Economic analysis

6.55 The submission presented a modelled economic evaluation based on an indirect comparison of RCTs.

6.56 The submission did not present economic evidence for elafibranor as a monotherapy for UDCA intolerant patients or as third-line treatment in OCA non-responders separately. The PSCR provided a revised economic model with placebo +/- UDCA as an additional comparator. This was not considered as, being provided with the PSCR, it was not evaluated.

6.57 The ESC considered that a cost-minimisation approach comparing elafibranor to OCA may have been more appropriate, given the clinical claim that elafibranor was non-inferior in terms of clinical effectiveness compared to OCA. The ESC noted that a cost-minimisation approach was further supported as it considered that the superiority claim compared to OCA in terms of safety was not adequately demonstrated.

6.58 The ESC noted that the equi-effective doses may be:

> Elafibranor 80 mg once daily, based on recommended dose in the draft Product Information =
>
> Obeticholic acid 5 or 10 mg daily, based on the recommended dose in the Product Information (noting that the published prices of the 5 mg and 10 mg tablets are the same).

6.59 The ESC considered a cost-minimisation approach would be informative for the PBAC and that this should be presented in the pre-PBAC response.

6.60 The pre-PBAC response stated that the differences in safety profiles between elafibranor and OCA supported the use of a CUA analysis.

[37] Vernon et al. (2021) Psychometric validation and meaningful change thresholds of the Worst Itching Intensity Numerical Rating Scale for assessing itch in patients with chronic kidney disease-associated pruritus. *J Patient Rep Outcomes.* 5: 134.

6.61 Table 14 presents the key components of the economic evaluation.

Table 14: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Elafibranor +/- UDCA versus OCA +/- UDCA
Time horizon	Age of patients = 57 years based on ELATIVE trial. Assumed lifetime (43 years) time horizon. The time horizon in the model was long compared to the duration of follow-up in the ELATIVE trial (52 to 104 weeks). Changing the time horizon from 43 years to 30 years has a minimal effect on the ICER.
Outcomes	QALYs gained, and LYs gained.
Methods used to generate results	A Markov cohort-based state-transition model.
Health states	10 health states: Biochemical States • Mild risk of PBC disease progression: ALP ≤ 200 U/L (i.e. 1.67 x ULN) and normal bilirubin (i.e. TB ≤ 20 µmol/L) • Moderate risk of PBC disease progression: ALP > 200 U/L and normal bilirubin • High risk of PBC disease progression leading to liver failure: Abnormal bilirubin (i.e. TB > 20 µmol/L) and rising or CC. Liver Disease States • Decompensated cirrhosis (DCC) • Hepatocellular carcinoma (HCC) • Pre-liver transplant (Pre-LT) • Liver transplant (LT) • Post-liver transplant (Post-LT) • Primary biliary cholangitis (PBC) re-emergence • Dead The health states were consistent with that previously considered by the PBAC for OCA as treatment for PBC (paragraph 6.19, obeticholic acid, PSD, November 2020 PBAC meeting).
Cycle length	3 months. A half cycle correction was applied.
Transition probabilities	Movement between mild, moderate and high-risk of PBC progression biochemical health states: Transition probabilities for 0-3, 3-6 and 6-9, 9-12 months: 1. ELATIVE trial data for the ELA +/- UDCA arm. 2. Indirect comparison results for the OCA +/- UDCA arm (OCA odds of cholestasis response = 0.26). The ESC considered that application of an odds ratio of 0.26 was not consistent with the claim of non-inferior efficacy (see paragraph 6.62). Biochemical health states → Liver disease health states: Various previously accepted PBAC data inputs, published data and model calibration (paragraph 6.19, obeticholic acid, PSD, November 2020 PBAC meeting). Some of the transition probabilities were unable to be verified. Compliance and discontinuation rates: ELA +/- UDCA and OCA +/- UDCA compliance rate = 94.83% based on ELATIVE trial data drug exposure days. ELA +/- UDCA discontinuation rate = extrapolation functions fitted to discontinuation rates from the ELATIVE trial. The proportion of patients who discontinued at 12 months was 12.09%. The requested PBS restriction did not include a continuation criterion. 49% of patients did not experience cholestasis response at 12 months with ELA in the ELATIVE trial; however non-responders were not assumed to discontinue treatment at this point. The discontinuation rate was extrapolated using an exponential function.

Component	Summary
	OCA +/- UDCA OR of discontinuation = 2.73 based on all-cause discontinuation in the indirect comparison. The ESC noted that this analysis was not presented in the indirect comparison results and thus could not be verified. Further, the ESC noted that the indirect comparison of discontinuations due to pruritus was not statistically significant. See paragraph 6.63. Adverse events 1. Pruritus severity (no itch, mild itch, clinically significant itch) - ELA: Patient-level PBC-40 Itch Domain scores from the ELATIVE trial. - OCA: Mean difference of PBC-40 itch for OCA relative to ELA from the indirect comparison. The ESC noted that it was not appropriate to apply the mean difference of PBC-40 itch for OCA relative to ELA from the indirect comparison, which was not significantly different from the null. Changing the mean difference of occurrence of PBC-40 Itch Domain from 1.87 to 1 at 1 month and 12 months slightly reduced the ICER from $[redacted] to $[redacted]/QALY gained. 2. TEAEs (grade 2+ pruritus, UTI and fatigue) - ELA: ELATIVE trial. - OCA: OR of pruritus as a TEAE based on the indirect comparison. Other TEAEs assumed to be similar.
Utilities	Biomarker health states The utility values for mild (0.84), moderate (0.84) and high-risk (0.55) health states were primarily based on the NICE appraisal TA443 of OCA, which were originally sourced from Younossi (2001) and Wright (2006). Liver disease component The utility values for the liver disease health states (DCC=0,38, HCC = 0.45, pre-LT = 0.38, LT = 0.57, post LT = 0.67, re-emergence of PBC = 0.67) were based on: TA330 and KOL opinion. Some utility values were unable to be verified. Adverse events The submission applied disutilities by pruritus severity (mild = -0.01, clinically significant = -0.08) and pruritus TEAEs (-0.11). The model may have double-counted disutilities from pruritus. Disutilities by pruritus severity were based on a regression analysis of the ELATIVE trial; however, the disutility associated with mild itch was not statistically significant (P=0.630). The disutility for pruritus TEAEs was based on a clinician estimate which was uncertain. Once off disutilities for UTI (-0.06) and fatigue (-0.07) (based on the literature) for the duration of one cycle were also applied. The reference and the disutility in Abrahamian et al (2011) for a UTI disutility could not be verified.
Costs and resource use	It was assumed that 95% of patients treated with elafibranor or OCA receive concomitant UDCA based on the ELATIVE trial. The costs of mild and moderate-risk PBC health states were based on MBS items, and the cost of high-risk PBC, DCC and HCC health states were based on MBS items, AR-DRGs and the published literature. The submission applied the National Hospital Cost Data Collection cost weights for (AR-DRG) Version 11.0, 2020-21 costs. The submission inflated the costs as if they were valued in 2014 dollars instead of 2020-21 dollars which overinflated the costs. Pre- and post-liver transplant healthcare resource use were sourced from the NICE appraisal HST17 for odevixibat and Rice et al. (2021) respectively. The costs from the NICE appraisal TA443 for obeticholic acid, NICE appraisal HST17 for odevixibat for treating progressive familial intrahepatic cholestasis. Healthcare resource use associated with the re-emergence of PBC was assumed to be equal to the healthcare resource use associated with the high-risk health state. The high liver disease risk health state and the re-emergence of PBC cost was assumed to be half the amount of DCC.

Component	Summary
	End of life costs were included for patients who die in the DCC and HCC health states ($15,072), where there was expected to be palliative care, and were sourced from published literature (Gola 2015 and NICE appraisal TA666 based on UK sources). The cost of adverse events was based on MBS and PBS item numbers. Some medicines used to cost adverse events are not listed on the PBS for relevant indications.
Software package	Excel.2024, Version 2410, (Build 18129.20116).

Source: Complied during the evaluation from Table 2-10, p75; p 104; Table 3-1, p128; p137-139 of the submission.
ALP = Alkaline Phosphatase; AR-DRG = Australian related diagnostic related groups; CEA = Cost-Effectiveness Analysis; CUA = Cost-Utility Analysis; DCC = Decompensated Cirrhosis; ELA = elafibranor; HCC = Hepatocellular Carcinoma; HRQoL= health-related quality of life; ICER = Incremental Cost-Effectiveness Ratio; LT = Liver Transplantation; LYG = Life Years Gained; MBS = Medical Benefits Schedule; NICE = National Institute for Health and Care Excellence; OCA = Obeticholic Acid; OR = odds ratio; PBC = Primary Biliary Cholangitis; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PFIC = progressive familial intrahepatic cholestasis; PSD = Public Summary document; QALY = Quality-Adjusted Life Year; TB = Total Bilirubin; TEAE = treatment emergent adverse events; UDCA = Ursodeoxycholic Acid; ULN = Upper Limit of Normal
The redacted values correspond to the following ranges:
[1] $55,000 to < $75,000

6.62 The submission applied the results of the indirect comparison (cholestasis response) to estimate the transition probabilities between the mild, moderate and high-risk of PBC progression biochemical health states. In particular, the odds ratio (OR) of cholestasis response with OCA versus elafibranor applied in the model was 0.26 (i.e. favoured elafibranor). The ESC considered that this was not appropriate as:

- it was not consistent with the clinical claim that elafibranor was non-inferior in terms of effectiveness compared to OCA;
- the indirect comparisons of elafibranor compared to OCA in terms of cholestasis response were not statistically significantly different.

The ICER was sensitive to applying a OR of 1.0. The pre-PBAC response acknowledged that the application of the odds ratio of 0.26 was not consistent with a clinical claim of non-inferior effectiveness.

6.63 The model applied an OR of 2.73 for all-cause discontinuation with OCA versus elafibranor (i.e. a higher risk of discontinuation with OCA). The ESC noted that the analysis supporting this result was not presented in the submission and therefore could not be verified. Further, the ESC noted that the indirect comparison of discontinuations due to pruritus was not statistically significantly different. The ICER was sensitive to applying a OR for all-cause discontinuation of 1.0. The pre-PBAC response maintained, based on expert clinical opinion that the all-cause discontinuation rate for OCA was likely at least double that of elafibranor, that this OR of 2.7 was justified.

6.64 The submission conducted regression and descriptive analyses on the EQ-5D-3L utility values that were obtained by mapping EQ-5D-5L data from the ELATIVE trial, using the Hernandez-Alava et al. (2020) mapping algorithm. However, the submission argued that there were insufficient observations in the high-risk health state (N=78) to reliably inform utility values across all PBC biomarker health states. Consequently, the utilities

for the mild, moderate and high biomarker risk health states were based on Younossi (2001) and Wright (2006). Wright (2006) included hepatitis C patients. The ESC considered that the utility values from the ELATIVE trial should be used. The ICER was sensitive to applying utilities from the ELATIVE trial.

6.65 Table 15 summarises the key drivers of the model.

Table 15: Key drivers of the model

Description	Method/Value	Impact Base Case: [redacted][1]/QALY gained.
Applying alternative biomarker utilities from the ELATIVE trial (EQ-5D-3L)[a]	The utility values applied in the model were mild-risk=0.84; moderate-risk=0.84; and high-risk=0.55 from Younossi (2001) and Wright (2006).[38] Trial-based utilities from the ELATIVE trial were available.	High. Favours ELA. Applying utility values for the mild, moderate and high-risk health states from the ELATIVE trial estimated from the regression analysis increased the ICER from [redacted][1] to [redacted][1]/QALY gained. Applying values from ELATIVE estimated from the descriptive analysis increased the ICER from [redacted][1] to [redacted][1]/QALY gained.
OCA: OR of cholestasis response	OCA OR of cholestasis response = 0.26. This was not consistent with the clinical claim that elafibranor was non-inferior in terms of effectiveness compared to OCA. Further, the indirect comparisons of elafibranor compared to OCA in terms of cholestasis response were not statistically significantly different.	Moderate. Favours ELA. Changing the OR from 0.26 (in favour of elafibranor) to 1.0 (reflecting no difference in effectiveness) increased the ICER from [redacted][1] to $[redacted][1]/QALY gained.
OCA: OR of all-cause discontinuation	OCA OR of all-cause discontinuation = 2.73. This analysis was not presented in the indirect comparison results and thus, the value could not be verified. Further, the indirect comparison of discontinuations due to pruritus was not statistically significantly different.	Moderate. Favours ELA. Changing the OR from 2.73 to 1 increased the ICER from [redacted][1] to [redacted][1]/QALY gained.

Source: Compiled during the evaluation from Table 3.1 of the submission & Sheet 'Model Parameters', cell D33 & Elafibranor for the treatment of primary biliary cholangitis health state utility value analysis (2023).Technical report.
ICER = Incremental cost-effectiveness ratio; ELA = elafibranor; OCA = obeticholic acid; OR = odds ratio; PBAC = Pharmaceutical benefits advisory committee; PSD = Public summary document; QALY = Quality adjusted life years
[a] Utility values applied were from the regression analysis. Regression and descriptive analyses were performed on the EQ-5D-3L utility values that were obtained by mapping EQ-5D-5L data from the ELATIVE trial, using the Hernandez-Alava et al. (2020) mapping algorithm.
The redacted values correspond to the following ranges:
1 $75,000 to < $95,000

6.66 The incorporation of disutilities due to pruritus (i.e., pruritus TEAEs, mild itch and clinically significant itch) did not significantly change the ICER. Removing the pruritus disutilities decreased the ICER from $75,000 to < $95,000 to $75,000 to < $95,000/QALY gained which was counterintuitive. The PSCR stated that the ICER reduced when disutilities due to pruritus were removed due to the higher discontinuation rate for OCA, which resulted in OCA patients effectively avoiding the disutility of pruritus. The ESC noted that if the odds ratio for discontinuation of OCA compared to elafibranor was set at 1.0 the resulting ICERs, with and without

[38] Wright et al. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess.* 2006 Jul;10(21):1-113

disutilities for pruritus, are $75,000 to < $95,000 per QALY and $75,000 to < $95,000 per QALY respectively.

6.67 Table 16 presents the results of the stepped economic evaluation.

Table 16: Results of the stepped economic evaluation

Step and component	ELA	OCA	Increment
Step 1: Trial-based costs and outcomes			
Costs[a]	[redacted]	$41,831	[redacted]
Cholestasis response at 1 year	0.5093	0.46 (5-10 mg) 0.47 (10 mg)	0.0493 (5-10 mg) 0.0393 (10 mg)
Incremental cost/additional cholestasis response			[redacted][1] (5-10 mg) [redacted][2] (10 mg)
Step 2: Time horizon 1 year and life years gained			
Costs[a]	[redacted]	$41,831	[redacted]
LY	0.895	0.895	0.0003
Incremental cost/extra LYG			[redacted][3]
Step 3: Time horizon extended to lifetime horizon			
Costs[a]	[redacted]	$190,347	[redacted]
LY	17.891	14.962	2.929
Incremental cost/extra LYG			[redacted][4]
Step 4: Discounting ([redacted]%) included			
Costs[a]	[redacted]	$162,078	[redacted]
LY	11.235	9.982	1.252
Incremental cost/extra LYG			[redacted][2]
Step 5: Incorporation of medical resource costs			
Costs[a]	[redacted]	$381,509	[redacted]
LY	11.235	9.982	1.252
Incremental cost/extra LYG			[redacted][4]
Step 6: Incorporation of utilities			
Costs[a]	[redacted]	$381,509	[redacted]
QALYs	7.802	6.532	1.270
Incremental cost/extra QALY gained			[redacted][1]
Step 7: Incorporation of adverse events disutilities (base case)			
Costs[a]	[redacted]	$381,509	[redacted]
QALYs	7.550	6.306	1.244
Incremental cost/extra QALY gained			[redacted][1]

Source: Table 3-15, submission and compiled during the evaluation based on 20241025 Elafibranor_CEM _FINAL_20241115.xlsm
ELA = elafibranor; LYG = life years gained; OCA = obeticholic acid; QALY = Quality adjusted life-years
[a] The submission applied a [redacted]% price discount to elafibranor, including the AEMP and dispensing fees. This was incorrect. Changed sheet 'Data Store', cell K233 to $[redacted].
STEP 6: Remove adverse event disutilities: sheet 'Quality of life', cells F28:F30 and F37:F38 changed to 0. STEP 5: Life years gained only; STEP 4: Remove medical resource costs, sheet 'Data Store', cells D267:D279; D282:D286; D311:D313; D325:D327; D330:D334; D339:D347; H330:H334; I306:J306 changed to 0; STEP 3: Reduce discount rate: Sheet 'Settings', cells G29:G30 changed to 0; STEP 2: Reduce time horizon, Sheet 'Settings', cell G17 change 'time horizon' to 1 year (=58-ageVar); STEP 1: Cholestasis response as per indirect comparison results.
The redacted values correspond to the following ranges:
1 $75,000 to < $95,000
2 $95,000 to < $115,000
3 > $1,055,000
4 $55,000 to < $75,000

6.68 The ESC considered the results of the economic evaluation should be considered with caution as:

- The submission applied the results of the indirect comparison (cholestasis response) to estimate the transition probabilities. This was not appropriate as the results were not statistically significantly different and were not consistent with the claim of non-inferior clinical effectiveness (see paragraph 6.62).
- The submission applied an OR of all-cause discontinuation with OCA vs elafibranor of 2.73 (i.e. a higher risk of discontinuation with OCA). This analysis was not presented in the indirect comparison results and therefore could not be verified. Further, the indirect comparison of discontinuations due to pruritus was not statistically significantly different (see paragraph 6.63).
- The submission applied estimates of both pruritus severity, informed by the PBC-40 itch domain, and the risk of pruritus TEAEs in the economic model. This may have double-counted the incidence of pruritus.

6.69 The results of key univariate sensitivity analyses are summarised in Table 17.

Table 17: Key sensitivity analyses[a]

Analyses	Incremental cost	Incremental QALY	ICER	% change to ICER
Revised base case	[redacted]	**1.24**	[redacted][1]	
Time horizon (base case 43 years)				
20 years	[redacted]	1.03	[redacted][1]	[redacted]%
30 years		1.22	[redacted][1]	[redacted]%
Utilities (base case: mild risk = 0.84; moderate risk = 0.84, high risk = 0.55)				
EQ-5D ELATIVE regression analysis: mild risk = 0.81; moderate risk = 0.79; high risk = 0.79	[redacted]	1.07	[redacted][1]	[redacted]%
EQ-5D ELATIVE descriptive analysis: mild risk = 0.80; moderate risk = 0.75; high risk = 0.75		1.09	[redacted][1]	[redacted]%
Response				
Transition probabilities from the moderate and high-risk health states to the mild-risk health state: changed the OR of response from 0.26 to 1.0	[redacted]	1.11	[redacted][1]	[redacted]%
Pruritus				
OCA mean difference of PBC-40 itch relative to elafibranor changed from 0.97 at 1 month to 0; and changed from 1.87 at 12 months to 0	[redacted]	1.23	[redacted][1]	[redacted]%
Pruritus clinically significant itch disutility changed from -0.08 to 0	$97,324	1.27	[redacted][1]	-[redacted]%
Changed TEAE pruritus disutility, pruritus mild itch disutility, and clinically significant itch disutility to 0	$97,324	1.27	[redacted][1]	-[redacted]%
Discontinuation				
Treatment discontinuation extrapolation functions (base case: exponential)				
Lognormal	[redacted]	1.58	[redacted][1]	[redacted]%
Gompertz		1.56	[redacted][1]	[redacted]%
OR of all-cause discontinuation with OCA changed from 2.73 to 1.0		0.26	[redacted][1]	[redacted]%
Duration of the treatment effect on discontinuations (OR = 2.73) changed from lifetime to 1 year.		0.51	[redacted][1]	[redacted]%

Source: Complied during the evaluation from Elafibranor_CEM _FINAL_20241115.xlsm
DPMQ = Dispensed Price for Maximum Quantity; DCC = decompensated cirrhosis; ELA = elafibranor; ICER = Incremental cost-effectiveness ratio; KOL = Key opinion leader; LT = liver transplant; OCA = obeticholic acid; OR = odds ratio; PBAC = Pharmaceutical benefits advisory committee; PBC = primary biliary cholangitis; PSD = Public summary document.
a The submission applied a [redacted]% price discount to elafibranor, including the AEMP and dispensing fees. This was not appropriate. Changed sheet 'Data Store', cell K233 to $[redacted].
The redacted values correspond to the following ranges:
1 $75,000 to < $95,000

6.70 The model was most sensitive to the source of the utilities for the biomarker health states, the OR of cholestasis response with OCA (based on the indirect comparison), and the OCA OR of all-cause discontinuation.

Drug/cost/patient/year

6.71 Table 18 presents the intervention costs per patient per year of treatment.

Table 18: Intervention costs per patient per annum

	ELA (+/-UDCA)			OCA +/-UDCA		
	Trial dose and duration	**Model**	**Financial estimates**	**Trial dose and duration**	**Model**	**Financial estimates**
Mean dose	80 mg/day Compliance rate: 98.39%	80 mg/day Compliance rate: 94.83%	80 mg/day	5 mg (6 months); titrated to 10 mg/day if required Compliance rate: NR	5 mg (6 months); titrated to 10 mg/day if required Compliance rate: 94.83%	5 - 10 mg/day
Mean duration	Discontinuation rate: 8.3% at Week 52	Discontinuation rate: 12.09% at 1 year	72 months	Discontinuation rate: OCA 5mg-10mg 9.9%; OCA 10mg 12.3%	Discontinuation rate: 25.61% at 1 year.	72 months
Cost/patient/ month	$[redacted][a]	$[redacted][b]	Effective DPMQ: $[redacted]	NR	$3,650[c]	Published DPMQ: $3,793.60
Cost/patient/ year	NR	$[redacted][d]	$[redacted][e]	NR	$41,831[d]	$46,187[f]

Source: Complied during the evaluation from p69 and p153 of the submission, Table 11, p78 of ELATIVE CSR (gft505b3191 csr body-final.pdf), Sheet,' Data Store', cells C232:M248

DPMQ = Dispensed Price for Maximum Quantity; ELA = elafibranor; NR = Not reported; OCA = obeticholic acid; UDCA = ursodeoxycholic acid.

[a] $[redacted]/30*(365.25/12)*98.39%

[b] $[redacted]/30*(365.25/12)*94.83%

[c] $3,793.60/30*(365.25/12)*94.83%

[d] Step 1 in the stepped economic evaluation: Set all costs but drug costs to $[redacted] and set time horizon to 1 year.

[e] $[redacted]/30*365.25

[f] $3,793.60/30*365.25; price of OCA 5 mg and 10 mg is the same

6.72 The total cost per patient per year with elafibranor was $[redacted] in the economic model and $[redacted] in the financial estimates. The difference was driven by the application of a compliance rate and discontinuation rate in the economic model.

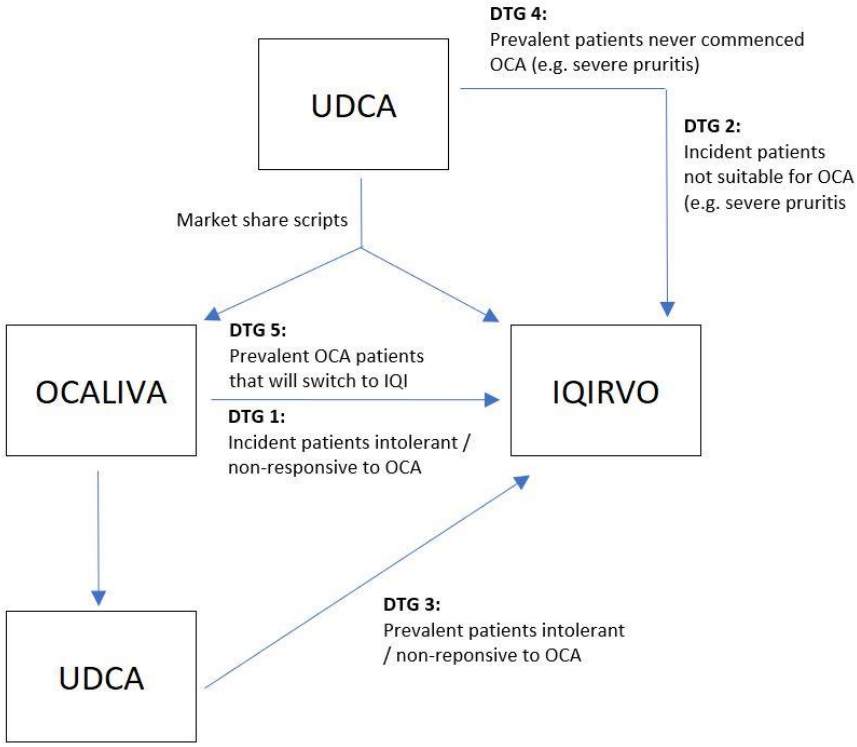
Estimated PBS usage & financial implications

6.73 This submission was considered by DUSC.

6.74 The submission used a mixed approach combining both a market share and epidemiological approach. The evaluation considered that this was appropriate as some patients may be eligible for treatment with elafibranor, but not currently prescribed OCA.

6.75 Figure 4 presents the prevalent and incident cohorts in the epidemiological approach.

Figure 4: Epidemiological sources for elafibranor



Source: Figure 1, p150 of the submission. DTG = duration of treatment group, IQIRVO = elafibranor, OCA = Obeticholic acid, UDCA = ursodeoxycholic acid.

6.76 Table 19 presents the key inputs for the financial estimates.

Table 19: Key inputs for financial estimates

Data	Value	Source	Comment
Epidemiological approach			
Eligible population			
Incident patients intolerant / non-responsive to OCA (DTG 1)	[redacted][1] patients in Years 1 and 2, [redacted][1] patients in subsequent years. Based on: 567 continuing scripts for OCA in Jun 2024 – Aug 2024 = 189 patients on OCA (see DTG 3). 40.1% of patients will be intolerant / non-response to OCA. 90% of patients elect any treatment, and of those [redacted]% would take OCA once elafibranor is listed.	OCA PBS service data, Services Australia online. The percentage of patients who will be intolerant / non-response to OCA was taken from PBS Services data for OCA. Uptake rate assumed. The market share for OCA once elafibranor is listed was assumed.	The DUSC considered it unclear how this group was derived. The DUSC noted that if patients were intolerant to OCA, they would not be considered an incident patient.
Incident patients not suitable for OCA (DTG 2)	[redacted][1] patients in Year 1, [redacted][1] Year 2, [redacted][1] Year 3, [redacted][1] year 4, [redacted][1] Year 5, [redacted][1] year 6. Based on: 306,201 scripts for UDCA in Jan 2019-Aug 2024 = 449 patients on UDCA per annum. Discontinuation from UDCA was 5.73% pa. [redacted]% of patients would elect treatment with elafibranor.	UDCA PBS service data, Services Australia online. Annual rate of discontinuation from UDCA of 5.73% was based on Lindor et al (1994). Uptake rate assumed.	The DUSC considered there was potential for overlap between the DTG 1 and DTG 2 groups as it was unclear why these patients would be unsuitable for OCA. The DUSC noted that the submission used UDCA PBS service data to inform these estimates. The DUSC noted that the data was taken from the intolerance rate for UDCA but considered that not all patients would require second line therapy. Further, the DUSC noted that UDCA may be used off-label for other cholestatic conditions and as such, may not reflect use for PBC.
Prevalent patients who were intolerant / non-responsive and discontinued OCA (DTG 3)	[redacted][1] patients in Year 1, [redacted][1] patients in subsequent years. Based on: 1,894 initiation scripts for OCA in Sept 2021-Aug 2024 = 316 patients initiated on OCA. 567 continuing scripts for OCA in Jun 2024-Aug 2024 = 189 patients on OCA and 127 patients who discontinued. [redacted]% of discontinued patients would elect treatment with elafibranor.	OCA PBS service data, Services Australia online. Uptake rate assumed.	The DUSC considered that the treatment uptake rate was reasonable; however, noted that it may be overestimated if patients continue UDCA if their disease status or ALP levels improve.

Data	Value	Source	Comment
Prevalent patients that might seek additional treatment following UDCA that did not commence OCA (DTG 4)	[redacted][1] patients in Year 1, [redacted][1] patients in subsequent years. Based on: 63,512 scripts for UDCA in Sept 2023-Aug 2024 = 5,695 patients on UDCA. 3% of patients would not be suitable for OCA treatment. [redacted]% of patients not commencing OCA would elect treatment with elafibranor.	UDCA PBS service data, Services Australia online. The 3% was based on the proportion of participants excluded from the POISE trial due to severe pruritus reported by Nevens et al (2016). Uptake rate assumed.	The DUSC noted that it was unclear why participants with severe pruritus were excluded from the POISE trial as, in clinical practice, all patients who require second line therapy would be at least offered OCA. The DUSC noted the submission used UDCA PBS service data to inform these estimates. The DUSC noted that UDCA may be used off-label for other cholestatic conditions and as such, may not reflect use for PBC.
Prevalent patients currently on OCA treatment switching to elafibranor (DTG 5)	[redacted][1] patients in Year 1, [redacted][1] patients in subsequent years. Based on: 567 continuing scripts for OCA in Jun 2024-Aug 2024 = 189 patients on OCA (see DTG 3). [redacted]% of patients would switch to elafibranor.	OCA PBS service data, Services Australia online. Switch rate assumed.	The switch rate was not consistent with the market share approach of 70% uptake. The DUSC noted that patients responding well to OCA would not switch to elafibranor The DUSC considered this parameter was dependent upon the future availability of OCA.
Duration of treatment	72 months for each treatment arm.	Economic model.	Although consistent with the economic model, this was uncertain, given the duration of the clinical trials was much shorter (12-24 months). The treatment duration of initiating patents was assumed to be 6 months This assumption was corrected during the evaluation to 5.91 months.
Market share approach			
OCA scripts	1,894 initiation scripts for OCA since Sept 2021	OCA PBS service data, Services Australia online.	-
Market share of elafibranor	[redacted]% of current OCA usage will switch to elafibranor	Market share assumed.	This was uncertain.

Data	Value	Source	Comment
Future growth in OCA scripts	Yr 1: 42.4% Yr 2: 14.2% Yr 3: 4.4% Yr 4: 1.4% Yr 5: 0.4% Yr 6: 0.1%	Submission projection of monthly OCA scripts from PBS Services data. Assumed a reduction in growth of 9.3% every year in future.	This was uncertain. The DUSC noted recent regulatory actions undertaken by the European Medicines Association (EMA) and the United States Food and Drug Administration (FDA) regarding revoking market authorisation following the release of the COBALT trial (study 747-302) results.
Grandfathered patients			
Grandfathered patients	Based on an estimated late 2025 listing, the submission projected [redacted][1] patients will be treated on the patient familiarisation program.	Patient familiarisation program	-
Costs			
Elafibranor	- Effective DPMQ: $[redacted]	Requested price	-
OCA	Published DPMQ $3,793.60.	PBS item numbers 12623J, 12630R, 12631T, 12640G, 12645M	-
Patient copayments	Various	Co-payments applicable in 2020-1.[a]	Updated to 1 January 2024 co-payments during the evaluation.[b]
MBS costs	$0	Submission assumption	-
Pruritus treatment	$0	Submission assumption	-

Source: Table 4.1 of the submission.
DPMQ = dispensed price for maximum quantity, DTG = duration of treatment group; OCA = Obeticholic acid, UDCA = Ursodeoxycholic acid, PBS = Pharmaceutical Benefits Scheme, RPBS = Repatriation Pharmaceutical Benefits Scheme, MBS = Medicare Benefits Schedule.
[a] National Health Amendment (General Co-payment) Bill 2022, https://www.aph.gov.au/Parliamentary_Business/Bills_Legislation/bd/bd2223a/23bd013
[b] https://www.pbs.gov.au/info/healthpro/explanatory-notes/front/fee
The redacted values correspond to the following ranges:
[1] < 500

6.77 Table 20 presents the estimated use and financial implications (effective price of elafibranor, published price of OCA).

Table 20: Estimated use and financial implications (effective price of elafibranor, published price of OCA)[a]

	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	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Estimated financial implications of elafibranor						
Cost to PBS/RPBS less copayments	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][6]	[redacted][6]
Estimated financial implications for OCA						
Cost to PBS/RPBS less copayments	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Net financial implications						
Net cost to PBS/RPBS	[redacted][8]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]
Net cost to MBS/Services Australia	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
Net cost to PBS/RPBS/MBS/ Services Australia	[redacted][8]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]

Source: Table 4.1of the submission.
OCA = Obeticholic acid. PBS = Pharmaceutical Benefits Scheme, RPBS = Repatriation Pharmaceutical Benefits Scheme, MBS = Medicare Benefits Schedule.
a Corrected values calculated during the evaluation. These values include correction of script volume, duration of treatment, removal of DTG 5 cohort and updated co-payments.
The redacted values correspond to the following ranges:
[1] < 500
[2] 500 to < 5,000
[3] 5,000 to < 10,000
[4] $10 million to < $20 million
[5] $20 million to < $30 million
[6] $30 million to < $40 million
[7] net cost saving
[8] $0 to < $10 million

6.78 The net cost to the PBS/RPBS using the effective price of elafibranor and public price of OCA was $0 to < $10 million in Year 1, increasing to $20 million to < $30 million in Year 6 and totalling $100 million to < $200 million over the first 6 years.

6.79 Many parameter inputs were not justified and uncertain, for example, the proportion of patients electing treatment with elafibranor and the assumed market share for OCA if elafibranor is listed.

6.80 The DUSC considered that the estimates were highly uncertain. The DUSC noted that in clinical practice, there would likely be three populations who would be treated with elafibranor:

1. Prevalent patients who were intolerant of OCA.
   - This population is represented by DTG 3 in the submission (<500patients).
2. Prevalent patients currently on OCA who may switch to elafibranor.
   - This population is represented by DTG 5 in submission.
   - The DUSC, noting the recent regulatory actions undertaken by the European Medicines Association (EMA) and the United States Food and Drug Administration (FDA) regarding revoking market authorisation following the release of the COBALT trial (study 747-302) results, considered that if OCA was

withdrawn in Australia, all patients would switch to treatment with elafibranor.

3. Incident patients (who require treatment in addition to UDCA or who are intolerant of UDCA) who need second line therapy.

6.81 The DUSC considered most incident patients (approximately 90%) would be treated with elafibranor instead of OCA given the marketing concerns from the EMA and FDA and the risk of severe pruritus with OCA.

Quality Use of Medicines

6.82 The submission raised no quality use of medicines issues. The DUSC noted the ease of dosing and administration of elafibranor (daily oral administration).

6.83 Primary biliary cholangitis is a relatively rare condition with prescribing initiated by specialist gastroenterologist/hepatologist. General practitioner (GP) and practice nurse education will be needed to ensure they are equipped to manage ongoing supply, especially given the adverse effect profile.

Financial Management – Risk Sharing Arrangements

6.84 The submission did not propose a risk-sharing arrangement. There is a current risk-sharing arrangement for OCA.

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

7 PBAC Outcome

7.1 The PBAC recommended elafibranor for the treatment of primary biliary cholangitis (PBC). 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 (RSA) for OCA.

7.2 The PBAC acknowledged the consumer input 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 (UCDA). The clinician noted that uptake of OCA in these patients has been lower than expected as it is associated with increased pruritus and other adverse events.

7.3 The PBAC considered that elafibranor would be used as an alternative to OCA in the second line setting. The PBAC considered that it was likely that a number of stable patients on OCA (with or without UDCA) would switch to elafibranor. The PBAC considered that most elafibranor use would be in combination with ursodeoxycholic acid (UDCA), but noted that for those patients' intolerant to UDCA, elafibranor would

likely be used as monotherapy. The PBAC also considered that it was reasonable that elafibranor should be available for use in the third line setting for patients who have an inadequate response to, or are intolerant of, OCA, noting however that there was minimal clinical evidence in this population.

7.4 The PBAC considered that the initial and continuing restrictions for elafibranor should align with the current OCA restrictions as outlined in paragraph 3.2. The PBAC noted that the following changes should be made to both the elafibranor and OCA restrictions:

- 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
- Unnecessary wording should be removed from the treatment criteria (e.g. 'with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion', 'following this authority application' and 'combination').

7.5 The PBAC considered that the nomination of OCA as the main comparator was reasonable, with UDCA monotherapy or no treatment relevant comparators in the third line setting.

7.6 The PBAC noted that the submission was based on indirect treatment comparisons between elafibranor (data from the ELATIVE trial, N = 161) and OCA (data from the POISE trial, N = 217), with placebo as the common comparator. The PBAC, noting the transitivity issues outlined in paragraph 6.14, considered that this approach was appropriate.

7.7 The PBAC noted that the key primary outcome, cholestasis response, was the same in the ELATIVE and POISE trials and was assessed 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 PBAC noted that following the results of the COBALT trial (see paragraph 5.4) the relationship between the surrogate endpoint and disease progression was uncertain; however on balance, the PBAC considered that the use of cholestasis response to assess non-inferiority was reasonable at this point in time.

7.8 The PBAC noted that compared to placebo, elafibranor was associated with a significantly higher proportion of patients achieving cholestasis response (50.9% of elafibranor patients vs 3.8% of placebo patients; unadjusted RD = 47.2%; 95% CI: 36.4, 57.9) and ALP normalisation (14.8% of elafibranor patients vs 0% of placebo patients; unadjusted RD = 14.8%; 95% CI: 8.1, 21.5) at Week 52 (see Table 4).

7.9 The PBAC noted that the submission presented three indirect treatment comparisons comparing elafibranor to OCA in terms of cholestasis response, change from baseline in ALP levels and ALP normalisation at 52 weeks (see paragraph 6.29). The PBAC noted that, although the submission did not nominate minimum clinically important

differences and there were no statistically significant differences between elafibranor and OCA in any of the comparisons, the point estimates favoured elafibranor (see Table 7 and Table 8).

7.10 The PBAC considered that the clinical claim that elafibranor was non-inferior compared to OCA in terms of effectiveness was reasonable.

7.11 The PBAC noted that in the ELATIVE trial elafibranor was associated with a reduction in pruritis compared to placebo based on the 5-D Itch Scale and the Itch Domain of the PBC-40. However, the PBAC considered that the clinical significance of the differences was unclear, noting that an improvement in global quality of life, as measured by the total PBC-40 scale and EQ-5D-5L, was not observed.

7.12 The PBAC noted that the indirect treatment comparisons suggested elafibranor was associated with less pruritus based on the 5-D Itch scale and PBC-40 Itch-domain (see Table 10) compared to OCA, and there was a reduced occurrence of pruritus treatment emergent adverse events and discontinuations due to pruritus (see Table 11). However, the PBAC noted that there were differences across the trials which affected the assumption of transitivity; in particular, the POISE trial excluded patients with severe pruritus. Overall, the PBAC, noting that pruritus was a symptom of PBC, considered that there was likely a reduction in PBC-related pruritus with elafibranor compared with OCA; however, the magnitude of the reduction and associated impact on health-related quality of life and on the overall management of PBC was unclear.

7.13 The submission claimed that elafibranor was superior to OCA, primarily based on the assumption that elafibranor resulted in less pruritus. The PBAC did not accept the submission's claim of superior safety compared with OCA given the issues associated with the pruritus comparisons discussed above. The PBAC acknowledged that pruritus was a significant issue for patients with PBC, but considered that overall, a claim of superior safety had not been demonstrated. Overall, the PBAC considered that elafibranor was non-inferior compared to OCA.

7.14 The PBAC noted that the submission presented a cost utility analysis comparing elafibranor with OCA incorporating benefits of reduced pruritis and associated reductions in treatment discontinuations. The PBAC considered the magnitude of the differences were unable to be reliably estimated based on the available evidence, noting the transitivity issues with the indirect treatment comparisons and the lack of a statically significant difference for discontinuations. On this basis, 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 elafibranor 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 elafibranor in accordance with the PBAC Guidelines, September 2016 v5.0, which allow a price advantage over the comparator on the basis of reduced cost offsets, which in this case would be due reduced costs associated with the management of pruritus.

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

Elafibranor 80 mg once daily = obeticholic acid 5 mg or 10 mg once daily.

7.16 The PBAC agreed with the DUSC in considering that there would be three populations who would be treated with elafibranor: (i) prevalent patients who are intolerant of OCA; (ii) prevalent patients who are currently receiving OCA who may switch to elafibranor; and (iii) incident patients who require second-line treatment in addition to UDCA or are intolerant of UDCA.

7.17 The PBAC noted that the financial impact of listing elafibranor would be reduced compared to the submission estimates when the price of elafibranor was cost-minimised to OCA.

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

7.19 The PBAC advised that continuing treatment of elafibranor, like OCA, is suitable for prescribing by nurse practitioners.

7.20 The PBAC advised that elafibranor should not be exempt from the Early Supply Rule.

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

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

7.23 The PBAC noted that this submission was not eligible for an Independent Review, as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№. of Rpts**	**Available brands**
ELAFIBRANOR					
Elafibranor 80 mg tablet, 30	NEW	1	30	5	Iqirvo
Restriction Summary [new] / Treatment of Concept: [new]					
	Category / Program: ☒ GENERAL - General Schedule (Code GE)				

Concept ID (for internal Dept. use)		**Prescriber type:** ☒Medical Practitioners
		Restriction type: ☒Authority Required – immediate assessment (telephone/online)
Prescribing rule level		**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.
		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.
		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.
		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 obeticholic acid.
		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, (i) 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 at least 18 years of age
		Prescribing Instructions:

	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: Laboratory readings requested in this authority application must be no older than 52 weeks.

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№. of Rpts**	**Available brands**
ELAFIBRANOR					
Elafibranor 80 mg tablet, 30	NEW	1	30	5	Iqirvo

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) [new/existing code]
Prescribing rule level		**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.
		Administrative Advice: **Continuing Therapy Only:** 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: 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.
		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
		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 obeticholic acid.
		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:

	The improvement in the qualifying laboratory reading(s) has/have been documented in the patient's medical records.
	Administrative Advice: Laboratory readings requested in this authority application must be no older than 52 weeks.

MEDICINAL PRODUCT **medicinal product pack**		**PBS item code**	**Max. qty packs**	**Max. qty units**	**№. of Rpts**	**Available brands**
ELAFIBRANOR						
Elafibranor 80 mg tablet, 30		NEW	1	30	5	Iqirvo
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 – immediate assessment (telephone/online)					
Prescribing rule level	**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					
	Administrative Advice: **Continuing Therapy Only:** 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: 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: 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.					
	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]					
	AND					
	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 obeticholic acid.					
	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: 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: 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: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

8.2 Amend the existing obeticholic acid restrictions as follows:

1. Add new concept to OCA to exclude concomitant treatment with elafibranor:
   - 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)
   - 12645M / obeticholic acid 5 mg tablet, 30 (Grandfather arrangements - Supply Only)
   - 12631T / obeticholic acid 10 mg tablet, 30 (Grandfather arrangements - Supply Only)

	~~**Clinical criteria:**~~ ***Treatment criteria:***
	Patient must not be undergoing concurrent treatment with elafibranor.

2. Update to concept 13395 (removal of word 'cholelithiasis') to be flowed on to OCA only for PBS item codes:
    - 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)
    - 12645M / obeticholic acid 5 mg tablet, 30 (Grandfather arrangements - Supply Only)
    - 12631T / obeticholic acid 10 mg tablet, 30 (Grandfather arrangements - Supply Only)

	Administrative Advice: *Not for use in the treatment of sclerosing cholangitis ~~or cholelithiasis.~~*

3. Update to concept 27503 (removal of words from concept 27502 'with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion') to be flowed on to OCA only for PBS item codes:
    - 12623J / obeticholic acid 5 mg tablet, 30 (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~~

4. Update to concept 27495 (removal of words 'following this authority application' from concept 27494 and 27493; removal of 'combination' from concept 27494; and addition of '/contraindicated') to be flowed on to OCA only for PBS item codes:
    - 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)
    - 12645M / obeticholic acid 5 mg tablet, 30 (Supply Only GF restriction)
    - 12631T / obeticholic acid 10 mg tablet, 30 (Supply Only GF restriction)

	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*

5. Update to concept 27490 (removal of words from concept 27489 'with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion') to be flowed on to OCA only for PBS item codes:

- 12640G / obeticholic acid 10 mg tablet (Continuing treatment)
- 12630R / obeticholic acid 5 mg tablet, (Continuing treatment)
- 12645M / obeticholic acid 5 mg tablet, 30 (Grandfather arrangements - Supply Only)
- 12631T / obeticholic acid 10 mg tablet, 30 (Grandfather arrangements - Supply Only)

	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~~

6. Update concept 27505 (addition of '/contraindication') to be flowed on to OCA only for PBS items codes:
    - 12623J / obeticholic acid 5 mg tablet, 30 (initial treatment)
    - 12645M / obeticholic acid 5 mg tablet, 30 (Grandfather arrangements - Supply Only)
    - 12631T / obeticholic acid 10 mg tablet, 30 (Grandfather arrangements - Supply Only)

	Clinical criteria:
	Patient must have experienced an intolerance*/contraindication* to ursodeoxycholic acid of a severity requiring permanent treatment discontinuation, prior to initiating treatment with this drug

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

9 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.

10 Sponsor's Comment

The sponsor had no comment.