5.10 OBETICHOLIC ACID, Tablet, 5 mg, 10 mg, Ocaliva®, Emerge Health

1 Purpose of Application

1.1 Authority Required listing for obeticholic acid (OCA) for treatment of primary biliary cholangitis (PBC). OCA has not been previously considered by the PBAC for this indication.

1.2 The requested basis for listing was cost-effectiveness of OCA in combination with ursodeoxycholic acid (OCA+UDCA) compared to UDCA plus placebo for UDCA inadequate responders, and OCA monotherapy compared to placebo for UDCA intolerant patients.

Table 1: Key components of the clinical issue addressed by 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	• For inadequate responders to UDCA: OCA 5-10mg titration (as defined for the titration group in POISE; 5 mg for the first six months of treatment, followed by 10 mg for the subsequent months) + UDCA (13-15mg per kilogram of body weight). • For UDCA-intolerant patients: OCA 5-10mg titration.
Comparator	• For UDCA inadequate responders: UDCA + placebo. • For UDCA-intolerant patients: placebo
Key outcomes	The primary composite endpoint was an ALP level of less than 1.67 times the upper limit of the normal range, with a reduction of at least 15% from baseline, and a total bilirubin level at or below the upper limit of the normal range at 12 months. Secondary efficacy end points included levels of ALP, GGT, alanine aminotransferase, aspartate aminotransferase, total and conjugated bilirubin, and albumin; prothrombin time; international normalized ratio; plasma bile acid levels.
Clinical claim	For patients with an inadequate response to UDCA, OCA plus UDCA is superior to UDCA alone in reducing ALP and bilirubin levels and other important clinically relevant endpoints. For patients intolerant to UDCA, OCA is superior to placebo in reducing ALP and bilirubin levels and other important clinical endpoints. OCA is well tolerated. There is a numerically higher rate of AEs due to increased pruritus when used in combination to UDCA or as monotherapy. The overall safety profile is manageable, with a low rate of AE-related treatment discontinuations.

AE: Adverse Event, ALP: alkaline phosphatase; CMA: cost minimisation analysis; CSR: clinical study report; GGT: gamma-glutamyl transferase.
Source: Table1.1.1, p32 of the submission.

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

2 Requested listing

Suggested additions are in italics, suggested deletions in strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	DPMQ	Proprietary Name and Manufacturer
OBETICHOLIC ACID Tablet 5 mg	30	5	Published: $[redacted] Effective: $[redacted]	Ocaliva® Emerge Health Pty Ltd

Category/Program:	Section 85 (General Schedule)
Prescriber type:	☐Dental ☒Medical Practitioners ☒~~Nurse practitioners~~ ☐Optometrists ☐Midwives
Condition:	Primary biliary cholangitis
PBS Indication:	Primary biliary cholangitis
Treatment phase:	Initial treatment
Restriction:	☒Streamlined
Treatment criteria:	Patient must be treated by a gastroenterologist ~~and/~~or hepatologist *or in consultation with a gastroenterologist or hepatologist.*
Clinical criteria:	Treatment must be in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, OR Treatment must be as monotherapy, in adults unable to tolerate UDCA *AND* *Patient must have an alkaline phosphatase (ALP) of less than or equal to 1.6 times the upper limit of normal (ULN), OR* *Patient must have a total bilirubin greater than the ULN, but less than 2 times the ULN,* *AND* *Patient must not have severe liver disease, OR* *Patient must not have immunodeficiency diseases.* ~~Recommended starting dose is Ocaliva® 5 mg once daily, in adults. Based on an assessment of tolerability after 6 months, the dose should be increased to 10 mg once daily, to achieve optimal response.~~
Administrative Advice:	Not for use in the treatment of sclerosing cholangitis or cholelithiasis. ~~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 gastroenterologist.~~ ~~Maximum Dosage: 10 mg once daily.~~ Special pricing arrangements apply

Category/Program:	Section 85 (General Schedule)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Primary biliary cholangitis
PBS Indication:	Primary biliary cholangitis
Treatment phase:	Continuing treatment
Restriction:	☒Streamlined
Treatment criteria:	Patient must be treated by a gastroenterologist ~~and/~~or hepatologist *or in consultation with a gastroenterologist or hepatologist.*
Clinical criteria:	*Patient must have previously been issued with an authority prescription for this drug for this condition,* AND Patient must have adequately tolerated 5mg dose at 6-month assessment

Administrative Advice:	Not for use in the treatment of sclerosing cholangitis or cholelithiasis. Special pricing arrangements apply **Note** 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 gastroenterologist *or a hepatologist or in consultation with a gastroenterologist or hepatologist. Further information can be found in the Explanatory Notes for Nurse Practitioners.* ~~Maximum Dosage: 10 mg once daily.~~

Name, Restriction, Manner of administration and form	**Max. Qty**	**№.of Rpts**	**DPMQ**	**Proprietary Name and Manufacturer**
OBETICHOLIC ACID Tablet 10 mg	30	5	Published: $[redacted] Effective: $[redacted]	Ocaliva® Emerge Health Pty Ltd

Category/Program:	Section 85 (General Schedule)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Primary biliary cholangitis
PBS Indication:	Primary biliary cholangitis
Treatment phase:	Continuing treatment
Restriction:	☒Streamlined
Treatment criteria:	Patient must be treated by a gastroenterologist ~~and/~~or hepatologist *or in consultation with a gastroenterologist or hepatologist.*
Clinical criteria:	*Patient must have previously been issued with an authority prescription for this drug for this condition,* AND Patient must have adequately tolerated 5 mg dose at 6 months assessment. ~~Based on an assessment of tolerability after 6 months, the dose should be increased to 10 mg once daily to achieve optimal response.~~ ~~Maximum dose is 10 mg.~~
Administrative Advice	Not for use in the treatment of sclerosing cholangitis or cholelithiasis. Special pricing arrangements apply **Note** 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 gastroenterologist *or a hepatologist or in consultation with a gastroenterologist or hepatologist. Further information can be found in the Explanatory Notes for Nurse Practitioners.* ~~Maximum Dosage: 10 mg once daily.~~

2.1 The proposed PBS restriction was not consistent with the patients recruited into the POISE trial, which excluded patients with severe liver disease and immunodeficiency diseases and required patients to have either an alkaline phosphatase (ALP) ≥ 1.6 x upper limit of normal (ULN) or total bilirubin > ULN but < 2 x ULN. The ESC agreed with the suggestion in the Pre-Sub-Committee Response (PSCR, p1) to amend the proposed restriction to align with the POISE trial criteria.

2.2 The submission did not propose any specific continuation criteria and stated that "patients should continue to take OCA for as long as they continue to benefit from treatment… patients should be assessed at six months for tolerability of OCA and if adequately tolerated, the patient dose should be increased to 10 mg to achieve maximum benefit from OCA". The draft TGA product information states that 'dosage adjustments are needed for patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment'. In the economic model, patients no longer receive OCA if they experience decompensated cirrhosis (DCC), hepatocellular cancer (HCC), are put on the waiting list for liver transplant, receive a liver transplant, or experience PBC recurrence after liver transplant. Accordingly, the ESC advised that PBS subsidised treatment should cease if a patient experiences one these events. The ESC considered it may also be appropriate to include a stopping or continuation rule for patients who do not demonstrate an adequate biochemical response to treatment with obeticholic acid, given that less than half of patients treated with OCA achieved the primary efficacy end point in the POISE Trial. In the pre-PBAC response (p3), the sponsor stated that inclusion of a stopping rule could be considered.

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

3 Background

Registration status

3.1 The submission was made under the TGA/PBAC Parallel Process. Obeticholic acid was approved for registration by the TGA on 18 July 2018 for:

> Treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

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

4 Population and disease

4.1 PBC was recently renamed from primary biliary cirrhosis. PBC is a rare, progressive, autoimmune, non-viral disease of the liver that gradually destroys the interlobular bile ducts. While the cause of the disease is unknown, a combination of multiple genetic factors and environmental factors are thought to trigger PBC.

4.2 The submission estimated there are approximately 1,275 PBC patients in Australia based on the prevalence of PBC at 51 per million population (Sood et al, 2004). However, Watson (1995) estimated a lower PBC prevalence rate at 19.1 per million population, resulting in 481 PBC patients in Australia based on current population estimates. PBC is more prevalent in adults aged over 40 years, females, and people of European descent.

4.3 The clinical management algorithms were based on the 2017 European Association for the Study of the Liver (EASL) guidelines as there are currently no Australian specific treatment guidelines for PBC. The ESC considered that the clinical algorithms were broadly appropriate; noting that they should include a stopping rule for patients who are intolerant or fail to respond to OCA.

4.4 The submission proposed that OCA should be used in combination with UDCA for patients with an inadequate response to UDCA; or as monotherapy for patients who are intolerant to UDCA. The recommended starting dose is 5 mg once daily. Based on the assessment of tolerability after six months, the dose should be increased to 10 mg once daily to achieve optimal response; this is referred to as OCA 5-10 mg titration hereafter.

4.5 The OCA dose should be subsequently reduced if patients experience severe pruritus (itchy skin) or they have moderate to severe hepatic impairment. The submission stated that the dose should be reduced to 5 mg once weekly for moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment. If an adequate reduction in ALP and/or total bilirubin is not achieved after 3 months of OCA 5 mg once weekly, and the patient is tolerating the medicinal product, then the dose should be increased to 5 mg twice weekly (at least three days apart between doses) and subsequently to 10 mg twice weekly (at least three days apart between doses) depending on response and tolerability. No dose adjustment is needed for mild hepatic impairment (Child-Pugh Class A).

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

5 Comparator

5.1 The submission proposed the following main comparators:

- UDCA inadequate responders: UDCA monotherapy; and
- UDCA intolerant patients: placebo or no treatment.

5.2 The main arguments provided in support of this nomination were that UDCA is the only medicine approved by the TGA and listed on the PBS to treat PBC; and up to 40% of patients have an inadequate response or are intolerant to UDCA, and there are currently no available treatment options for these patients.

5.3 The ESC considered that the nominated comparators were reasonable.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on one head-to-head randomised trial (POISE) comparing:

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

6.4 The submission also presented two supplementary randomised trials comparing:

- OCA as monotherapy vs placebo (747-201 trial, placebo: N=24; OCA 10mg: N=20; OCA 50mg: N=16), and
- OCA + UDCA vs UDCA + placebo (747-202 trial, placebo: N=38; OCA 10mg: N= 38; OCA 25mg: N=48; OCA 50mg: N=41).

6.5 The submission also presented the open-label extension studies of the POISE trial (POISE LTSE) (N=193). All patients in the POISE LTSE received OCA at a dose of 5mg (including those who been taking OCA 10 mg in the double-blind phase) +/- UDCA for the first 3 months, after which time dose could be increased to 10mg.

6.6 Table 2 presents the details of the trials presented in the submission.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
POISE	A Phase 3, double blind, placebo controlled trial and long term safety extension of obeticholic acid in patients with primary biliary cirrhosis (POISE) Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis	Intercept Pharmaceuticals 2015 NEJM 2016;375(7):631-43.
747-201	Kowdley K, Luketic V, Chapman RW, et al. A randomized trial of obeticholic acid monotherapy in patients with primary biliary cholangitis.	Hepatology 2018; 67 (5): 1890-1902
747-202	Hirschfield GM, Mason A, Luketic V, Lindor K, Gordon SC, Mayo M, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid.	Gastroenterology 2015 Apr;148(4):751-61 e8

Source: Table 2.2.2, p60 -63 of the submission

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

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
OCA + UDCA vs UDCA+ placebo for UDCA inadequate responders or OCA vs placebo for UDCA intolerant						
POISE Trial	217	R, DB 12 months	Moderate	PBC	Serum ALP and total bilirubin levels, together as a composite endpoint in the OCA 10mg group.	Used
747-201 Trial	60	R, DB 12 weeks	Moderate	PBC	Serum ALP change from baseline to end of study	Not used
747-202 Trial	165	R, DB 12 weeks	Moderate	PBC	Serum ALP change from baseline to end of study in each of the OCA groups	Not used

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised.
Source: Figure2.4.5, p99 of the submission; Figure 2.4.6, p103 of the submission; Figure 2.4.7, p105 of the submission, Table 2.4.32, p113-116 of the submission.

6.8 Trial 747-201 evaluated OCA monotherapy at a dose of 10 mg or 50 mg versus placebo and Trial 747-202 evaluated OCA 10 mg, 25 mg or 50 mg daily in combination with UDCA versus placebo with UDCA. Both trials used OCA 10 mg dosing without titration from a starting dose of 5 mg. The submission stated that "given the differences in the dosing of OCA and the recommended dosing, both Phase II trials are presented as supplementary evidence, providing efficacy and safety data for OCA 10 mg dosing (without titration from a starting dose of 5mg)". This was considered reasonable.

6.9 Pruritus was a common adverse event in patients receiving OCA +/- UDCA, especially among patients who received higher doses of OCA. Consequently, there was a risk of unblinding in all trials if pruritus began just after commencement of OCA treatment. The PSCR (p2) stated that pruritus is a common symptom of PBC and that in the POISE trial over two-thirds of patients exhibited symptoms at baseline and that approximately 35% of patients without pruritus at baseline developed pruritus on commencing OCA and 15% of placebo patients had worsening pruritus. The rate of pruritus in both treatment groups returned to baseline levels after three to six months. The PSCR therefore concluded that it would be difficult to unblind a patient based solely on the emergence or increased severity of pruritus. The ESC and PBAC considered that unblinding due to the occurrence of pruritus introduced a moderate potential for bias.

6.10 The submission noted that a higher discontinuation rate in the OCA 5-10 mg titration +/- UDCA group of the POISE trial (10%) and OCA 10 mg +/- UDCA group (12%), compared with the placebo group +/- UDCA (0%), which was mostly due to pruritus. The higher discontinuation rate contributed to incomplete outcome data bias. However, for efficacy analyses in the POISE trial, patients with missing data were assumed to be non-responders, which was a conservative approach to handling missing data. No patients in the trial were lost to follow-up. The evaluation considered that the POISE trial had a moderate risk of bias.

6.11 The overall risk of bias in the 747-201 (OCA monotherapy) and 747-202 (OCA combination) trials was also considered to be moderate as there were more withdrawals in the OCA treatment groups (mostly due to pruritus) than placebo:

- 747-201: withdrawal rates of 20% in the OCA 10 mg group and 44% withdrawals in the OCA 50 mg group compared with 0% for placebo.
- 747-202: withdrawal rates of 16% in OCA 10 mg + UDCA, 12% in OCA 25mg + UDCA, 38% in OCA 50mg + UDCA, compared with 0% in UDCA + placebo.

6.12 The submission used a composite of ALP and bilirubin levels to assess PBC progression. The primary outcome presented by the submission was the percentage of patients that achieved a composite endpoint at Month 12 of:

- ALP < 1.67x ULN with
- ≥ 15% decrease from baseline in ALP, and
- total bilirubin < ULN.

6.13 The PSCR (p2) stated that due to the slow progression and the chronic nature of PBC, the composite end-point provided the optimal assessment of patient response. The ESC and PBAC considered that the use of biochemical markers to monitor disease progression in PBC was well validated. EASL Guidelines indicate that levels of ALP and total bilirubin correlate with disease severity and progression to fibrosis and cirrhosis.

6.14 The POISE trial was powered to detect a difference in the composite outcome in the OCA 10 mg +/- UDCA group versus placebo +/- UDCA. This is different to the proposed PBS indication and the economic model, which used the data from the OCA 5-10mg titration +/- UDCA group.

Comparative effectiveness

6.15 Table 4 presents the key efficacy results of the POISE trial.

Table 4: Primary efficacy outcome at Month 12 of POISE (ALP < 1.67x ULN, total bilirubin ≤ ULN, and ALP decrease of ≥ 15% from Baseline) by population

Population	OCA +/- UDCA n/N (%)	PBO +/- UDCA n/N (%)	CMH test p value	Odds ratio (95% CI)	Risk ratio (95% CI)	Risk difference (95% CI)
OCA 10mg +/-UDCA	34/73 (46.6%)	7/73 (9.6%)	<0.0001	8.22 (3.33, 20.31)	4.86 (2.30, 10.24)	0.37 (0.24, 0.50)
OCA 5-10mg titration +/- UDCA	32/70 (45.7%)	7/73 (9.6%)	<0.0001	NR	NR	NR

ALP: alkaline phosphatase; CI: confidence interval; CMH: Cochran–Mantel–Haenszel test; NR: not reported OCA: obeticholic acid; PBO: placebo; UDCA: ursodeoxycholic acid; ULN: upper limit(s) of normal.
Source: Table 2.5.1, p129 of the submission, p114 of the POISE CSR.

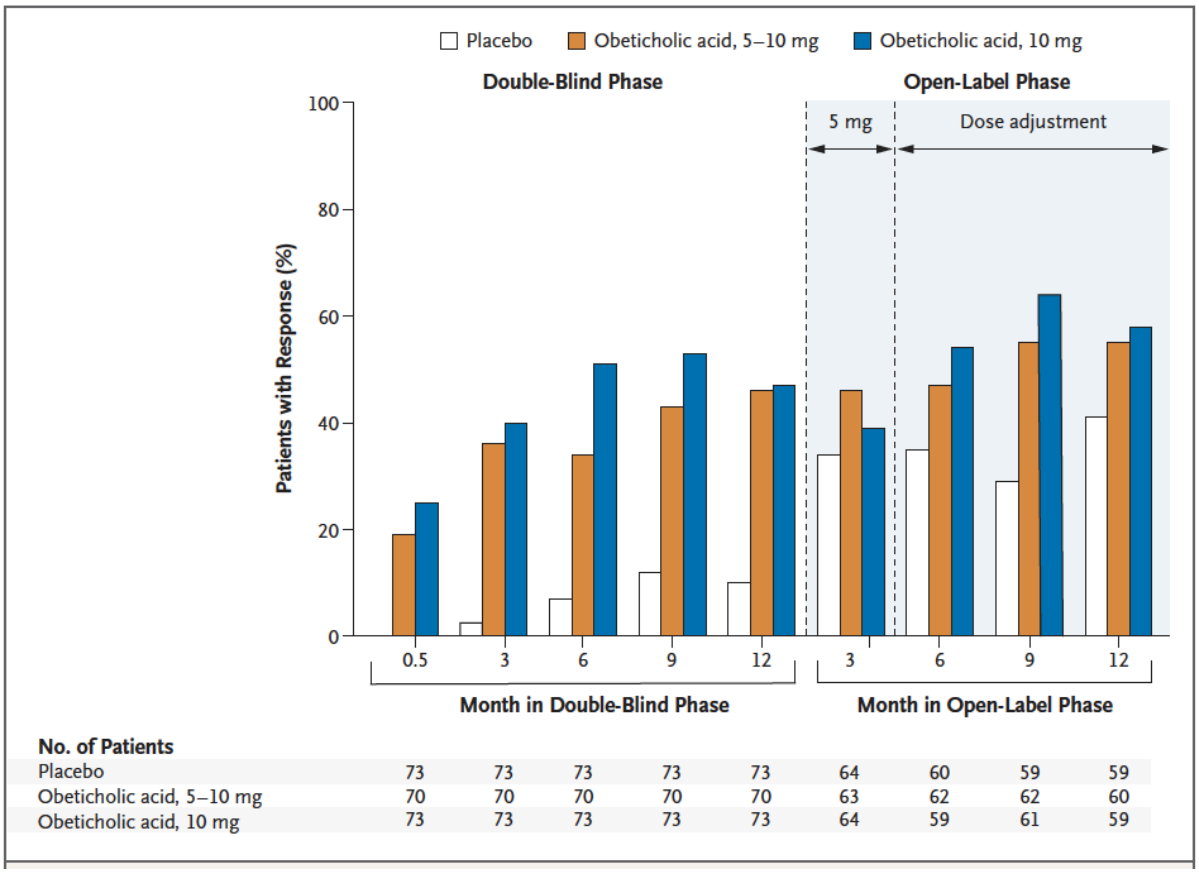
6.16 At Month 12 of the POISE trial, the ESC noted that less than half of patients in the OCA 10 mg +/- UDCA arm (46.6%, n=34) and in the OCA 5-10 mg titration +/- UDCA arm (45.7%, n=32) achieved the composite endpoint (ALP < 1.67 x ULN, total bilirubin ≤ ULN, and ALP decrease of ≥ 15% from baseline), compared with 9.6% of patients (n=7) in the placebo +/- UDCA (p<0.0001). The pre-PBAC Response (p1) stated that a finding of less than half of patients achieving the primary endpoint was significant as the size of the incremental benefit (approx. 46% versus 9.6%) was large. Additionally,

as OCA was a second line treatment option, patients receiving OCA would have already failed first line treatment and were at a high risk of disease progression.

6.17 The POISE trial did not report the results of OCA combination therapy (i.e. plus UDCA) and OCA monotherapy separately. Given that the sample size of patients who received the OCA monotherapy was small (OCA 5-10 mg titration, N=5; OCA 10 mg, N=6; placebo, N=5), it was difficult to assess the effectiveness of OCA monotherapy based on the POISE trial alone. The 747-201 trial provided additional evidence of efficacy and safety for OCA 10 mg as monotherapy, but the sample size was also small (OCA 10mg group N=20). In the pre-PBAC Response (p1), it was noted that the small sample size for patients receiving OCA monotherapy was in-line with the proportion of patients intolerant to UDCA.

6.18 The results from the POISE long term safety extension (LTSE) demonstrated that 40-50% of patients in the OCA 5-10 mg titration +/- UDCA and OCA 10 mg +/- UDCA did not achieve the primary efficacy outcome after Month 24 – see Figure 1. The ESC noted that very few additional patients showed response at Month 24 compared to Month 12.

Figure 1: Primary efficacy of POISE trial and the long term safety extension study



No. of Patients									
Placebo	73	73	73	73	73	64	60	59	59
Obeticholic acid, 5–10 mg	70	70	70	70	70	63	62	62	60
Obeticholic acid, 10 mg	73	73	73	73	73	64	59	61	59

Source: Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. N Engl J Med. 2016 Aug 18;375(7):631-43.

6.19 In the 747-201 trial there was a statistically significant improvement in ALP levels from baseline to week 12 with OCA 10mg monotherapy compared with placebo (p<0.0001). The mean (SD) percentage change in ALP was -44.5% (24.4) for the OCA 10 mg monotherapy group versus +0.4% (15.3) for placebo.

6.20 In the 747-202 trial there was a statistically significant improvement in ALP levels in the modified intent to treat (mITT) group from day 0 to day 85 with OCA 10mg + UDCA compared with UDCA + placebo (p<0.0001). The OCA 10 mg + UDCA group had a mean reduction in ALP level of 24% (95% CI: -30, -18), compared with a 3% reduction in the placebo group (95% CI: -7, 2).

Comparative harms

6.21 Table 5 presents a summary of patient-relevant harms, based on the POISE, 747-201 and 747-202 trials.

Table 5: Summary of key adverse events in the randomised trials

Trial ID	Placebo +/- UDCA n/N (%)	OCA 5-10 mg titration +/- UDCA n/N (%)	OCA 10 mg +/- UDCA n/N (%)
POISE Trial			
Any TEAE	66/73 (90%)	65/70 (93%)	69/73 (95%)
Total number of TEAEs	452	471	467
Any Related TEAE (at least "Possibly" related)	38/73 (52%)	42/70 (60%)	54/73 (74%)
A related TEAE of pruritus	27/73 (37%)	35/70 (50%)	48/73 (66%)*
Any SAEs	3/73 (4%)	11/70 (16%)*	8/73 (11%)
Total number of SAEs	8	15	11
Mild TEAEs	29/73 (40%)	16/70 (23%)	19/73 (26%)
Moderate TEAEs	28/73 (38%)	27/70 (39%)	29/73 (40%)
Severe TEAEs	9/73 (12%)	22/70 (31%)*	21/73 (29%)*
Any TEAE leading to Study Discontinuation	2/73 (3%)[a]	5/70 (7%)[b]	8/73 (11%)[c]
Study Discontinuation due to a TEAE of pruritus	0/73	1/70 (1%)	7/73 (10%)*
Deaths	0/73	1/70 (1%)	0/73
747-201 Trial (OCA monotherapy)			
≥ 1 TEAE	21/23 (91%)	-	18/20 (90%)
TEAE of pruritus or pruritus generalised	8/23 (35%)	-	14/20 (70%)
Related TEAE	11/23 (48%)	-	15/20 (75%)
Any SAE	1/23 (4%)	-	0/20
Mild TEAEs	18/23 (78%)	-	16/20 (80%)
Moderate TEAEs	8/23 (35%)	-	9/20 (45%)
Severe TEAEs	5/23 (23%)	-	7/20 (35%)
Withdrawal due to a TEAE	0/23	-	3/20 (15%)
Discontinuation due to pruritus	0/23	-	3/20 (15%)
747-202 Trial (OCA combination)			
≥ 1 TEAE	32/38 (84%)	-	34/38 (89%)
TEAE of pruritus or pruritus generalised	19/38 (50%)	-	18 /38 (47%)
Related TEAE	22/38 (58%)	-	28/38 (74%)
TEAEs of pruritus or pruritus generalised	17/38 (45%)	-	18/38 (47%)
Any SAE	1/38 (3%)	-	0/38
Deaths	0/38	-	0/38
Mild TEAEs	31/38 (82%)	-	25/38 (66%)
Moderate TEAEs	15/38 (39%)	-	17/38 (45%)
Severe TEAEs	3/38 (8%)	-	6/38 (16%)
Withdrawal due to a TEAE	1/38 (3%)	-	6/38 (16%)
Discontinuation due to pruritus	0/38	-	3/38 (8%)

NR: not reported; OCA: obeticholic acid; SAE: serious adverse event; TEAE: treatment emergent adverse event; UDCA= ursodeoxycholic acid.

a One subject additional experienced a TEAE of osteoarthritis that resulted in withdrawal of investigational product. The subject was discontinued from the study, which was determined by the Investigator to be withdrawal of consent.

b Four subjects in the titration group discontinued from the study due to a TEAE prior to being up-titrated to OCA 10 mg.

c One Subject experienced a TEAE of fatigue, which was recorded as a discontinuation on the AE eCRF, however the subject remained in the study and investigational product was not changed.

* P ≤ 0.05 vs placebo group using a Chi-squared test, or Fisher's Exact test where n ≤ 5 in either group

Source: Table 2.5.20, p162, Table 2.5.23, p167, Table 2.5.24, p167 of the submission.

6.22 In the POISE trial:

- A similar proportion of patients reported treatment emergent adverse events (TEAE) across all treatment arms (OCA 5-10 mg titration +/-UDCA: 93%, OCA 10mg +/- UDCA: 95%, Placebo+/- UDCA: 90%), but more patients experienced related

TEAEs with OCA (OCA 5-10 mg titration +/-UDCA: 60%, OCA 10mg +/- UDCA: 74%, Placebo+/- UDCA: 52%).

- A higher proportion of patients in the OCA 10 mg +/-UDCA arm (66%) experienced a treatment-related TEAE pruritus compared with placebo+/- UDCA (37%).
- A higher proportion of patients in the OCA 5-10 mg titration arm +/- UDCA arm (16%) experienced one or more serious adverse events (SAE) compared with placebo+/- UDCA (4%).
- A higher proportion of patients in the OCA 5-10 mg titration arm (31%) and the OCA 10 mg arm (29%) experienced one or more severe TEAEs compared to placebo+/- UDCA (12%), which led to a higher rate of study discontinuation.

6.23 In the 747-201 trial (OCA monotherapy), a higher proportion of patients in the OCA 10 mg monotherapy arm (75%) experienced related TEAEs (most were pruritus) compared to placebo (48%), which led to a higher rate of study discontinuation.

6.24 In the 747-202 trial (OCA combination), a higher proportion of patients in the OCA 10mg + UDCA arm (74%) experienced related TEAEs compared to placebo + UDCA (58%). The most common TEAE was pruritus: 47% for OCA 10 mg + UDCA vs 50% in placebo + UDCA, and 8% of patients discontinued due to pruritus in the OCA 10mg + UDCA group. There was one SAE in the placebo group and no deaths in the study.

Benefits/harms

6.25 A summary of the comparative benefits and harms for OCA 5-10 mg titration +/- UDCA or OCA 10mg +/- UDCA versus UDCA +/- placebo is presented in Table 6.

Table 6: Summary of comparative benefits and harms for OCA 10mg +/- UDCA and Placebo +/-UDCA

Trial	OCA +/- UDCA n/N	PBO +/- UDCA n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				OCA +/- UDCA	PBO +/- UDCA	
Benefits						
Primary outcome **Surrogate endpoints: ALP < 1.67x ULN with ≥ 15% decrease from baseline in ALP, and total bilirubin < ULN**						
POISE (OCA 5-10mg titration)	32/70	7/73	**4.77 (2.25, 10.09)**	45.7	9.6	***36.1 (22.6, 49.6)***
POISE (OCA 10mg)	34/73	7/73	**4.86 (2.30, 10.24)**	46.6	9.6	***37.0 (23.7, 50.3)***

Primary outcome **Surrogate endpoint: Percentage change in serum ALP from baseline to the end of trial**							
	OCA 10mg +/- UDCA			**Placebo+/-UDCA**			**Mean difference*: OCA 10mg +/- UDCA vs. PBO +/- UDCA (95% CI)**
	N	**Mean Δ baseline**	**SD**	**N**	**Mean Δ baseline**	**SD**	
747-201 trial (OCA monotherapy)	20	-44.5%	24.4	23	0.4%	15.3	NR (P<0.0001)
747-202 trial (OCA combination)	38	-23.7%	17.8	38	-2.6%	12.5	NR (P<0.0001)

Harms						
	OCA +/- UDCA n/N	**PBO +/- UDCA n/N**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				OCA +/- UDCA	**PBO +/- UDCA**	
Pruritus						
POISE (OCA 5-10mg titration)	39/70	28/73	**1.45 (1.02, 2.08)**	55.7	38.4	**17.4 (1.2. 33.5)**
POISE (OCA 10mg)	50/73	28/73	**1.79 (1.28, 2.48)**	68.5	38.4	**30.1 (14.7, 45.6)**
747-201 trial (OCA monotherapy)	14/20	8/23	**2.01 (1.07, 3.77)**	70.0	34.8	**35.2 (7.2, 63.2)**
747-202 trial (OCA combination)	18/38	19/38	0.95 (0.60, 1.50)	47.4	50.0	-2.6 (-25.1, 19.8)
TEAEs						
POISE (OCA 5-10mg titration)	65/70	66/73	1.03 (0.93,0.80)	92.9	90.4	2.5 (-6.6, 11.5)
POISE (OCA 10mg)	69/73	66/73	1.04 (0.95, 1.15)	94.5	90.4	4.1 (-4.4, 12.6)
747-201 trial (OCA monotherapy)	18/20	21/23	0.99 (0.81,1.20)	90	91.3	-1.3 (-18.8, 16.2)
747-202 trial (OCA combination)	34/38	32/38	1.06 (0.89,1.27)	89	84	5.3 (-9.9, 20.4)
SAEs						
POISE (OCA 5-10mg titration)	11/70	3/73	**3.82(1.11,13.13)**	15.7	4.1	**11.6(1.9, 21.3)**
POISE (OCA 10mg)	8/73	3/73	2.67 (0.74, 9.66)	11.0	4.2	6.8 (-1.6, 15.3)
747-201 trial (OCA monotherapy)	0/20	1/23	0.38 (0.02, 8.86)	0.0	0.04	-0.04 (-0.13, 0.04)
747-202 trial (OCA combination)	0/38	1/38	0.33 (0.01, 7.93)	0.0	0.03	-0.03 (-0.08, 0.02)

*Maximum duration of follow-up: POISE=12 months, 747-201 trial= 14 weeks; 747-202 trial= 14 weeks;

CI: confidence interval; OCA: obeticholic acid; PBO: placebo; RD: risk difference; RR: risk ratio; SAE: serious adverse event; TEAE: treatment emergent adverse event; UDCA: ursodeoxycholic acid.

Source: Complied during the evaluation based on Table 2.5.1, p129 of the submission, Table 2.5.20 of the submission, p162, Table 2.5.21, p164 of the submission.

6.26 On the basis of direct evidence presented by the submission (POISE trial), for every 100 patients treated with OCA 5-10 mg titration +/- UDCA in comparison to placebo +/- UDCA and over a maximum duration of follow-up of 12 months:

- Approximately 36 additional patients would achieve the primary surrogate endpoint;
- Approximately 17 additional patients would experience pruritus; and
- Approximately 12 additional patients would experience at least one SAE.

6.27 On the basis of direct evidence presented by the submission (POISE trial), for every 100 patients treated with OCA 10mg +/- UDCA in comparison to placebo +/- UDCA and over a maximum duration of follow-up of 12 months:

- Approximately 37 additional patients would achieve the primary surrogate endpoint;
- Approximately 30 additional patients would experience pruritus.

Clinical claim

6.28 The submission described OCA 5-10 mg titration + UDCA as superior in terms of effectiveness compared with UDCA + placebo for patients with prior inadequate response to UDCA and non-inferior in terms of safety compared with UDCA + placebo.

6.29 Additionally, the submission described OCA 5-10 mg titration monotherapy as superior in terms of effectiveness compared with placebo for patients who are intolerant to UDCA and non-inferior in terms of safety compared with placebo.

6.30 The ESC considered that the therapeutic claim of superior effectiveness of OCA 5-10 mg titration + UDCA compared with UDCA + placebo in patients who had an inadequate response to UDCA was reasonable; however, the magnitude of benefit was uncertain due to the following issues:

- The sample size of the key clinical trial, POISE, was small (N=217), which increased the uncertainty in the results. The ESC acknowledged that this reflected the rare nature of the disease.
- The mean duration of the POISE trial was short (12 months) given that PBC is a chronic disease and treatment is ongoing. Consequently, the long term effectiveness of OCA for the treatment of PBC is uncertain. The submission provided a POISE trial extension study (POISE LTSE); however, it was an open label study and also had a small sample size (N=193).
- The ESC noted that a subgroup in POISE undergoing assessment of hepatic fibrosis (a secondary efficacy outcome) did not show any benefit from OCA[1]. Hence, the effect of OCA on histological progression was uncertain. The pre-PBAC Response (p1) claimed that benefits were noted for additional surrogate markers of hepatic fibrosis and inflammation.

6.31 The ESC considered that the therapeutic claim of non-inferior safety of OCA 5-10 mg titration compared to UDCA + placebo in patients who had an inadequate response to UDCA was not reasonable. A higher proportion of patients in the OCA 5-10 mg titration arm (31%) experienced more severe TEAEs compared to UDCA + placebo (12%) in the POISE trial. In addition, a higher proportion of patients in the OCA 5-10 mg titration

[1] p640, Nevens et al. NEJM 2016;375(7):631-43.

arm +/- UDCA arm (16%) experienced one or more serious adverse events (SAE) compared with UDCA + placebo (4%). The PSCR (p2) stated that none of the SAEs were considered to be related to the investigational product.

6.32 The ESC considered that the therapeutic claim of superior efficacy of OCA 5-10 mg titration compared with placebo in UDCA intolerant patients was not possible to assess due to insufficient data. The POISE trial included 16 patients who were intolerant to UDCA and the results were not presented separately.

6.33 The ESC considered that the therapeutic claim of non-inferior safety of OCA 5-10 mg titration compared to placebo in UDCA intolerant patients was not possible to assess due to insufficient data. The 747-201 trial provided additional safety evidence for OCA 10 mg as monotherapy, but the sample size was also small (OCA 10 mg, N = 20). In the pre-PBAC Response (p1), it was noted that the small sample size was in line with the proportion of patients who were intolerant to UDCA.

Economic analysis

6.34 The submission presented a stepped economic evaluation based on direct randomised trials (the POISE trial) and implemented a modelled evaluation. The types of economic evaluation presented were cost-utility analysis and cost-effectiveness (per responder and per life year gained) analyses.

6.35 The submission presented four different comparisons. Two were based on the published price and two, described below, on the effective price:

- OCA 5-10 mg titration + UDCA versus UDCA monotherapy for UDCA inadequate response patients.
- OCA 5-10 mg titration monotherapy versus no treatment for UDCA intolerant patients.

6.36 Table 7 presents the key components of the economic evaluation.

Table 7: Summary of model structure and rationale

Component	Summary
Type of analysis	Cost-utility analysis (CUA)
Outcomes	Quality adjusted life years (QALYS) and life years (LY) gained
Time horizon	Lifetime (50 years), POISE clinical trial 12 months duration plus the POISE Long Term Extension Study (LTSE) (5 years). The time horizon in the model was long compared to the duration of follow-up in the POISE trial. The ESC considered that the ICER was highly sensitive to the time horizon, which contributed to the uncertainty of the results.
Methods used to generate results	A semi-Markov state-transition model which captures patients costs and outcomes over a lifetime horizon (up to 100 years of age dependent on starting age).
Health states	10 health states (biochemical [first 3 states]; liver disease [last 7 states]) Biochemical States • Low risk of PBC disease progression: ALP ≤200 U/L (i.e. 1.67x ULN) and normal bilirubin (i.e. TB ≤20 µmol/L) • Moderate risk of PBC disease progression: ALP >200 U/L and normal bilirubin

Component	Summary
	• High risk of PBC disease progression leading to liver failure: Abnormal bilirubin (i.e. TB >20 µmol/L) and rising or CC. <u>Liver Disease States</u> • Decompensated cirrhosis • Hepatocellular cancer • Pre-liver transplant • Liver transplant • Post-liver transplant • PBC re-emergence • Dead The submission assumed that patients treated with OCA +/- UDCA can move back and forth between the biochemical health states, while patients treated with placebo +/- UDCA can only progress to more severe health states. The ESC considered the assumption that patients treated with UDCA monotherapy or receiving no treatment are unable to improve (move to lower risk biochemical health states) was inconsistent with the POISE trial and Corpechot (2000), in which 9.6% and 3% of patients, respectively, experienced response with UDCA monotherapy.
Cycle length	3 months
Population used in the model	Age: 47.3 years, based on the POISE trial. The age of patients in the economic model was the same as the age of patients at diagnosis, not the age of patients at recruitment into POISE (55.8 years). This was not appropriate. It may take time for patients to stop responding to treatment with UDCA. A lower age reduces the risk of all-cause mortality, and thus favours OCA.
	Baseline health state distribution: Low risk: 0% Moderate risk: 76.85% High risk: 23.15% Based on the POISE trial. The ESC noted that the distribution of patients in the health states at baseline was unable to be verified during the evaluation.
Transition probabilities	<u>Low risk ↔ High risk</u> OCA monotherapy (UDCA intolerant) or OCA + UDCA (UDCA inadequate response): POISE. The transition probabilities between biochemical health states for OCA patients were based on a small sample size (N=68). The same transition probabilities were used for OCA monotherapy as for OCA +/- UDCA, even though only 7% (n=16) patients in the POISE trial received OCA monotherapy, which is uncertain. The model assumed that patients treated with OCA 5-10 mg titration do not progress from the biochemical health state they are in at year 2 for the rest of the patient's lifetime. The ESC considered this implausible given the progressive nature of the disease. UDCA monotherapy (UDCA inadequate response): Model calibration using data from POISE. The submission estimated transition probabilities for UDCA monotherapy using a different methodology than used for OCA. While it was based on POISE data, the data was unable to be verified. The PBAC considered that applying the POISE data directly for UDCA monotherapy patients during the first 12 months, as per patients treated with OCA, would be more transparent, consistent with the OCA transition probabilities, and thus would have maintained the benefits of randomisation. No treatment (UDCA intolerant): Corpechot (2000). The ESC noted that the application of Corpechot (2000) data into the model effectively meant that the model was based on a naïve comparison between the POISE trial and the trial reported by Corpechot (2000) which had not been clinically evaluated and

Component	Summary
	in which patients had less severe disease as it compared UDCA to placebo only. The PBAC considered that it would have been more appropriate to use data from the POISE trial. Assuming that patients treated with UDCA monotherapy or no treatment are unable to improve (move to lower risk health states) was inconsistent with the POISE trial and Corpechot (2000) in which 9.6% and 3% of patients, respectively, experienced response with UDCA monotherapy. The PSCR (p3) stated that to receive OCA, patients must either be intolerant to UDCA or to have had an inadequate response to UDCA. Therefore, if they improved on UDCA treatment, they would be ineligible for OCA. The ESC disagreed with the argument provided in the PSCR, stating that it was inconsistent with the trial data which indicated a response with UDCA treatment in patients who were deemed to have had an inadequate response at baseline.
	Biochemical health states → Liver disease health states Various published data sources and model calibration Most transition probabilities were unable to be verified based on the information presented by the submission.
Utilities	Biochemical states The low and moderate risk state utilities were sourced from a quality of life study in chronic viral hepatitis and cholestatic liver disease patients (Younossi et al, 2001). The utilities from Younossi et al (2001) were unable to be verified. High risk utility was sourced from an economic evaluation of a hepatitis C treatment (Wright et al, 2006). This was reasonable. Liver disease states Each of the liver disease state utilities were sourced from the Wright et al (2006) economic evaluation, with some health states receiving a 15% decrease based on KOL opinion that PBC patients are likely to have worse utility values. The decrease in some of the utility values for the liver disease states seemed reasonable; however, the magnitude of the decrease was uncertain. The submission did not provide details of the KOLs. The submission stated that the HCC health state was not subject to the 15% decrease; yet, applied a 15% decrease in the economic model. The submission applied a higher utility value for PBC re-emergence post liver transplant than for transplant patients without PBC re-emergence. This was illogical. None of the utility values were sourced from Australian studies. The ESC considered that the application of utility values was inconsistent and noted that a number of values could not be verified. Adverse events The submission did not apply disutilities to adverse events. The ESC considered this unreasonable. This was likely to favour OCA given that a higher proportion of patients receiving OCA experienced pruritus.

ALP: alkaline phosphatase; CC: compensated cirrhosis; KOL: key opinion leader; OCA: obeticholic acid; PBC: primary biliary cholangitis/cirrhosis; TB: total bilirubin; UDCA: ursodeoxycholic acid; ULN: Upper limit of normal.
Source: Table 3.1.1, p184 of the submission *and compiled during the evaluation*

6.37 Table 8 summarises the key drivers of the model.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Time horizon	Lifetime (50 years): POISE clinical trial (12 month duration); and the POISE Long Term Extension Study (5 years).	High, favours OCA
Progression after 2 years with OCA	Assumed to be nil.	High, favours OCA
Transition probabilities between biochemical health states with UDCA monotherapy	Model calibration using data from POISE. Assumed that patients could not improve.	Moderate, favours OCA

OCA: obeticholic acid; UDCA: ursodeoxycholic acid
Source: Compiled during the evaluation

6.38 Table 9 presents the results of the stepped economic evaluation.

Table 9: Results of the stepped economic evaluation (effective, corrected price)

Data	Costs			Health outcomes			ICER
	OCA titration (+/- UDCA)	Placebo (+/- UDCA)	Increment	OCA titration (+/- UDCA)	Placebo (+/- UDCA)	Increment	
Step 1 (**UDCA inadequate responder individuals: OCA titration + UDCA vs UDCA monotherapy**): Trial-based analysis using the 12-month POISE trial data (outcomes = POISE primary efficacy outcome: ALP <1.67 x ULN, total bilirubin ≤ULN, and ALP decrease of ≥15% from Baseline), effective prices [ICER = $/Responder Gained]	$[redacted]	$[redacted]	$[redacted]	50%	10%	40%	$[redacted]
Step 2a (**UDCA inadequate responder individuals: OCA + UDCA vs UDCA monotherapy**): Model-based analysis; added costs related to adverse event and disease management; transformed POISE outcomes into biochemical and liver-related health states; made model population specific to the inadequate responder population; added life-years as an outcome; extrapolated to 50 years; discounted costs and outcomes at 5% p.a, effective prices [ICER = $/Life-Year Gained]	$[redacted]*	$[redacted]	$[redacted]	16.28	12.15	4.13	$[redacted]
Step 2b (**UDCA intolerant individuals: OCA vs no treatment**): Model-based analysis; Step 2a with model population specific to the UDCA intolerant population, effective prices [ICER = $/Life-Year Gained]	$[redacted]*	$[redacted]	$[redacted]	16.19	11.25	4.94	$[redacted]
Step 4a (**UDCA inadequate responder individuals: OCA + UDCA vs UDCA monotherapy**): Model-based analysis; effective prices [ICER = $/Quality-Adjusted Life-Year Gained]	$[redacted]*	$[redacted]	$[redacted]	13.26	7.75	5.51	$[redacted]
Step 4b (**UDCA intolerant individuals: OCA versus no treatment**): Model-based analysis; effective prices [ICER = $/Quality-Adjusted Life-Year Gained]	$[redacted]*	$[redacted]	$[redacted]	13.15	6.63	6.52	$[redacted]

ALP: alkaline phosphatase; ICER: Incremental cost-effectiveness ratio; OCA: obeticholic acid; QALYs: quality adjusted life years; UDCA: ursodeoxycholic acid; ULN: Upper limit of normal.

*Based on an OCA weighted effective price of $[redacted] ($[redacted]*53% + $[redacted]*47%) (instead of $[redacted] applied by submission). Source: Sheet 'Deterministic results' in Attachment 11 of the submission.

The redacted table shows ICERs in the range of $45,000 – $75,000 to $105,000 – $200,000 per responder, life year or QALY gained.

6.39 The ESC considered that the model lacked transparency and clinical plausibility, was highly sensitive to key assumptions and was not sufficiently valid to inform decision making. In particular, the ESC considered that the results should be interpreted with caution for the following reasons:

- The ESC noted that most of the transition probabilities from the biochemical health states to the liver disease health states and between the liver disease health

states were unable to be verified during the evaluation and that the verification of these values was not addressed in the PSCR.

- The time horizon in the model (50 years) was long compared to the duration of follow-up in the POISE trial (12 months) and considering the mean age of patients in the POISE trial (56 years) and the progressive nature of the disease. In addition, the ESC noted that the mean age of patients in the model (47 years) was based on the age at diagnosis of PBC (instead of the mean age in the POISE trial of 56 years), introducing additional uncertainty regarding applicability of trial results.

- The model assumed that patients treated with OCA 5-10 mg titration do not progress from the biochemical health state they are in at Year 2, whereas patients treated with UDCA monotherapy or no treatment continue to progress and cannot improve. This assumption means that the model predicts that treatment with OCA +/- UDCA results in an 80% reduction in patients at high risk ('abnormal bilirubin and rising, or compensated cirrhosis (CC)'), an 85% reduction in patients experiencing decompensated cirrhosis (DCC), liver transplant and liver-related death, and a 95% reduction in hepatocellular carcinoma (HCC). The PSCR (p3) and pre-PBAC Response (p2) stated that patients remained in the same health state from Year 2 to reflect the sustained reduction in ALP and bilirubin for up to five years, as demonstrated by the results of the POISE LTSE. The ESC considered these assumptions were implausible in the long term given the response rates seen in the trial, the uncertainty surrounding the UDCA intolerant patients and the progressive nature of PBC.

- The assumption that patients treated with UDCA monotherapy or receiving no treatment are unable to improve (move to lower risk biochemical health states) was inconsistent with the POISE trial and Corpechot (2000)[2], in which 9.6% and 3% of patients, respectively, experienced response with UDCA monotherapy. The PSCR (p3) stated that to receive OCA, patients must either be intolerant to UDCA or to have had an inadequate response to UDCA. Therefore, if patients improved on UDCA treatment they would be ineligible for OCA. The ESC disagreed with the argument provided in the PSCR, stating that the assumption was inconsistent with the trial data which indicated a response with UDCA treatment in patients who were deemed to have had an inadequate response at baseline.

- The submission estimated transition probabilities for UDCA monotherapy using model calibration using data from POISE, rather than directly applying the transition probabilities as was used than for OCA +/- UDCA. While the transition probabilities were based on POISE data, the data were unable to be verified. Applying the POISE data directly for UDCA monotherapy patients during the first

[2] *Corpechot (2000) was a randomised trial that compared 13–15 mg/kg/day UDCA (N=53) or placebo (N=50) for two years. After two years, placebo patients crossed over to UDCA for a further two years, whilst patients already on UDCA remained on UDCA.*

12 months, as per patients treated with OCA, would have been more transparent, consistent with the OCA transition probabilities, and would have maintained the benefits of randomisation. The PSCR (pp3-4) stated that the transition probabilities used to reflect progression on UDCA or placebo were based on data from various literature sources, which allowed for longer-term data to be used and reduced uncertainty. For patients intolerant to UDCA, the PSCR stated that using the POISE comparator arm (i.e. UDCA treatment) was not appropriate, and that RCTs comparing UDCA to placebo were therefore used instead. For patients with inadequate responses to UDCA, the POISE trial was not considered to reflect the long term clinical endpoints like liver transplantation and death. The ESC considered that the application of new evidence into the model essentially resulted in the model being based on a naïve indirect comparison of results against the POISE trial which had not been clinically evaluated. The ESC considered that it would have been more appropriate to use data from the POISE trial.

- The utility values applied in the model were inconsistent and lacked face validity; for example, a higher utility was applied for patients with PBC re-emergence post liver transplant than for patients post-transplant without PBC re-emergence. In addition, the submission did not apply disutilities to adverse events. This was likely to favour OCA given that a higher proportion of patients receiving OCA experienced pruritus. The PSCR (p4) confirmed that the model did not include disutilities for adverse events, but that costs were applied for adverse events. The PSCR (p4) stated that a sensitivity analysis was conducted using different costs for adverse events which showed a minimal effect on the ICER, and thus it was likely that adding disutilities to adverse events would also have a minimal effect. The ESC considered this response was uninformative; the application of adverse event costs has no bearing on the issue of whether disutilities are applied. The ESC reiterated its view that disutilities for pruritus should have been included. The pre-PBAC Response (p2) claimed that PBC is a pruritic disease, and, if well managed, this has a limited impact on quality of life.
- In the model OCA and UDCA treatment costs ceased once patients progressed to the liver disease health states. Given that the submission did not proposed a stopping rule in the PBS restriction, treatment costs may be underestimated. The pre-PBAC Response (p2) stated that inclusion of a stopping rule in the proposed restriction would be considered.

6.40 Tables 10 and 11 summarise the results of the sensitivity analyses.

Table 10: UDCA Inadequate Responders Population (effective, corrected price)*

Parameter (Base case ICER = $[redacted])	Base case value	Lower bound	Upper bound	Lower bound ICER per QALY gained	Upper bound ICER per QALY gained
Discount rate - Cost	5%	0%	3.5%	$[redacted]	$[redacted]
Background transition: transition to Bili: Abnormal and rising, or CC for OCA treated patients: Quarterly probability	0%	-	1.054%	-	$[redacted]
Discount rate - Outcomes	5%	0%	3.5%	$[redacted]	$[redacted]
Time horizon (years)	50	20	50	$[redacted]	$[redacted]
ALP: > 1.67 ULN and Bili: Normal to Bili: Abnormal and rising, or CC: Quarterly probability	3.11%	2.49%	3.73%	$[redacted]	$[redacted]
Utility: Bili: Abnormal and rising, or CC	0.55	0.44	0.65	$[redacted]	$[redacted]
Utility: ALP: ≤ 1.67 ULN and Bili: Normal	0.84	0.80	0.88	$[redacted]	$[redacted]
Population age (years)	47	38	57	$[redacted]	$[redacted]
Bili: Abnormal and rising, or CC to HCC: Quarterly Probability	0.35%	0.04%	1.02%	$[redacted]	$[redacted]
Utility: ALP: > 1.67 ULN and Bili: Normal	0.84	0.80	0.88	$[redacted]	$[redacted]
Bili: Abnormal and rising, or CC to decompensated cirrhosis: Quarterly Probability	2.76%	2.21%	3.31%	$[redacted]	$[redacted]
Transition: Bili: Abnormal and rising, or CC-decompensated cirrhosis	2.76%	2.21%	3.31%	$[redacted]	$[redacted]
Post LT to death: Quarterly Probability	0.63%	0.93%	2.11%	$[redacted]	$[redacted]
Utility: Decompensated cirrhosis	0.38	0.31	0.46	$[redacted]	$[redacted]
Liver transplant costs	$167,151	$133,721	$200,581	$[redacted]	$[redacted]
Utility: 6-month post-transplant	0.57	0.46	0.68	$[redacted]	$[redacted]

ALP: alkaline phosphatase; Bili: bilirubin; CC: compensated cirrhosis; HCC: Hepatocellular cancer; ICER: Incremental cost-effectiveness ratio; LT: liver transplant; QALY: quality adjusted life year; ULN: Upper limit of normal.
*Based on a OCA cost of $[redacted] per annum
Source: Conducted during the evaluation using sheet 'DSA' in Attachment 11.

The redacted table shows ICERs in the range of $15,000/QALY – $45,000/QALY to more than $200,000/QALY.

Table 11: UDCA Intolerant Population (effective, corrected price)*

Parameter (Base case ICER = $74,501)	Base case value	Lower bound	Upper bound	Lower bound ICER per QALY gained	Upper bound ICER per QALY gained
Background transition: transition to Bili: Abnormal and rising, or CC for OCA treated patients: Quarterly probability	0%	-	6.801%	-	$[redacted]
Discount rate – Cost	5%	0%	3.5%	$[redacted]	$[redacted]
Discount rate – Outcomes	5%	0%	3.5%	$[redacted]	$[redacted]
Time horizon (years)	50	20	50	$[redacted]	$[redacted]
Utility: Bili: Abnormal and rising, or CC	0.55	0.44	0.65	$[redacted]	$[redacted]
Utility: ALP: ≤ 1.67 ULN and Bili: Normal	0.84	0.80	0.88	$[redacted]	$[redacted]
ALP: > 1.67 ULN and Bili: Normal to Bili: Abnormal and rising, or CC: Quarterly probability	6.80%	5.44%	8.16%	$[redacted]	$[redacted]
Utility: ALP: > 1.67 ULN and Bili: Normal	0.84	0.80	0.88	$[redacted]	$[redacted]
Bili: Abnormal and rising, or CC to HCC: Quarterly Probability	0.35%	0.04%	1.02%	$[redacted]	$[redacted]
Population age (years)	47	38	57	$[redacted]	$[redacted]
Bili: Abnormal and rising, or CC to decompensated cirrhosis: Quarterly Probability	2.76%	2.21%	3.31%	$[redacted]	$[redacted]
Transition: Bili: Abnormal and rising, or CC-decompensated cirrhosis	2.76%	2.21%	3.31%	$[redacted]	$[redacted]
Post LT to death: Quarterly Probability	0.63%	0.93%	2.11%	$[redacted]	$[redacted]
Utility: Decompensated cirrhosis	0.38	0.31	0.46	$[redacted]	$[redacted]
Liver transplant costs	$167,151	$133,721	$200,581	$[redacted]	$[redacted]
Utility: 6-month post-transplant	0.57	0.46	0.68	$[redacted]	$[redacted]

ALP: alkaline phosphatase; Bili: bilirubin; CC: compensated cirrhosis; HCC: Hepatocellular cancer; ICER: Incremental cost-effectiveness ratio; LT: liver transplant; QALY: quality adjusted life year; ULN: Upper limit of normal.
*Based on a OCA cost of $[redacted] per annum
Source: Conducted during the evaluation using sheet 'DSA' in Attachment 11.

The redacted table shows ICERs in the range $15,000/QALY – $45,000/QALY to more than $200,000/QALY.

6.41 Table 12 summarises the results of the sensitivity analyses when trial-based UDCA transition rates were applied to the first 12 months.

Table 12: Summary of sensitivity analyses on applying the UDCA transition rates in the first 12 months (effective prices)*#

Parameter	OCA +/- UDCA	Placebo	Increment
UDCA inadequate responders			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	13.26	8.36	4.90
ICER ($/QALY)			$[redacted]
UDCA intolerant			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	13.15	6.98	6.18
ICER ($/QALY gained)			$[redacted]

*Based on an OCA cost of $[redacted] per annum

Transition probability for progressing from low/moderate risk to high risk after year 2 = transition probability from low to high for UDCA monotherapy = 1.054% for UDCA inadequate responders, and 6.801% for UDCA intolerant.

Source: Compiled during the evaluation.

The redacted table shows ICERs in the range of $75,000/QALY – $105,000/QALY.

6.42 The submission claimed that the model was most sensitive to:

- The discount rate for costs and outcomes; and
- The analysis time horizon. The PSCR (p3) stated that reducing the time horizon to 20 years resulted in an increase of around $15,000/QALY – $45,000/QALY or 15% to the ICER. The ESC considered this was a significant change.

6.43 The evaluation found that the results were also sensitive to the assumption of nil progression from Year 2 onwards, especially for UDCA intolerant patients. Given the absence of data, applying a hypothetical transition probability equal to that from low to high risk for UDCA monotherapy (1.054%) and no treatment (6.801%) increased the ICER from $75,000/QALY – $105,000/QALY gained to $105,000/QALY – $200,000/QALY gained for UDCA inadequate responders, and from $45,000/QALY – $75,000/QALY gained to more than $200,000/QALY gained for UDCA intolerant patients (effective, corrected prices).

6.44 Applying the POISE data directly for UDCA monotherapy patients during the first 12 months, as per patients treated with OCA, increased the ICER from $75,000/QALY – $105,000/QALY gained to $105,000/QALY – $200,000/QALY gained for UDCA inadequate responders, and from $45,000/QALY – $75,000/QALY gained to $75,000/QALY – $105,000/QALY gained for UDCA intolerant patients (effective, corrected prices). Changes in the other transition probabilities had limited impact on the ICER due to a) the number of transition probabilities, and b) the narrow range tested during the sensitivity analyses.

Drug cost/patient/year

6.45 The submission miscalculated the weighted cost of treatment with OCA using published prices (used the price of 5 mg for 10 mg and vice versa). Furthermore, the CSR (Table 52) suggests that 47% of patients were titrated and received 10 mg per day

and 53% were not titrated and received 5 mg per day. The recalculated intervention costs per patient per year of treatment are provided in Table 13.

Table 13: Intervention costs per patient

Patient population	UDCA + placebo	OCA titration – published price	OCA titration – effective price
UDCA inadequate responders	$2,287, based on: UDCA dose = 15.4 mg/kg Weight = 69.80 kg Days treated = 346 days UDCA cost = $0.0061/mg.	$[redacted] (including UDCA), based on: UDCA dose = 16.7 mg/kg Weight = 69.80 kg Days treated = 358.8 days UDCA Cost = $0.0061/mg. OCA dose: 47% receive 5 mg and 53% receive 10 mg. Days treated = 358.8 days OCA cost = $[redacted]/mg and $[redacted]/mg for 5 mg and 10 mg, respectively (published prices).	$[redacted] (including UDCA), based on: UDCA dose = 16.7 mg/kg Weight = 69.80 kg Days treated = 358.8 days UDCA Cost = $0.0061/mg. OCA dose: 47% receive 5 mg and 53% receive 10 mg. Days treated = 358.8 days OCA cost = $[redacted]/mg and $[redacted]/mg for 5 mg and 10 mg, respectively (effective prices).
UDCA intolerant	$[redacted] (placebo only)	$[redacted] (OCA only), based on: OCA dose: 47% receive 5mg and 53% receive 10mg. Days treated = 358.8 days Cost = $[redacted]/mg and $[redacted]/mg for 5 mg and 10 mg, respectively (published prices).	$[redacted] (OCA only), based on: OCA dose: 47% receive 5mg and 53% receive 10mg. Days treated = 358.8 days OCA cost = $[redacted]/mg and $[redacted]/mg for 5 mg and 10 mg, respectively (effective prices).

Source: Table 3.8.1, p222 of the submission and calculated during the evaluation using a weighted effective price of $[redacted] ($[redacted]*53% + $[redacted]*47%) (instead of $[redacted] applied by submission) based on sheet 'Treatment costs' in Attachment 11.

Estimated PBS usage & financial implications

6.46 The estimated extent of use and financial implications of listing OCA on the PBS were considered by the DUSC.

6.47 The submission used an epidemiological approach to estimate the financial impact of listing OCA on the PBS and RPBS for the treatment of PBC. The key data sources were Watson (1995) and Sood (2004) for the prevalence of PBC, Corpechot (2008) for the proportion of eligible patients, POISE for adherence, and data on file for usage of 5 mg versus 10 mg.

6.48 Table 14 presents the estimated use and financial implications. The submission added, rather than subtracted, the co-payments. The revised estimates are provided in the table below.

Table 14: Estimated use and financial implications

	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts, PBS[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts, RPBS[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of OCA (effective price)						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for cholestramine (treatment for pruritus)						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS/MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[a] Assuming 12.17 per year as estimated by the submission.
Source: Table 4.2.1 and Table 4.2.2, p240, Table 4.2.5, p242, Table 4.5.6, p249 of the submission and corrected during evaluation

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be $30 – $60 million per year.

6.49 The net cost to the PBS/RPBS over six years was estimated to be more than $100 million per year.

6.50 The DUSC considered that the estimates presented in the submission were uncertain and likely to be underestimated. The main issues were:

- The prevalence of PBC may have been underestimated. The submission used a linear extrapolation of two Australian research studies from 1993 and 2002 to estimate prevalence. The DUSC considered that this should have been tested by triangulating the data with UDCA PBS utilisation data, which indicated that there were approximately 2,575 PBC patients in 2017, suggesting that the submission's PBC prevalence estimates were underestimated. The pre-PBAC Response (p3) claimed that UDCA PBS utilisation data could overestimate the PBS population as it might also include use to reduce gallstone formation, improve bile flow in patients with cystic fibrosis, in newborn infants with impaired bile flow and after bariatric surgery.
- The proportion of patients eligible for treatment may have been underestimated as patients currently treated with UDCA may switch to OCA monotherapy to avoid diarrhoea. The UDCA non-responder rate may be higher if obeticholic acid was available. In the pre-PBAC Response (p3) it was noted that the majority of patients experience inadequate efficacy (92-94%), rather than intolerance to UDCA; therefore, the number of patients switching to OCA following diarrhoea with UDCA would be small. The uptake rates (20% in Year 1, which increased to 75% in Year 6)

were uncertain and may have been underestimated. DUSC did not agree with the PSCR which suggested low uptake rates were justified as patients would wait until their annual review to see their physician. DUSC considered patients would approach their physicians earlier if they became aware that a new treatment was available on the PBS.

- The adherence rate of 93.6% may have been overestimated as the completion rate at 12 months was 90% for the OCA 5-10 mg titration group and 88% for the OCA 10 mg group in the POISE trial. The pre-PBAC Response (p3) conceded that there could be some overestimation of the adherence rate. Adjusted dosing regimens were also not accounted for, which may have contributed to an overestimation of the number of prescriptions per year. The MBS costs attributable to doctor's visits may have been overestimated. DUSC was of the opinion that patients with PBC will visit their doctor regularly, irrespective of the occurrence of side effects, and therefore an increase in number of visits is not expected. The pre-PBAC Response (p3) agreed with DUSC.

6.51 In addition, the DUSC were concerned that there was potential for use outside of the restriction in UDCA responders. The DUSC and PBAC considered that OCA may be added to be added to UDCA therapy in an effort to improve biochemical markers, such as bilirubin, which are correlated with an increase in survival. In the pre-PBAC Response (p3) the sponsor indicated that a Risk Sharing Arrangement through a Deed of Agreement could be implemented to mitigate the risk of leakage.

Quality Use of Medicines

6.52 The submission did not provide any information on the quality use of medicine. The evaluation considered that information for prescribers and patient materials should be provided, especially given that this is a rare condition, the proposed PBS restriction is for it to be listed under Section 85, and prescribers are unlikely to be familiar with the medication.

For more details on PBAC's view, see Section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of obeticholic acid (OCA) as a second-line agent in the treatment of primary biliary cholangitis (PBC). Although acknowledging the clinical need for effective PBC treatments, the PBAC considered that the magnitude of the clinical benefit was uncertain, the incremental cost-effectiveness ratio (ICER) was unacceptably high and uncertain and the estimated financial impact was high.

7.2 The PBAC considered that the proposed clinical management algorithms, in which OCA was used in combination with ursodeoxycholic acid (UDCA) in patients who have an inadequate response to UDCA and as monotherapy in patients who are intolerant

to UDCA, were broadly appropriate. However, the PBAC considered that they should include a stopping rule for patients who are intolerant, or fail to respond, to OCA.

7.3 The PBAC considered that the proposed PBS restriction should align with the inclusion and exclusion criteria of the POISE trial which excluded patients with severe liver disease and immunodeficiency diseases and required patients to have either an alkaline phosphatase (ALP) ≥ 1.6 x upper limit of normal (ULN) or total bilirubin > ULN but < 2 x ULN. The PBAC also considered that the proposed restriction required the inclusion of specific continuing and stopping criteria and explicit instructions surrounding the need for dosage adjustment in patients who experience severe pruritus or moderate or severe hepatic impairment.

7.4 The PBAC considered that UDCA monotherapy was the appropriate comparator for patients who have an inadequate response to UDCA and that placebo was the appropriate comparator for those who are UDCA intolerant.

7.5 The PBAC considered that the therapeutic claim of superior effectiveness for OCA plus UDCA compared to UDCA monotherapy in patients who were inadequate UDCA responders was reasonable. However, the PBAC noted that the magnitude of the benefit was uncertain given the small sample sizes of the clinical trials and the short mean duration of follow-up (12 months) in the key trial, POISE, given that PBC is a chronic disease. The PBAC also considered that the low rate of response (less than half of OCA treated patients achieved the primary outcome in POISE) contributed to the uncertainty.

7.6 The PBAC considered that the therapeutic claim of non-inferior safety for OCA plus UDCA compared to UDCA monotherapy in patients who were inadequate UDCA responders was not reasonable based on the incidence of adverse events in the POISE trial.

7.7 The PBAC considered it was not possible to assess the efficacy or safety of OCA monotherapy against placebo in patients who were intolerant to UDCA due to insufficient data.

7.8 The PBAC acknowledged that PBC is a rare disease and that this was reflected in the quantity of the clinical evidence, particularly with regards to the population of patients who are intolerant to UDCA.

7.9 The PBAC considered that the economic model presented in the submission lacked transparency and clinical plausibility and was insufficient to inform decision making. The PBAC considered that the ICERs presented in the submission were unacceptably high, sensitive to changes in key variables and should be interpreted with caution. The PBAC raised a number of concerns, including:

- a number of the transition probabilities from the biochemical health states to the liver disease health states and between the liver disease health states were unable to be verified;

- the 50 year time horizon of the model was long compared to the duration of follow-up in the POISE trial (12 months);
- the mean age of patients entering the model was 47, which based on the age of diagnosis of PBC, rather than 56, which was the mean age of patients in the POISE trial;
- patients treated with OCA remained in the same biochemical health state from Year 2 onwards. This lacked validity considering the progressive nature of the disease; and
- other structural and input issues noted by ESC and outlined in paragraph 6.39 above.

7.10 The PBAC considered that although the utilisation estimates presented in the submission were likely to be underestimated (see paragraph 6.50), the financial impact of OCA to the PBS/RPBS estimated in the submission was high ($30 – $60 million in Year 6 for less than 10,000 patients). The PBAC noted that the significant opportunity cost of listing OCA was a concern in the context of the uncertain magnitude of the clinical benefit and the unreliability of the ICER.

7.11 The PBAC was concerned that there was potential for OCA to be used in combination with UDCA in patients with an adequate response to UDCA in an effort to further improve biochemical markers, which are correlated with an increase in survival. The PBAC considered that a Risk Sharing Arrangement would be an appropriate method of mitigating the risk of leakage.

7.12 The PBAC noted that the condition primary biliary cirrhosis has recently been renamed primary biliary cholangitis. The PBAC recommended that the ursodeoxycholic acid PBS restriction should be updated to reflect the updated terminology.

7.13 The PBAC considered that any future resubmission should be a major submission to allow for evaluation of the economic modelling and financial impact.

7.14 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor understands the reasons for the PBAC's decision. Feedback from the Committee on the issues which require further clarification is appreciated and Emerge Health is committed to working with the PBAC, the clinical community and patient organisations to ensure obeticholic acid (OCA) is accessible to patients as a second-line agent in the treatment of primary biliary cholangitis (PBC).