NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Seladelpar for previously treated primary biliary cholangitis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using seladelpar in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: July 2025

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using seladelpar in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 20 August 2025
- Second evaluation committee meeting: 10 September 2025
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Seladelpar should not be used to treat primary biliary cholangitis, including pruritus, in adults:

- with ursodeoxycholic acid (UDCA), if the primary biliary cholangitis has not responded well enough to UDCA, or
- alone, if UDCA cannot be tolerated.

1.2 This recommendation is not intended to affect treatment with seladelpar that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Seladelpar is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because the available evidence does not suggest that seladelpar offers value for money in this population.

Why the committee made these recommendations

Usual treatment in NHS practice for primary biliary cholangitis is UDCA. If UDCA does not work well enough, licensed add-on treatments include obeticholic acid or elafibranor. People who cannot tolerate UDCA may also have obeticholic acid or elafibranor. But there are uncertainties about the treatment pathway.

Clinical trial evidence shows that seladelpar reduces liver enzymes, which are raised in primary biliary cholangitis, more than placebo. This suggests that seladelpar could

delay the condition getting worse. Clinical trial evidence also shows that seladelpar reduces pruritus (itch) compared with placebo.

Seladelpar has not been compared in a clinical trial with obeticholic acid or elafibranor. The results of an indirect comparison are highly uncertain. It is unclear whether seladelpar reduces liver enzymes compared with obeticholic acid or elafibranor. But there may be a reduced itch with seladelpar compared with obeticholic acid.

It is not clear if the company's economic model fully reflects the effect of itching and other aspects of primary biliary cholangitis on quality of life. The cost-effectiveness estimates are uncertain and are above the range that NICE considers an acceptable use of NHS resources. So, seladelpar should not be used.

2 Information about seladelpar

Marketing authorisation indication

2.1 Seladelpar (Livdelzi, Gilead) is indicated for 'the treatment of primary biliary cholangitis (PBC), including pruritus, in adults in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for seladelpar.

Price

2.3 The list price of seladelpar is £3,155.00 per 30-tablet pack of 10 mg tablets (excluding VAT; company submission).

2.4 The company has a commercial arrangement, which would have applied if seladelpar had been recommended.

Carbon reduction plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Gilead will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Gilead, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Primary biliary cholangitis

3.1 Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune condition that leads to a build-up of bile in the liver. This happens because the body's immune system destroys bile ducts in the liver, causing cholestasis. This means that the flow of bile through the liver and biliary system is impaired or stalled. Over time, chronic cholestasis leads to scarring of the liver (fibrosis and cirrhosis) and liver failure, and can ultimately lead to death. The cause of PBC is not known, but it is thought to be a mix of environmental and genetic factors. PBC is typically diagnosed by testing for biochemical indicators of liver function (such as alkaline phosphatase [ALP]). Many people do not have symptoms until they have significant liver damage. Common symptoms include itchy skin (pruritus) and fatigue. Around 20,000 people in the UK have PBC, with an annual incidence of 2 to 3 per 100,000. PBC is more common in women (90%) and in people aged over 40 (75%). The patient group submissions described the challenges of living with PBC, such as severe fatigue and severe itching. The patient expert elaborated that there is both the physical fatigue felt in the body, affecting movement and the ability to do daily activities, and the mental and physical exhaustion that comes with itch. The patient expert and patient group submissions emphasised that the chronic symptoms greatly affect people with PBC and their families and carers. They said that symptoms affect quality of life, sleep and the

ability to work or manage daily activities. The patient experts reported that people with PBC often experience a delayed diagnosis, which can lead to feelings of isolation, confusion and frustration because of unexplained symptoms. While having a diagnosis can bring relief, the rarity of the condition means that many people have never heard of it, and this can reinforce feelings of isolation. PBC can progress unpredictably to cirrhosis or liver cancer, with some people eventually needing a liver transplant. This adds to feelings of anxiety and uncertainty. The committee concluded that PBC has a substantial effect on people's lives.

Clinical management

Treatment pathway and positioning of seladelpar

3.2 There are no NICE guidelines specifically for the treatment of PBC. The most relevant available guidelines were the British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. These were developed before the appraisal of newer treatments such as NICE's technology appraisal guidance on elfibranor for previously treated primary biliary cholangitis (from now, TA1016). The clinical expert explained that first-line treatment for PBC is UDCA. People whose PBC has an inadequate response to UDCA (as defined as ALP above 1.67 times the upper level of normal [ULN]) have obeticholic acid (OCA), elafibranor or fibrates (off-label treatment), with or without UDCA as a second-line treatment. People who cannot tolerate UDCA have OCA, elafibranor or fibrates. OCA is recommended in NICE's technology appraisal guidance on OCA for treating primary biliary cholangitis (from now, TA443) and elafibranor is recommended in TA1016. The care pathway is structured in a way that to start licensed second-line treatments, people must first be seen by a multidisciplinary team. Patient organisations explained that there are frustrations with variation in care and difficulties accessing specialist teams, especially for the approximately 40% of people who need second-line treatment after UDCA. Access to these treatments can vary, and some, like OCA, have

more side effects. Treatments for symptoms, such as colestyramine for itching, can also be difficult to take. The company proposed that seladelpar should be primarily positioned as a second-line treatment for people who have an inadequate response to, or cannot tolerate, UDCA. It said that it may also be considered a third-line option for people who cannot tolerate or whose condition has not responded to OCA. The clinical expert noted that seladelpar and elafibranor have similar mechanisms of action. The reported benefit of seladelpar in normalising ALP levels meant that the clinical expert would be keen to use it as early in the treatment pathway as possible. The clinical expert noted that people needing OCA and seladelpar may be different: people with high transaminase levels may benefit from having OCA, and people with pruritus may benefit from having seladelpar. This is because OCA has an increased risk of worsening pruritus, and seladelpar may reduce pruritus. The committee noted that the clinical effectiveness of seladelpar in later lines of treatment is uncertain because data on third-line use is limited. The committee concluded that seladelpar would be positioned as a second-line treatment and that it may also be used at third line.

Excluding fibrates as comparators

3.3 Fibrates are anti-pruritic agents, but they are not licensed for treating PBC. They were not included as comparators in the NICE scope. In TA443 and TA1016, fibrates were not considered second-line treatments. Instead, they were viewed as add-on treatments for pruritus. In TA1016, bezafibrate was included in the model only for its role in treating pruritus. It was not considered a standalone second-line treatment in that context. The EAG considered that fibrates were a relevant comparator. The EAG explained that 1 of its 3 clinical experts had stated that fibrates were their preferred second-line treatment in clinical practice. It also highlighted a UK audit that found that 50% of people whose PBC had responded inadequately to UDCA had treatment with fibrates. The EAG also noted that fibrates were considered within NHS England's medicines repurposing programme, before the programme was suspended for

reasons including structural changes at NHS England. The EAG considered that fibrates were a relevant comparator. The clinical expert at the committee meeting said that fibrates were used as a second-line treatment. He noted that around 20% to 25% of people use fibrates as a second-line treatment, including a small proportion who used them as monotherapy at this position in the treatment pathway. The clinical expert noted that fibrates would only be used in the short term and around 1 in 10 people may need to stop because of liver injury. The patient expert expressed concern that some people with PBC are unable to access specialist treatment centres where OCA is available. Instead, these people are prescribed fibrates as an alternative. The patient expert was particularly concerned about people with PBC being prescribed fibrates. They said that fibrates have limited evidence of effectiveness and had not been through the regulatory process to assess their clinical effectiveness and safety for treating PBC and associated pruritus. The clinical expert agreed that although the preferred option would be to use the licensed second-line treatments, off-label fibrates were currently being used in clinical practice. The company disagreed that fibrates were a comparator, noting the inconsistency with previous appraisals and that fibrates are not licensed for treating PBC. The committee recalled that:

- A particular benefit of seladelpar was the reduction in pruritus: the marketing authorisation for seladelpar states that it is for the treatment of PBC, including pruritus, whereas the marketing authorisations for elafibranor and OCA state that these treatments are for treating PBC.
- There were people in clinical practice having fibrates as a second-line treatment as an alternative to OCA.
- NICE methods allow consideration of off-label treatments as comparators if there is evidence of their use in clinical practice.

The committee thought that overall, fibrates were potentially a comparator for people with PBC with pruritus in NHS clinical practice. It considered that it would be informative to see a comparison of benefits

and costs of seladelpar compared with fibrates. The committee concluded that it was appropriate to re-issue the scope, listing fibrates as a potential comparator to allow exploration of this. The committee also noted that input from NHS England, patients and clinicians would help the committee to define the comparators.

Clinical effectiveness

RESPONSE data source

3.4 The main source of clinical-effectiveness evidence for seladelpar was the RESPONSE trial. This was a phase 3, randomised, double-blind, placebo-controlled study that lasted for 12 months. It evaluated seladelpar in people with PBC that had an incomplete response or who could not tolerate UDCA. A total of 193 people were enrolled in the trial. Of these, 128 had seladelpar 10 mg, with a reduced 5 mg dose used in cases of intolerance. The remaining 65 people had placebo. Both the seladelpar and the placebo arms could include UDCA use, and around 94% of people in each arm had UDCA. There were 17% of people who had previously had OCA or fibrates. The primary outcome was the proportion of people achieving a composite biochemical response at month 12. This was defined as:

- ALP less than 1.67 times the ULN
- a reduction in ALP of at least 15%, and
- total bilirubin at or below 1.0 times the ULN.

Key secondary outcomes included the proportion of people with ALP normalisation (1.0 times at or below the ULN) at 12 months. The clinical and patient experts emphasised that an ALP level above normal, even if it was less than 1.67 times the ULN, was still associated with disease progression. So, they said that ALP normalisation was an important outcome. Another key secondary outcome was change from baseline in weekly averaged pruritus numerical rating scale score. The committee

noted that although ALP levels were an important outcome in terms of disease progression, they may not always reflect the symptoms people with PBC experience. The committee concluded that trial outcomes were informative for decision making.

RESPONSE results

3.5 In the RESPONSE trial, 61.7% of people in the seladelpar arm met the composite outcome at 12 months compared with 20% in the placebo arm. This composite outcome was primarily driven by improvements in ALP-related measures. The EAG noted that baseline bilirubin levels were already low in both the treatment and placebo arms. This suggests that people in RESPONSE were probably at an earlier stage of disease, when changes in bilirubin would be less pronounced. At 12 months, 25% of people in the seladelpar arm and no people in the placebo arm had normalised ALP levels. Among people with moderate to severe pruritus at baseline, having seladelpar statistically significantly reduced the pruritus numerical rating scale score compared with placebo. There was a least-squares mean change from baseline to -3.2 with seladelpar, compared with -1.7 with placebo. The committee concluded that seladelpar was clinically effective at improving ALP levels and reducing pruritus compared with placebo.

Positive treatment response for people having placebo in seladelpar trials

3.6 In RESPONSE, 20% of people in the placebo arm had meaningful clinical improvement in ALP response, despite having no active treatment other than background treatments. The committee noted that this placebo response was high. It noted that this positive response was not explained by changes in background treatment or UDCA dosing, which remained consistent with peoples' previous use. The EAG highlighted that such placebo responses are common in PBC trials. A clinical expert suggested that improved adherence to UDCA during clinical trials may contribute to these effects. Better adherence could lead to better outcomes, even in the

absence of new treatments. The committee suggested that it was possible that the positive treatment response was because of regression to the mean. The EAG noted that this could introduce uncertainty when comparing data from RESPONSE with data from trials for other treatments, especially if placebo effects differ across trials. There may also be uncertainty about real-world adherence over time and how well trial results reflect NHS clinical practice. The committee agreed that it was plausible that the placebo effect was caused by increased adherence to UDCA. But it thought that similar adherence to UDCA would also be expected in the seladelpar arm. The committee said that the relative treatment-effect estimates were not likely to be biased by adherence to UDCA, because the same effect would be seen in both trial arms. It concluded that the reason for the observed placebo response was uncertain.

Indirect comparison approach

Bayesian NMA and MAIC

3.7 There are no head-to-head trials directly comparing seladelpar with the comparators included by the company in the final scope (OCA and elafibranor). Instead, the company relied on indirect treatment comparisons (ITCs) using data from the following trials:

- RESPONSE for comparing seladelpar plus UDCA with UDCA plus placebo
- ELATIVE for comparing elafibranor plus UDCA with UDCA plus placebo
- POISE, COBALT and NCT03633227 for comparing OCA plus UDCA with UDCA plus placebo.

The company used different methodological approaches for comparing seladelpar with each comparator. To compare seladelpar with OCA, the company used a Bayesian network meta-analysis (NMA). For the

comparison with elafibranor, it used an anchored matching-adjusted indirect comparison (MAIC). The company thought that a Bayesian NMA was unsuitable for comparing seladelpar with elafibranor. This was because of differences in baseline bilirubin and cirrhosis rates between the RESPONSE and ELATIVE trials, which the company suggested violated the transitivity assumption. That is, the trials differed in ways beyond the treatments being compared, limiting the validity of indirect comparisons. The EAG did not think that differences in bilirubin or cirrhosis rates warranted this different approach. The company noted that there were differences in the definitions of ULN for the ALP measures and the specific ULN cut-offs by sex. The company recalculated the outcomes for seladelpar to adjust for differences in the sex-specific cut-offs between RESPONSE, POISE and ELATIVE. The MAIC method adjusted individual patient data from RESPONSE to match the baseline characteristics of the ELATIVE trial population. Four treatment-effect modifiers: age, baseline ALP, bilirubin, and cirrhosis were used for matching. These modifiers were consistent with those used in TA1016 and were supported by literature and expert opinion. The EAG did not consider it appropriate to use a separate approach for each comparator. It also noted that the MAIC analysis resulted in a small effective sample size (36% of the original sample), suggesting that differences between the populations in RESPONSE and ELATIVE were difficult to reconcile with matching. The EAG suggested that a Bayesian NMA is a more appropriate method overall. The committee concluded that it was not appropriate to use a separate method for each comparison and that a Bayesian NMA should be used for all indirect comparisons.

NMA uncertainty

3.8 The committee noted the extremely large credible intervals around the relative treatment-effect estimates for seladelpar compared with elafibranor and with OCA in the ALP outcomes. This indicated that there was a large degree of uncertainty around the results. The committee

thought that without further explanation, the credible interval raised concerns about the validity of the model. The company highlighted that in the appraisal of elafibranor there were wide credible intervals for the comparison of elafibranor with OCA. The committee noted that in the results reported in the individual trials (the naive results), seladelpar had a smaller estimated treatment effect than the estimate for OCA or elafibranor. But it noted that in the Bayesian NMA it had a larger treatment effect. The committee considered that this lacked face validity. The company raised some potential differences between the trials (such as key effect modifiers, including baseline bilirubin levels and the proportion of people with cirrhosis). It did this to explain why the results from the ITC were different to the original trial results. The committee was very concerned with the analysis and did not have confidence in the results from the company's indirect comparison. It asked for:

- the company to submit its Bayesian NMA model code with scenarios presented to explore uncertainty in the model
- updated reporting of the company's Bayesian NMA, including clear reporting of the original trial values and sources of numerical data for the comparators
- an explanation of how the trials and trial populations differed, with particular reference to effect modifiers
- an explanation of any difference between the reported trial results and the relative effects resulting from the Bayesian NMA
- consideration that Turner priors are suitable for odds ratios and would need careful justification to be used for an NMA of relative risks.

Adverse events and patient-reported outcomes

3.9 For adverse events and patient-reported outcome measures (PROMs) the company used the Bayesian NMA. Although there were potential issues with the NMA methodology and its reporting, the credible intervals around the adverse events and PROM results were narrower than around the ALP outcomes. The NMA suggested that seladelpar was associated with

less pruritus at 12 months compared with both the 5mg and the 10mg dose of OCA and the placebo. Seladelpar also had lower odds of upper respiratory tract infections compared with placebo and elafibranor. In terms of patient-reported outcomes, seladelpar showed a numerical reduction in pruritus at 12 months compared with placebo and OCA. But the 95% credible interval did not include no effect on the 5-D itch scale. The EAG noted that no minimum clinically important difference had been established for either the 5-D itch or PBC-40 scales. Although the company had presented results for elafibranor PROMs, these had come from a subset of people from the ELATIVE trial. The EAG commented that it had not seen the baseline characteristics for this group. The committee concluded that the results from the NMA appeared to support clinical opinion that seladelpar improves pruritus compared with OCA. But it would welcome clarity on the NMA as outlined in section 3.8 and comments on the clinical meaningfulness of these results in response to consultation.

Economic model

Company's modelling approach

3.10 The company used a cohort-level Markov state-transition model to evaluate the cost effectiveness of seladelpar, with or without UDCA, compared with OCA or elafibranor with or without UDCA. The model had 2 components, with health states defined by ALP levels and liver-disease progression. Transitions between health states were driven by ALP levels, which were used as a proxy for increased or decreased risk of disease progression. Disease progression was defined as the transition to the compensated cirrhosis or elevated bilirubin health state. After this point, the condition can no longer improve and will continue to worsen over time. The model incorporated both costs and the impact on health-related quality of life (utilities) for people in ALP and liver-disease states. It also accounted for the burden of pruritus at varying levels of severity within these health states. The model was run over a lifetime horizon of up to 50

years to capture long-term outcomes and costs. The committee noted that the model had a similar structure to the models used in the appraisals of OCA and elafibranor. But it included an additional health state for ALP normalisation, separate from the mild ALP normalisation health state (see section 3.4). The committee agreed that this was appropriate, and the model structure was appropriate for decision making.

Treatment discontinuation

3.11 For the first 12 months, the company's base case modelled treatment discontinuation rates directly from the clinical trials for seladelpar and each comparator. These included the RESPONSE trial for seladelpar, ELATIVE for elafibranor and POISE for OCA. But the EAG preferred using ITC-derived rates, which it said better accounted for differences in trial populations and aligned with the methodology used for other model parameters. These ITC-derived rates were notably higher for comparators, especially for OCA, which had a 26.95% discontinuation rate at 12 months compared with 9.59% in the company's base case. Seladelpar's discontinuation rate remained consistent at 6.73% across both approaches. For the period after 12 months, the company applied a discontinuation rate ratio of 0.28. This rate ratio was based on the ELATIVE and ELATIVE open-label extension study data for elafibranor and this ratio was applied to estimated discontinuation rates after 12 months for seladelpar and OCA. In contrast, the EAG favoured a lower ratio of 0.12 derived from RESPONSE and ASSURE (a long-term open-label trial of seladelpar). The clinical expert said that the EAG's rates seemed plausible. The committee concluded that it preferred the EAG's approach, with the caveat that the 12-month rates were derived from the ITC, which introduced uncertainty around these estimates (see section 3.7).

Utility values

Source of utility values

3.12 To derive utility values the company used disease-specific PBC-40 data collected in RESPONSE. It mapped this to EQ-5D-5L using real-world data from 90 people included in the ITCH-E study. It then also mapped from EQ-5D-5L to EQ-5D-3L using the Hernández-Alava algorithm. The company developed a mixed model for repeated measures (MMRM) to apply a disutility for each ALP health state. The MMRM model based on RESPONSE data also estimated disutility associated with pruritus. But the company instead used disutility values associated with pruritus from Smith et al. (2022). These values were based on EQ-5D-5L data from the GLIMMER study (a trial of linerixibat in people with moderate to severe pruritus over 16 weeks). The estimated disutilities from Smith et al. were larger compared with estimates from RESPONSE. The EAG favoured the MMRM-derived disutilities, arguing that they were more appropriate because of their internal consistency, alignment with UK cohort data, and direct use of RESPONSE data. The committee preferred the EAG approach. This was because it was based on trial data from people like those who would have treatment in clinical practice and it used data from a consistent source for all health states. But it acknowledged that this approach might underestimate the burden of pruritus because the disutility values were very small. The clinical expert said that it would expect a utility loss from pruritus. The committee said that the reason utility values decreased between the ALP health states was unclear. So, it was not possible to determine whether there had been double counting of disutility caused by pruritus. The committee noted that pruritus is caused by elevated bilirubin, which was only measured in the highest ALP elevation health state. The committee noted that the model did not explicitly model other symptoms of PBC (other than pruritus) that could also affect utility values. It recalled the large impact of fatigue reported by the patient expert. The committee also noted the EAG comment that the model included the costs of treatments for pruritus including fibrates, but did not model an improvement with treatment. The committee concluded that, although it preferred the EAG approach on utility values, there remained

uncertainty about whether the disutility associated with pruritus was underestimated using this approach. The committee said that additional evidence from the literature may be of value. The committee was also uncertain whether the model reflected the expected quality of life in the ALP health states. It said that a further explanation of why, and evidence of how, quality of life would differ between these health states was needed.

Cost-effectiveness estimates

Acceptable ICER

3.13 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically around the:

- methodology and results of the ITC, including whether seladelpar has a benefit in lowering ALP levels compared with OCA or elafibranor and the estimated treatment discontinuation rates from this (see section 3.7)
- relative benefits and costs compared with fibrates, which the committee said were potential comparators (see section 3.3)
- utility values, including:
  - the disutility associated with pruritus (see section 3.12)
  - differences in utility values across ALP health states, and the reason for any differences (see section 3.12).

Because the committee had requested analyses that may help to

resolve, reduce the magnitude or clarify the extent of the uncertainty, it did not identify an acceptable ICER range. The committee concluded that it would reconsider the acceptable ICER range at the second committee meeting. This would take into account any new analyses presented.

Company and EAG cost-effectiveness estimates

3.14 The ICERs cannot be presented because the comparators have confidential patient access schemes. But the company and EAG base-case ICERs and all presented scenarios were substantially above the range normally considered a cost-effective use of NHS resources. The committee's preferred model assumptions were mostly aligned with the EAG's, and included that:

- The baseline distribution of people across the modelled health states should reflect people who would have seladelpar in clinical practice, that is, people who have ALP elevation more than 1.67 times the ULN (see section 3.4).
- A Bayesian NMA should be done and validated for the ITC for all comparators (see section 3.8.
- The treatment discontinuation rates should be derived from the ITC and assumptions on the rate of discontinuation after 12 months should be derived from data from seladelpar trials, rather than from elafibranor trials (see section 3.11).
- The same data source (RESPONSE) should be used for utility values for ALP health states and pruritus (see section 3.12).

The committee was not satisfied that it had been presented with sufficient analyses to determine its preferred ICER range (see section 3.13). Because of uncertainties in the data it requested additional analyses, which were:

- A full description of the ITC and explanation of its uncertainty, with scenario analyses when appropriate to explore the impact of uncertainty (see section 3.8).
- A distribution of change from baseline on the pruritus scale in each treatment arm. This needs to include the proportion of people achieving a clinically meaningful improvement, to better inform the utility values and QALY gains associated with pruritus improvement (see section 3.9).
- Including fibrates as a comparator (see section 3.3).
- A commentary on how well the model reflects quality of life associated with PBC, with any supportive evidence from the literature (see section 3.12).

Other factors

Equality

3.15 The company noted that people with PBC may face long wait times for care, often between 3 and 4 months. They also have higher mortality rates while on liver transplant waiting lists compared with people with other liver diseases. Stakeholders for this appraisal noted that a recent UK-wide audit highlighted geographical disparities in access to specialist teams and second-line treatments, driven by differences in local resource availability. The committee was mindful of its duties under the Equality Act 2010. It identified that previous technology appraisals (for example, TA1016) identified other factors that should also be considered, such as:

- There is a particularly high prevalence of this condition in women, with around 90% of cases occurring in women globally.
- Men are more likely to present with advanced disease that responds poorly to treatment.
- Age also influences outcomes, with people diagnosed under 50 experiencing more severe and progressive disease and poorer treatment response than people diagnosed later in life.

- There are potentially poorer outcomes in men and younger people.
- Although the condition predominantly affects people over 40, younger women may have additional concerns about fertility.

The committee concluded that, although reducing differences in access and liver transplant waiting times were outside of its remit, it was mindful to consider current practice and its impact on patient experience. It said that it would also continue to consider potential differences in prevalence and outcomes within groups with protected characteristics under the Equality Act 2010.

Conclusion

Recommendation

3.16 The committee considered the clinical trial evidence for seladelpar in treating PBC, including its potential to improve liver biochemistry and pruritus compared with OCA and elafibranor, with or without UDCA. But it noted that seladelpar had not been directly compared with these treatments in clinical trials, and that the results of indirect comparisons were highly uncertain. The cost-effectiveness estimates were above the range NICE considers an acceptable use of NHS resources. So, seladelpar should not be used as an option for treating PBC.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

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

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Dr Megan John

Chair, technology appraisal committee D

NICE project team

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

Madiha Adam

Technical lead

Mary Hughes

Technical adviser

Kate Moore

Project manager

Elizabeth Bell

Principal technical adviser

ISBN: [to be added at publication]