

Obeticholic acid for treating primary biliary cholangitis

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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1 Recommendations

- 1.1 Obeticholic acid is recommended, within its marketing authorisation, as an option for treating primary biliary cholangitis in combination with ursodeoxycholic acid for people whose disease has responded inadequately to ursodeoxycholic acid or as monotherapy for people who cannot tolerate ursodeoxycholic acid. Obeticholic acid is recommended only if the company provides it with the discount agreed in the patient access scheme.

- 1.2 Assess the response to obeticholic acid after 12 months. Only continue if there is evidence of clinical benefit.

2 The technology

Information on obeticholic acid

Description of the technology	Ocaliva, Intercept Pharma. Obeticholic acid is a selective and potent agonist for the farnesoid X receptor (FXR), a nuclear receptor expressed at high levels in the liver and intestine. FXR is thought to be an important regulator of bile acid, inflammatory, fibrotic and metabolic pathways. FXR activation lowers intracellular hepatocyte concentrations of bile acids by suppressing de novo synthesis from cholesterol, and by increasing transport of bile acids out of the hepatocytes. These mechanisms limit the overall amount of bile acid circulating in the body while promoting secretion of bile by the liver and reducing hepatic exposure to bile acids.
Marketing authorisation	A conditional marketing authorisation was received for the treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid in people whose disease responded inadequately to ursodeoxycholic acid or as monotherapy in people who cannot tolerate ursodeoxycholic acid.
Adverse reactions	For full details of adverse reactions and contraindications, see the summary of product characteristics for obeticholic acid .
Recommended dose and schedule	The starting dose is 5 mg once daily. Based on an assessment of tolerability after 6 months, the dose should be increased to 10 mg once daily to have optimal response.
Price	Obeticholic acid 5 mg or 10 mg costs £2,384.04 per 30-tablet pack. Costs may vary in different settings because of negotiated procurement discounts. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of obeticholic acid, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The [appraisal committee](#) considered evidence submitted by Intercept Pharma and a review of this submission by the evidence review group. See the [committee papers](#) for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of obeticholic acid, having considered evidence on the nature of primary biliary cholangitis (PBC, previously known as primary biliary cirrhosis) and the value placed on the benefits of obeticholic acid by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical management of primary biliary cholangitis

- 4.1 The committee heard from patient experts that PBC has an asymptomatic phase, and may be diagnosed incidentally when blood tests are done for other reasons. Most patients are women, and when symptoms develop they can be non-specific and may be thought to be because of other causes, such as the menopause. But they can become debilitating, and include chronic fatigue, pruritus and joint pain. The committee was aware that if untreated, PBC shows an unpredictable rate of progression through various phases: preclinical, asymptomatic, symptomatic, and liver insufficiency. This can lead to premature death unless the patient has a successful liver transplant. Unfortunately, PBC can recur even after a successful transplant. The only disease-modifying treatment currently available is ursodeoxycholic acid and this is recommended for all patients diagnosed with PBC, to restore their liver function to as close to normal as possible. If PBC is successfully treated with ursodeoxycholic acid, the risk of progression is kept low and patients have a normal life expectancy. The patient experts explained that adjusting to a diagnosis of a progressive incurable disease was very difficult and to then find that the only available treatment was not working is a devastating blow. The committee heard that patients whose disease has responded inadequately to ursodeoxycholic acid are likely to progress rapidly and die from the disease within 5 to 7 years. The committee concluded that there is a high unmet need for patients who cannot tolerate ursodeoxycholic acid, or whose disease does not respond to it, and recognised that the availability of additional treatment options would be highly valued by patients and families.
- 4.2 The clinical experts advised that because the disease is asymptomatic in its early stages and diagnosis is difficult, patients may not be diagnosed until significant

liver damage has occurred. The first biochemical sign of PBC is an elevated alkaline phosphatase level (ALP). As liver disease progresses, the total bilirubin level will also rise, which is an indicator of significant liver damage. Cirrhosis is probably already present at this stage. When managing PBC, it is important to define the person's risk of progression to severe liver complications and death from the disease. This mainly includes the biomarkers ALP and total bilirubin, but there are other factors such as early age of onset, which may be associated with more aggressive disease. The clinical experts explained that biochemical markers such as ALP and total bilirubin levels are appropriate to decide whether patients are at low or high risk of disease progression. The committee was aware that ALP and total bilirubin levels have been shown to correlate with transplant-free survival up to 15 years. The clinical experts confirmed that these biochemical markers are appropriate and validated surrogate outcomes for PBC. The committee concluded that it was appropriate to use ALP and total bilirubin levels as surrogate outcomes to assess the clinical effectiveness of obeticholic acid.

- 4.3 The clinical experts advised that guidelines from the British Society of Gastroenterology and UK-PBC and European Association for the Study of the Liver recommend ursodeoxycholic acid for all patients with PBC. Response to treatment is assessed at 1 year based on ALP levels. The committee heard that threshold ALP levels of at least 1.67 times the upper limit of normal (or elevated total bilirubin levels consistent with later stage disease [greater than the upper limit of normal]) are widely used to identify patients whose condition has responded inadequately to treatment with ursodeoxycholic acid. The experts noted that about 20% to 30% of patients have disease which does not respond to treatment with ursodeoxycholic acid, and a further 5% to 10% cannot tolerate it because of adverse effects. The clinical experts stated that although fibrates were included in the final scope, they are not used very often in clinical practice. Also, they are not disease-modifying drugs and so for these reasons fibrates are not an appropriate comparator. Therefore, for patients who cannot tolerate ursodeoxycholic acid, or whose disease does not respond to it, liver transplant is the only available effective treatment. The committee heard from the patient expert that there is a high level of fear associated with liver transplant because it involves major surgery with potential complications, and uncertain outcomes. Patients feel helpless while waiting for a liver transplant because their condition is rapidly progressing and there is limited availability of donated livers; many patients die while on the waiting list. Also, patients are concerned that a liver

transplant does not always cure the disease and there is a risk of transplant failure or recurrence of PBC. The committee concluded that ursodeoxycholic acid monotherapy is the most appropriate comparator for obeticholic acid plus ursodeoxycholic acid in people with PBC that does not adequately respond to ursodeoxycholic acid. No treatment is the most relevant comparator for people who cannot tolerate ursodeoxycholic acid.

Clinical effectiveness of obeticholic acid

- 4.4 The committee considered the clinical evidence for obeticholic acid plus ursodeoxycholic acid compared with ursodeoxycholic acid plus placebo from the POISE trial, and obeticholic acid monotherapy compared with placebo for adults who cannot tolerate ursodeoxycholic acid. The committee heard that people who took part in POISE were mainly women (91%) and younger than 65 years (81%). The mean age of patients entering the trial was 55.8 years, with a mean age at diagnosis of 47. Inclusion criteria included a serum ALP level of at least 1.67 times the upper limit of normal, and/or elevated total bilirubin level of at least 1.0 times the upper limit of normal. The clinical experts confirmed that these patient characteristics reflect those of people who would be considered for treatment with obeticholic acid in clinical practice. The committee heard that a small number of patients (n=11) in the trial could not tolerate ursodeoxycholic acid. It heard from the clinical experts that this reflects the relatively small number of patients in clinical practice who cannot take ursodeoxycholic acid. These patients were randomised to placebo or obeticholic acid monotherapy. The clinical expert stated that a phase 2 trial of obeticholic acid monotherapy in 50 patients had a similar response rate to that in POISE. The committee heard from clinical experts that the primary outcome (ALP level lower than 1.67 times the upper limit of normal, total bilirubin within the below or equal to upper limit normal and ALP decrease of at least 15% from baseline) used in POISE was quite challenging because of the need to fulfil all 3 criteria. They considered that ALP decrease of less than 15% was clinically meaningful. The committee also noted that not all patients in the titration arm of POISE had their dose of obeticholic acid adjusted up from 5 mg to the higher dose of 10 mg as recommended in the summary of product characteristics. Therefore they might not have had as great a benefit in the trial as would be seen in clinical practice. The committee concluded that the results of POISE are generalisable to the intended use of obeticholic acid in

clinical practice in England, but noted the lack of evidence for the clinical effectiveness of obeticholic acid monotherapy in those who cannot tolerate ursodeoxycholic acid.

- 4.5 The committee noted the higher number of people who were classed as responders according to the primary outcome in POISE for obeticholic acid plus ursodeoxycholic acid compared with placebo plus ursodeoxycholic acid (47% in the obeticholic acid 10 mg group and 46% in the obeticholic acid titration group compared with 10% in the placebo group, $p < 0.0001$ for both comparisons). Obeticholic acid plus ursodeoxycholic acid was also more effective at lowering ALP levels by at least 40% from the baseline (34% in the obeticholic acid 10 mg group and 30% in the obeticholic acid titration group, compared with 1% in the placebo group). Obeticholic acid plus ursodeoxycholic acid was more effective at lowering the total bilirubin level, which at 12 months was 9.7 for the obeticholic acid 10 mg group, 9.9 for the obeticholic acid titration group, and 13.2 for the placebo group. The committee concluded that obeticholic acid plus ursodeoxycholic acid is clinically effective in improving the surrogate outcomes associated with the progression of PBC.

Adverse events

- 4.6 The committee noted that in POISE the overall frequency of adverse events was similar in the 3 treatment groups. The committee heard that pruritus was the most common adverse event with obeticholic acid, occurring in 66% of patients taking 10 mg, and 50% of patients taking 5 mg, compared with 37% in the placebo arm. The clinical experts explained that pruritus is also a common symptom of PBC and they are experienced in managing it effectively. The patient expert told the committee that there is anecdotal evidence from the US that the pruritus may be temporary and may resolve after 3 months. The committee concluded that obeticholic acid is generally well tolerated and the adverse events can be managed satisfactorily.

Cost effectiveness

The model

- 4.7 The committee considered the company's cost-effectiveness evidence and the evidence review group (ERG) review. The company's de novo economic model assessed the cost effectiveness of obeticholic acid plus ursodeoxycholic acid compared with ursodeoxycholic acid alone based on the POISE population. The model comprised 2 parts: biomarker and liver disease. The biomarker part of the model had 3 health states: low, moderate and severe, which reflect the risk of disease progression. The liver disease part included significant liver disease, including decompensated cirrhosis, hepatocellular carcinoma, pre-transplant state, transplantation, re-emergence of PBC and death. Patients entered the biomarker part of the model in the moderate or severe risk state but could move between the 3 health states. They could only move to the liver disease part of the model from the severe risk state of the biomarker component. The committee noted that the model was similar to those used in previous appraisals, with the addition of a pre-liver transplant health state. It heard from the company that this health state was added to capture the deterioration in quality of life and the costs associated with rapidly progressing disease, and the significant and documented risk of PBC patients dying while awaiting transplant. The committee concluded that the structure of the model was suitable for decision-making and further considered some of the key assumptions within the model where it agreed that the ERG had raised valid issues for further consideration.

Transition probabilities

- 4.8 The transition probabilities governing the movement of patients in the biomarker part of the company's model in the first 12 months were based on several sources. Transition probabilities for the obeticholic acid plus ursodeoxycholic acid and obeticholic acid monotherapy arm were based on individual patient data from POISE. Transition probabilities for people whose disease has responded inadequately to ursodeoxycholic acid were calibrated based on PBC-specific data from the literature. These used 10-year liver transplant-free survival estimated from [GLOBE \(an international collaboration between medical centres doing PBC](#)

research) and UK risk scores. This was because POISE data for this arm were not available for all health states in the model or beyond the 12 months of the trial. For patients who cannot tolerate ursodeoxycholic acid, transition probabilities were estimated from a study of ursodeoxycholic acid compared with no treatment in PBC (Corpechot et al. 2000). Transition probabilities in the liver disease component were mostly derived from those used in NICE's technology appraisal guidance on sofosbuvir for treating chronic hepatitis C. The ERG noted that the way transition probabilities were calibrated in the ursodeoxycholic acid arm was not transparent, and for consistency it would be better to derive them from trial data. Also, the committee considered whether the assumption of no progression from the low or moderate risk state to the severe risk state after 12 months was plausible. The committee noted that clinical advice to the ERG was that this assumption was reasonable, based on the fact that existing data on ursodeoxycholic acid showed that an ALP level of normal or less than 1.67 times the upper limit of normal (which corresponds to the low-risk health state in the biomarker model) was associated with an excellent long-term prognosis with no overall effect on life expectancy. The committee heard from the company that this assumption was supported not only by data for ursodeoxycholic acid, but also by 5-year data from the extension of POISE, which showed a lasting response with obeticholic acid. The clinical experts also stated that a phase 2 trial of obeticholic acid as monotherapy reported only 5% progression over a 15-year time horizon, indicating lasting benefit. The committee concluded that the transition probabilities used in the obeticholic acid arm of the model are plausible but there is uncertainty about whether the transition probabilities used in the ursodeoxycholic acid arm are the most appropriate. Given the 12-month duration of the trial, there is some uncertainty about the long-term modelling in both treatment arms.

Utility values

- 4.9 Health-related quality-of-life data were not collected in POISE so the company used utility values from published literature (Younossi et al. 2001 and Wright et al. 2006, used in NICE's technology appraisal guidance on sofosbuvir for treating chronic hepatitis C). Utility values were assumed to be constant over time in each of the health states of the biomarker part of the model but decreased as patients moved to the liver disease part. The committee considered whether the

confidential decrement applied to the decompensated cirrhosis, pre-transplant and liver transplant states based on clinical advice to the company was appropriate. The committee heard from the clinical experts that they considered it reasonable to consider a lower utility for some of the advanced liver disease states in PBC compared with hepatitis because of the additional morbidity related to having cholestasis as well as fibrosis. Also, the committee noted that the company used a utility value of 0.84 for the low and moderate risk states in the biomarker part of the model. The ERG noted that this is higher than the UK age-adjusted utility, and also that utility was not age adjusted over time. The committee noted that the utility values were derived from published sources and that patients with PBC may be asymptomatic. It was aware of a study of utility in people with hepatitis C (Vera-Llonch et al. 2013, considered in NICE's guidance on sofosbuvir for treating chronic hepatitis C). This reported a utility of 0.91 pre-treatment, which was also noted by the authors to be higher than the corresponding published US population norm (mean [standard error] index 0.87 [0.01]) for people aged 45 to 54. The committee acknowledged the uncertainty associated with the utility values but accepted that they had been derived from published sources.

Cost-effectiveness results

4.10 The committee noted that the company's model predicted that obeticholic acid plus ursodeoxycholic acid increased both length of life and quality of life compared with ursodeoxycholic acid alone. The company's deterministic base-case incremental cost-effectiveness ratio (ICER, using the patient access scheme) for obeticholic acid plus ursodeoxycholic acid compared with ursodeoxycholic acid alone was £28,281 per quality-adjusted life year (QALY) gained (incremental costs £164,814; incremental QALYs 5.83). The committee also noted that the ICER for obeticholic acid compared with placebo in the population who cannot tolerate ursodeoxycholic acid was lower, at £21,351 per QALY gained. It considered that it would not be able to make separate recommendations for one or other group, particularly given the very limited clinical data for the population who cannot tolerate ursodeoxycholic acid. Therefore it gave further detailed consideration to the company's higher ICER for obeticholic acid plus ursodeoxycholic acid compared with ursodeoxycholic acid alone. It also examined the impact of uncertainty around the use of POISE data

and the utilities in the model. The committee considered the effect of the ERG's amendments to the company's model. It considered the transition probabilities in the ursodeoxycholic acid arm and the utilities used in the model (see the [committee papers](#)) to be the key areas of uncertainty in modelling the cost effectiveness of obeticholic acid in PBC.

- 4.11 The committee noted that in clinical practice, obeticholic acid would be recommended for a mixed group of patients: some who cannot tolerate ursodeoxycholic acid (5% to 10% of people) and a larger number (20% to 30%) whose disease had not responded adequately to ursodeoxycholic acid. Although the number of people in the trial who could not tolerate ursodeoxycholic acid was small, the cost-effectiveness estimates were consistently lower than for those whose disease did not respond to ursodeoxycholic acid. Therefore the ICER for the whole population of patients considered for treatment with obeticholic acid would be somewhere between the ICERs for the population who cannot tolerate ursodeoxycholic acid and the population whose disease has not responded to ursodeoxycholic acid.
- 4.12 The committee noted the ERG's concern related to the derivation of the transition probabilities used in the ursodeoxycholic acid arm for both the first 12 months and the longer term. This was an attempt to achieve consistency between progression of PBC in the model and that in the published literature. The committee noted that the ERG considered replacing existing trial data with the short-term transition probabilities obtained from the literature to be inappropriate. Although it considered calibrating the trial data to published evidence to obtain long-term data was justified by the lack of long-term data to inform patients' prognosis, the ERG noted that the calibration approach employed by the company was not transparent and that the resulting model predictions did not match the published evidence. The ERG considered unadjusted POISE data more appropriate in the ursodeoxycholic acid arm for the first 12 months, which increased the company base case from £28,425 per QALY gained to £32,897 per QALY gained (incremental costs £171,036; incremental QALYs 5.20). The ERG also considered that extrapolating the POISE 12-month data over the long term (beyond 12 months) in the biomarker component of the model was more appropriate than the company's approach of using published data on long-term outcomes in PBC. This would result in a further rise in the ERG's base case. The committee appreciated that long-term modelling presented significant

challenges. It accepted that without effective treatment people whose disease had not responded to ursodeoxycholic acid may progress at slightly different rates, but have a very poor prognosis. Liver disease may progress faster once it becomes established. This may not be captured in the first 12 months of treatment. The committee concluded that it was not unreasonable to use other published data to try to replicate the expected course of disease in those whose disease had not responded to ursodeoxycholic acid and considered the company's approach for decision making acceptable, although there remained uncertainty in the trajectory of disease progression in the ursodeoxycholic acid arm.

- 4.13 The committee further considered the utility values used. It noted that the ERG's suggested adjustment of utilities, to take account of lower utility in the UK population, and an age-related decrement, increased the ICER for obeticholic acid plus ursodeoxycholic acid to £33,458 per QALY gained compared with ursodeoxycholic acid alone (incremental cost £164,808; incremental QALYs 4.93). The committee concluded that there were many uncertainties around the utility values used in the model but considered that a utility value of 0.84 in the low and moderate risk group was not implausible and was in line with published evidence, and it agreed that an age-related decrement over time should have been incorporated into the model. The committee concluded that the most plausible ICER for people whose disease had not responded to ursodeoxycholic acid would be around the upper limit of what could be considered cost effective. It therefore considered what other factors might justify accepting it as a cost-effective use of NHS resources.

Innovation

- 4.14 The committee heard from the company that obeticholic acid is innovative because of its mechanism of action as a farnesoid X receptor agonist. Obeticholic acid also has an anti-inflammatory action, which may provide additional efficacy in this disease. The committee accepted the innovative nature of the treatment, and considered that this was a major change in the management of PBC. The committee noted in particular that the results in 47% of people in the obeticholic acid arm of POISE met the strict criteria for response, despite the current standard of care, ursodeoxycholic acid, not having been effective. This response

would be associated with a very favourable prognosis.

Other considerations

- 4.15 The committee was aware that if PBC was controlled, people could have an excellent outcome and normal life expectancy. However, people whose disease had not responded to, or had been unable to tolerate the only available preventative treatment, were likely to decline rapidly. The committee considered that the potential restoration of normal life expectancy was a huge benefit, and this was not often possible in such serious conditions.
- 4.16 The committee was aware that because people whose disease responds to obeticholic acid are at a much lower risk of disease progression, the drug may delay or prevent the need for liver transplant. The committee considered that avoiding liver transplant was of great importance to PBC patients. The committee heard that PBC is the most common indication for liver transplant in women over 50. It was also aware of the scarcity of donor organs and that other patients on the transplant waiting list for other reasons might benefit if obeticholic acid were available. The committee noted that this opportunity cost of liver transplant on other people on the waiting list had not been captured in the cost-effectiveness estimates of obeticholic acid for people with PBC.
- 4.17 The committee was aware that the clinical benefit of obeticholic acid may be underestimated in the trial because of the lack of adjustment up to the recommended dose in some patients. Taking all factors into consideration, the committee concluded that obeticholic acid could be considered a cost-effective use of NHS resources.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

- 4.18 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism

should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee's key conclusions

Key conclusion

- Section 4.16: Obeticholic acid is clinically effective in people with primary biliary cholangitis (PBC) who cannot tolerate or whose disease does not respond to ursodeoxycholic acid. A higher number of people on obeticholic acid plus ursodeoxycholic acid met the primary outcome based on alkaline phosphatase and total bilirubin levels than people treated with ursodeoxycholic acid alone. The committee has taken into consideration the innovative nature of obeticholic acid and the unmet need of patients for whom there was no effective treatment. The committee noted that the benefits of not needing a liver transplant for people whose disease is treated with obeticholic acid have not been included in the model. Obeticholic acid could be considered a cost-effective use of NHS resources.

Current practice

Clinical need of patients, including the availability of alternative treatments

- Section 4.1: Patients with PBC are currently treated with ursodeoxycholic acid, but patients who cannot tolerate it or whose disease does not respond to ursodeoxycholic acid have no other treatment option. The committee heard that there is a high unmet need for patients whose disease does not respond to, or who cannot tolerate ursodeoxycholic acid, and recognised that the availability of additional treatment options would be highly valued by patients and families.

The technology

How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?

- Sections 4.13 and 4.14: Obeticholic acid in combination with ursodeoxycholic acid or alone helps to normalise alkaline phosphatase (ALP) and total bilirubin levels and reduces the risk of PBC progression. People with normal liver biochemistry are expected to have an excellent prognosis with a normal life expectancy.
- Obeticholic acid is innovative because of its mechanism of action as a farnesoid X receptor agonist. It is a novel, innovative therapy for patients with PBC. It also has an anti-inflammatory action, which may provide additional efficacy in this disease.

What is the position of the treatment in the pathway of care for the condition?

- Section 4.3: Obeticholic acid is recommended in combination with ursodeoxycholic acid or as monotherapy in patients whose disease has responded inadequately to, or who cannot tolerate ursodeoxycholic acid.

Adverse reactions

- Section 4.6: Obeticholic acid is generally well tolerated and the adverse events can be managed satisfactorily. The main adverse effect of the treatment is pruritus.

Evidence for clinical effectiveness

Availability, nature and quality of evidence

- Section 4.4: Evidence for clinical effectiveness of obeticholic acid plus ursodeoxycholic acid and obeticholic acid monotherapy was based on a randomised controlled double blinded trial (POISE) which was assessed as good quality.

Relevance to general clinical practice in the NHS

- Section 4.4: The committee considered the people enrolled in the POISE to be generalisable to people with PBC in the NHS in England.

Uncertainties generated by the evidence

- Section 4.4: The committee considered there to be uncertainty in the clinical effectiveness of obeticholic acid monotherapy in those who cannot tolerate ursodeoxycholic acid because of the small number of patients in the pivotal trial. Clinical experts noted that the small patient number in the trial reflect the minority of patients who are unable to take ursodeoxycholic acid in clinical practice.

Estimate of the size of the clinical effectiveness including strength of supporting evidence

- Section 4.5: The higher number of people whose results met the primary outcome in POISE for obeticholic acid plus ursodeoxycholic acid compared with placebo plus ursodeoxycholic acid (47% in the obeticholic acid 10 mg group and 46% in the obeticholic acid titration group compared with 10% in the placebo group, $p < 0.0001$ for both comparisons). Obeticholic acid plus ursodeoxycholic acid was also more effective at lowering ALP levels by at least 40% from the baseline (34% in the obeticholic acid 10 mg group and 30% in the obeticholic acid titration group compared with 1% in the placebo group). Obeticholic acid plus ursodeoxycholic acid was more effective at lowering the total bilirubin level, which at 12 months was 9.7 for the obeticholic acid 10 mg group, 9.9 for the obeticholic acid titration group, and 13.2 for the placebo group.

Evidence for cost effectiveness

Availability and nature of evidence

- Section 4.7: The company's de novo economic model assessed the cost effectiveness of obeticholic acid plus ursodeoxycholic acid compared with ursodeoxycholic acid alone based on the POISE population. Also obeticholic acid monotherapy compared with placebo was assessed based on small patient numbers ($n=11$).

Uncertainties around and plausibility of assumptions and inputs in the economic model

- Section 4.10: The uncalibrated transition probabilities in the ursodeoxycholic acid arm and the age adjustment of utilities in health states of the model were considered to be

the key areas of uncertainty in modelling the cost effectiveness of obeticholic acid in PBC.

Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?

- Section 4.9: The utility values were derived from published sources of people with hepatitis C which were adjusted because people with PBC and substantial liver disease have a worse quality of life than people with hepatitis. There was uncertainty in the utility values because the utility for low and moderate risk of progression of PBC was higher than the UK age adjusted utility. However, the committee was aware that a study of utility in people with hepatitis C, a pre-treatment of 0.91 was also higher than the corresponding published US population norm for people aged 45 to 54. The committee acknowledged the uncertainty associated with the utility values. The committee agreed that an age-related decrement over time should have been incorporated into the model.

What are the key drivers of cost effectiveness?

- Sections 4.11 and 4.12: Using unadjusted POISE data in the ursodeoxycholic acid arm for the first 12 months increased the company base case from £28,425 per quality-adjusted life year (QALY) gained to £32,897 per QALY gained. Using lower utility in the UK population and an age-related decrement, increased the incremental cost-effectiveness ratio to £33,458 per QALY gained.

Most likely cost-effectiveness estimate (given as an ICER)

- Section 4.9: The committee was not able to define a most plausible ICER but concluded for people whose disease had not responded to ursodeoxycholic acid that it would be around the upper limit of what could be considered cost effective.

Additional factors taken into account

Patient access schemes (PPRS)

- Section 1: Obeticholic acid is recommended only if the company provides it with the

discount agreed in the patient access scheme.

5 Implementation

- 5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has PBC and the doctor responsible for their care thinks that obeticholic acid is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee A](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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