SMC2714

elafibranor film-coated tablets (Iqirvo®)

Ipsen Ltd

07 March 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows::

ADVICE: following a full submission

elafibranor (Iqirvo®) is accepted for use within NHSScotland.

Indication under review: for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

In a randomised, double-blind, phase III study, there was a significantly higher cholestasis response at 52 weeks to elafibranor compared with placebo in patients with primary biliary cholangitis who have had an inadequate response or intolerance to UDCA.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Elafibranor and its main active metabolite are dual peroxisome proliferator-activated receptor (PPAR) alpha and delta agonists. Activation of PPAR alpha decreases the synthesis of bile acid, increases bile acid detoxification and modulates the output of bile acid, resulting in reduced bile toxicity and less injury to cholangiocytes and hepatocytes. Activation of PPAR alpha also regulates transporters that absorb and secrete bile components, contributing to decreased bile toxicity and improving cholestasis. Activation of PPAR alpha and PPAR delta also has anti-inflammatory effects by acting on different pathways of inflammation, nuclear factor kappa B (NF-κB) and B-cell lymphoma 6 (BCL6) pathways, respectively.[1, 2]

Elafibranor is the first PPAR alpha and delta agonist to be licensed in the UK. It is administered orally at a dose of 80 mg once daily with or without food.[1]

1.2. Disease background

Primary biliary cholangitis is an auto-immune condition characterised by cholestasis due to destruction of biliary ductules which results in impairment of bile flow in the liver. This leads to toxic levels of hepatocellular bile acid and chronic, progressive liver disease. The course of disease progression is generally slow and patients are usually asymptomatic in early stages, despite underlying inflammatory injury of small bile ducts with cholangitis, and slight anomalies in serum liver biochemical tests. Clinical symptoms of cholestasis and biochemical abnormalities develop during an intermediate stage with progression to liver fibrosis. In late-stage primary biliary cholangitis, patients may develop progressive jaundice, portal hypertension and liver failure. Hepatocellular carcinoma may also develop in the advanced stage. Liver-related death may result when a liver transplant is not possible.

As the condition progresses, almost all patients become symptomatic with pruritus and fatigue being the most common symptoms. Other symptoms commonly reported include sicca complex, abdominal pain, arthralgia, restless legs, sleeplessness, depression and cognitive dysfunction.[2, 3]

Primary biliary cholangitis is a rare condition, estimated to affect around 35 per 100,000 people and an annual incidence of 2 to 3 per 100,000 people. It is more common in women than men with a ratio of 9:1.[2, 3]

1.3. Treatment pathway and relevant comparators

Ursodeoxycholic acid and obeticholic acid are the only other medicines licensed for the treatment of primary biliary cholangitis. Fibrates are used off-label for the second-line treatment of primary biliary cholangitis and other medicines are used off-label (colestyramine, rifampicin, naltrexone and sertraline) to control symptoms including for itch.[2, 3]

Ursodeoxycholic acid is recommended in guidelines for first-line use. Obeticholic acid is licensed for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid in adults with an inadequate response to ursodeoxycholic acid or as monotherapy in adults unable to tolerate ursodeoxycholic acid and was accepted for use within NHSScotland by SMC (SMC1232).

The submitting company considered obeticholic acid as the most relevant comparator.

1.4. Category for decision-making process

Elafibranor meets SMC orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of elafibranor for the treatment of primary biliary cholangitis comes from the ELATIVE study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study[2, 4, 5]

Criteria	ELATIVE study
Study design	A randomised, double-blind, phase III study versus placebo.
Eligible patients	• patients aged 18 to 75 years with a diagnosis of primary biliary cholangitis meeting at least two of the following diagnostic criteria: elevated ALP levels for ≥6 months; positive AMA titres >1:40; liver biopsy consistent with PBC. • had either received ursodeoxycholic acid for ≥12 months (and at a stable dose for ≥3 months) or were unable to tolerate ursodeoxycholic acid (no ursodeoxycholic acid for ≥3 months) • ALP level ≥1.67 times the upper limit of normal (ULN, where ULN is defined as 104 units/L for women and 129 units/L for men) • total bilirubin level ≤2 times ULN (where ULN is defined as 20.5 micromol/L)
Treatments	Elafibranor 80 mg (n=108) or placebo (n=53) orally once daily for ≥52 weeks. Treatment during the double-blind period could continue beyond week 52 in a variable treatment period until all patients had completed their week 52 assessment or until a maximum treatment duration of 104 weeks. Study patients were allowed to continue to take concomitant ursodeoxycholic acid, medicines for pruritus if stable doses for ≥3 months and statins or ezetimibe if stable doses for ≥2 months before screening.
Randomisation	Eligible patients were randomised in a ratio of 2:1 with stratification by ALP level >3 times the ULN or TB level >ULN (yes or no) and WI-NRS ≥4 (yes or no).
Primary outcome	Cholestasis response at week 52, defined as a composite of ALP < 1.67 x ULN and TB ≤ ULN and ALP decrease ≥ 15%.
Key secondary outcomes	- ALP normalisation at week 52 - change from baseline to week 52 in WI-NRS score in patients with WI-NRS score ≥4 at baseline - change from baseline to week 24 in WI-NRS score in patients with WI-NRS score ≥4 at baseline.
Statistical analysis	Efficacy analyses on the primary and first key secondary outcome were performed in the ITT population . Change from baseline in WI-NRS was analysed in the pruritus ITT population, which included all patients from the ITT population with baseline WI-NRS score ≥4. A hierarchical statistical testing strategy was applied to the primary and key secondary outcomes in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore, the results reported for these outcomes are descriptive only and non-inferential (no p-values reported).

Abbreviations: ALP = alkaline phosphatase; AMA = anti-mitochondrial antibodies; ITT = intention-to-treat; PBC=primary biliary cholangitis; TB = total bilirubin; ULN = upper limit of normal; WI-NRS = Worst Itch Numeric Rating Scale

At week 52, significantly more patients achieved a cholestasis response in the elafibranor group compared with the placebo group. There was also a significantly higher proportion of patients who achieved ALP normalisation at week 52 with elafibranor compared with placebo. However, the

difference between groups did not reach statistical significance for the second key secondary outcome and further formal statistical testing was stopped. These results numerically favour elafibranor over placebo but are descriptive only. During the study period, 95% of patients received concomitant ursodeoxycholic acid.[2, 5] Details are presented in Table 2.2.

Table 2.2: results for the primary and key secondary outcomes in ELATIVE study[2, 5]

	Elafibranor (n=108)	**Placebo (n=53)**
Primary outcome		
Cholestasis response at week 52, % (n/N)	51% (55/108)	3.8% (2/53)
Difference versus placebo (95% CI), p-value	47% (32% to 57%), p<0.001	
Odds ratio versus placebo (95% CI), p-value	37.6 (7.6 to 302), p<0.001	
Key secondary outcomes		
ALP normalisation at week 52, % (n/N)	15% (16/108)	0% (0/53)
Difference versus placebo (95% CI), p-value	15% (6.1% to 23%), p<0.001	
Odds ratio versus placebo (95% CI), p-value	Infinity (2.8 to infinity), p=0.002	
Patients with WI-NRS score ≥4 at baseline	**n=44**	**n=22**
Mean WI-NRS score at baseline	6.19	6.25
Change in WI-NRS to week 52	-1.93	-1.15
Difference versus placebo (95% CI), p-value	-0.78 (-1.99 to 0.42), p=0.20	
Change in WI-NRS to week 24	-1.60	-1.26
Difference versus placebo (95% CI), p-value	-0.34 (-1.49 to 0.80)	

Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; WI-NRS = Worst Itch Numeric Rating Scale

Results of subgroup analyses of the primary outcome were generally consistent with the primary analysis in the ITT population favouring elafibranor over placebo. However, the treatment effect was smaller in patients with more severe disease at baseline (ALP >3 x ULN and/or TB >0.6 x ULN).[2, 5]

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using additional secondary outcomes, not included in the hierarchical testing strategy. They included changes from baseline to week 52 using the itch domain of the primary biliary cirrhosis–40 (PBC-40) questionnaire (itch score range 0 to 5 with higher scores indicating worse quality of life), the 5-D itch scale (measures the degree, duration, direction, disability and distribution of itching; total score ranges from 5 to 25, with higher scores indicating worse itch-related quality of life), the patient reported outcome measurement information system (PROMIS) fatigue short form 7a (score range 29.4 to 83.2 with higher scores indicating worse outcomes), the Epworth Sleepiness Scale (ESS, score range 0 to 24 with higher scores indicating worse outcomes) and EQ-5D-5L. These instruments were used at screening, and weeks 4, 13, 26, 39 and 52 of the double-blind treatment period. There were improvements from baseline to week 52 with elafibranor compared with placebo but the least squares mean differences between treatment groups were small.[4, 5]

2.3. Supportive studies

Patients (n=138) who completed the double-blind treatment period could enter an extension study and receive open-label elafibranor for up to 5 years (up to 6 years from initial randomisation). Interim analysis presented by the company indicate that after 3 years of

continuous treatment with elafibranor during the double-blind period and extension, 85% (11/13) of patients had a biochemical response (ALP <1.67 x ULN, with ≥ 15% reduction from baseline and total bilirubin ≤ ULN) and 39% (5/13) achieved ALP normalisation.[4, 6]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence, the submitting company conducted a Bayesian network meta-analysis (NMA) to compare the efficacy of elafibranor (using data from ELATIVE study [5]) and obeticholic acid (using data from POISE study [7]) in adult patients with primary biliary cholangitis who have an inadequate response or intolerance to ursodeoxycholic acid. The assessed outcomes were a wide range of liver function biomarkers, adverse events/discontinuations and patient reported health outcomes as shown below in Table 2.3

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Network Meta Analysis (NMA)
Population	Adult patients with PBC who have an inadequate response or intolerance to ursodeoxycholic acid.
Comparators	Obeticholic acid
Studies included	ELATIVE[5] POISE[7]
Outcomes	**Liver function biomarkers:** - Odds of cholestasis response at 52 weeks - Mean change in ALP levels from baseline at 52 weeks - Odds of ALP normalisation at 52 weeks - Mean change from baseline in high density lipoprotein (HDL) cholesterol at 52 weeks **Patient reported health outcomes:** - Mean change in pruritus (using 5-D Itch and PBC-40 itch score questionnaires) from baseline at 52 weeks - Mean change in pruritus (5-D Itch and PBC-40 Itch dimension scores) using the earliest reported data after commencement of treatment. **Adverse events / discontinuations:** - Occurrence of pruritus of any severity as treatment-emergent adverse event within 52 weeks - Discontinuation due to pruritus within 52 weeks - All-cause discontinuation within 52 weeks
Results	Overall, the company concluded that elafibranor demonstrated favourable results for improving liver function biomarkers, reducing pruritus over 52 weeks and patients treated with elafibranor were less likely to discontinue treatment due to pruritus or any cause compared with obeticholic acid. However, there was no evidence of a difference between elafibranor and obeticholic acid in all outcomes (except change in HDL level) and the 95% credible intervals were very wide, indicating uncertainty in the relative effectiveness of elafibranor compared to obeticholic acid. The company considered that the results of the indirect comparison are confidential.

3. Summary of Safety Evidence

In the ELATIVE study at end of the double-blind treatment period, the median duration of exposure was 63.1 weeks in the elafibranor and 61.0 weeks in the placebo group, respectively.[1]

Any treatment-emergent adverse event (AE) was reported by 96% (104/108) of patients in the elafibranor group and 91% (48/53) in the placebo group and these were considered treatment-related in 39% and 40% respectively. In the elafibranor and placebo groups respectively, patients with a reported serious AE were 10% versus 13% and patients discontinuing therapy due to an AE was 10% versus 9.4%.[2, 5]

The most frequently reported treatment-related AEs of any grade in the elafibranor group versus the placebo group were: pruritus (8.3% versus 11%), nausea (7.4% versus 1.9%), constipation (3.7% versus 1.9%), headache (3.7% versus 1.9%) and fatigue (3.7% versus 3.8%).[2]

The SPC recommends that clinical and laboratory assessment of liver function and creatine phosphokinase should be done prior to initiation of elafibranor treatment and thereafter according to routine patient management.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the phase III double-blind study ELATIVE, elafibranor significantly improved the cholestasis response rate and proportion of patients achieving ALP normalisation at 52 weeks compared with placebo.[5]
- The ELATIVE study methodology was appropriate and was of randomised, double-blind design. The study population was generally reflective of patients who would be eligible for elafibranor in clinical practice. The majority of study patients (95%) were receiving ursodeoxycholic acid at baseline and were considered to have an inadequate response to rather than intolerance to it. Since ursodeoxycholic acid is considered to have a favourable safety profile, it was expected that the proportion of study patients who were intolerant to it would be small.[2, 5, 8]
- Elafibranor is the first PPAR alpha and delta agonist to be licensed in the UK and offers an additional licensed treatment option over obeticholic acid for the second-line treatment of primary biliary cholangitis.[1, 2] Clinical experts consulted by SMC indicated that obeticholic acid is unlikely to be prescribed to new patients in Scotland.

4.2. Key uncertainties

- The primary outcome of cholestasis response is a surrogate outcome of composite biochemical measures which has not been validated. However, in the absence of other validated outcomes, it has been accepted by regulatory authorities to support marketing authorisations. It is considered an intermediate measure of effect in primary biliary cholangitis and indicates liver function deterioration but its clinical relevance and correlation with predicting clinical benefit remains to be demonstrated for elafibranor.[2, 8]
- Although there was a significant increase in the proportion of patients achieving the more stringent first key secondary outcome of normalisation of ALP in the elafibranor group

compared with the placebo group, this was only achieved in a small proportion of elafibranor patients (15%).[2, 5]

- There are no direct data versus a relevant comparator. The submitting company did not consider fibrates a relevant comparator but clinical experts consulted by SMC indicated that bezafibrate is often used off-label for patients who have an inadequate response or are intolerant to ursodeoxycholic acid. There are no comparative data of elafibranor versus fibrates.
- The submitting company performed an NMA with obeticholic acid which they suggested found results favouring elafibranor. However, several limitations affected the robustness of the NMA including small patient numbers from only two studies, heterogeneity between patient characteristics and differences in some outcome definitions. The results suggested no evidence of a difference between elafibranor and obeticholic acid in all outcomes (except change in HDL level) and the credible intervals for the relative treatment effects were very wide, therefore the company's conclusions were considered highly uncertain. However, the results were similar to those reported in a recently published NMA of second-line treatments for primary biliary cholangitis.[9]
- Itch was assessed as a key secondary outcome at 52 and 24 weeks in the subgroup of the study population with moderate to severe pruritus at baseline (WI-NRS score of ≥4; 41% of the ITT population). In line with the hierarchical statistical testing, since results for change from baseline in WI-NRS at week 52 did not reach statistical significance, further formal statistical testing was stopped and subsequent results were considered descriptive only.[2, 5]
- Efficacy outcomes were assessed at the end of the 52-week double-blind treatment period, which met regulatory requirements when the study began but is shorter than the now recommended 2-year duration. This is considered insufficient to determine the longer term effects on controlling the progression of primary biliary cholangitis.[2, 8]
- The number of patients in the ELATIVE study was small (n=161) but this was considered acceptable for a rare, orphan condition. The majority of study patients were receiving ursodeoxycholic acid at baseline and were considered to have an inadequate response to rather than intolerance to it. Therefore, there are limited data (n=8) on the use of elafibranor as monotherapy. Further data on elafibranor monotherapy are awaited from ongoing studies.[2, 5]
- The majority of study patients (92%, 148/161) had not received prior obeticholic acid and it unclear what proportion had received an off-label fibrate. If the latter is low, then there is limited evidence to support the use of elafibranor in the third-line after failed second-line treatment.[5]
- The open-label extension of ELATIVE, an additional phase III study (ELFIDENCE) and a non-interventional, phase IV study in the real-world setting (ELFINITY) will provide further evidence on the clinical benefit of elafibranor on longer term outcomes. [1, 2]

4.3. Clinical expert input

Clinical experts consulted by SMC considered that there is an unmet need for further licensed treatment options for patients with primary biliary cholangitis. They considered that elafibranor is a therapeutic advancement offering an alternative that does not appear to exacerbate itch.

4.4. Service implications

Clinical experts consulted by SMC indicated that elafibranor did not have any notable service implications. Patients would require liver function monitoring before and during treatment but this would be part of the regular management of patients with primary biliary cholangitis.

5. Summary of Patient and Carer Involvement

No patient group submission was received.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (43 years), with a mean patient start age of 57 years
Population	Adults with primary biliary cholangitis who have had an inadequate response to ursodeoxycholic acid (UDCA), or are unable to tolerate UDCA.
Comparators	Elafibranor (with/without UDCA) is compared to obeticholic acid (OCA, with/without UDCA), and with UDCA alone as a second-line treatment
Model description	Markov cohort model with 10 health states to reflect PBC progression, with a PBC biomarker (BM) component which stratified patients into mild, moderate and high risk of progression according to BM status, and a liver disease component, with states for hepatocellular carcinoma (HCC), decompensated cirrhosis (DCC), and 3 liver transplant (LT) states (pre, LT, post). There is also a state for PBC re-emergence post LT, and a death state. Transitions to the liver disease component of the model was assumed possible from the moderate and high risk PBC progression states. Model cycle length was 3 months.
Clinical data	The primary clinical data for elafibranor and placebo arm (as a proxy for UDCA comparator) transition probabilities for the first 4 model cycles (12 months) in the PBC biomarker model component was the phase 3 ELATIVE study.[5] The whole patient population ITT analysis set was used in the economic analysis. The main clinical data providing transition probabilities for the comparison with OCA for the first 4 cycles was an NMA that included two studies (ELATIVE for elafibranor, POISE phase 3 study for OCA), with odds ratios(OR) from the NMA for achieving cholestatis response OCA vs elafibranor used as a base for deriving 12 month OCA transition probabilities in the PBC BM component.[5, 7] The economic analysis took account of the impact of three adverse events (pruritus UTI, fatigue) and pruritus outcomes on costs/utilities based on the ELATIVE and NMA data. An excess mortality of 1.2% was assumed for patients whilst in the high risk PBC BM state, based on clinical expert opinion. Excess mortality rates for liver transplant, DCC and HCC states were derived from the NICE TA443 submission for OCA.[10]
Extrapolation	Beyond the first four model cycles elafibranor and OCA outcomes were extrapolated assuming patients stay in the same state as in the 4th model cycle (12 months). For patients receiving UDCA, extrapolation beyond 12 months was based on applying last observation carried forward (LOCF) to transitions between cycle 3 and 4, which represented an overall

	worsening health state trajectory for the UDCA arm over time. In addition, in the base case it was assumed that patients receiving UDCA alone could not improve to better health states. Transitions from the PBC BM component high risk state to the liver disease component were estimated using data from the NICE TA443 submission for OCA[10], with transitions from the PBC BM moderate risk of progression state based on clinical expert opinion. Within the liver disease component transition probabilities were derived from prior NICE technology appraisals and published sources in PBC and hepatitis C. Treatment discontinuation for elafibranor was based on extrapolation of the ELATIVE study Kaplan-Meier data by fitting parametric functions to the data. The log-normal function was applied in the base case based primarily on clinical plausibility grounds as it was not the best fitting function. Alternative functions, including the best fitting were explored in scenario analysis. Relative OCA discontinuation was based on the odd ratio (OR) for all cause treatment discontinuation from the NMA. The likelihood of discontinuation was estimated to be higher for OCA than elafibranor. Patients discontinuing treatment were assumed to return to their baseline state and follow the UDCA disease progression trajectory.
Quality of life	Age adjusted utilities for each health state in the model were derived from prior NICE technology appraisals and published studies, including some adjustments using clinical expert opinion.[10-12] AE disutilities were from published/technology appraisal sources and clinical opinion, and disutilities for pruritus (mild, or clinically significant itch) were based on regression analysis of EQ 5D-5L data (mapped to EQ-5D-3L utilities) from the ELATIVE study.
Costs and resource use	Medicine acquisition costs have been estimated for elafibranor 80mg daily, OCA 5 mg (first 2 cycles) and 10mg (from cycle 3, i.e. 6 months) daily and UDCA (mean dose based on analysis of ELATIVE data). No medicine administration costs are assumed. Medicine and other healthcare resource use has been estimated to derive health state costs, AE costs, pruritus costs and end of life costs derived from prior technology appraisal, published and clinical expert opinion sources.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount was offered on the list price. A PAS discount is in place for OCA and this was included in the results used for decision-making by using estimates of the comparator PAS price.

*Other data were also assessed but remain confidential.**

6.2. Results

The base case results are presented in Table 6.2. Elafibranor is associated with higher drug acquisition costs vs UDCA, and there are additional costs versus OCA associated with longer duration of treatment, but cost is offset from health state resource use and lower costs for pruritus. Life years and QALY gains are driven by greater efficacy estimated for elafibranor vs both comparators so more patients in the mild PBC BM risk state vs OCA or mild/moderate state vs UDCA. This results in lower progression to the liver disease component of the model, and lower treatment discontinuation rates compared to OCA (which means patients receiving OCA discontinued sooner than elafibranor to revert to baseline and follow the worsening disease trajectory associated with UDCA alone). For the comparison versus OCA, SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues.

Table 6.2: **Base case results for elafibranor with PAS vs comparators**

elafibranor versus:	ICER (£/QALY)
OCA	CIC
UDCA alone	£28,307

Abbreviations: CIC = commercial in confidence; ICER= incremental cost-effectiveness ratio OCA: obeticholic acid; PAS = patient access scheme; QALY = quality adjusted life years; UDCA: ursodeoxycholic acid.

6.3. Sensitivity analyses

Sensitivity analysis performed demonstrated sensitivity to varying the OR for OCA all cause discontinuation by the 95%CI derived from the NMA. A range of sensitivity and scenario analyses were considered and descriptions of key scenarios are provided in table 6.3 below. Of the scenarios the most impactful were those combining assumptions regarding UDCA outcomes extrapolation and assuming no differences in elafibranor or OCA efficacy, treatment discontinuation, and pruritus outcomes (Scenarios 10-14, table 6.3).

Table 6.3 Selected scenario analyses, with elafibranor PAS applied

	Parameter	Base case	Scenarios	ICER (£/QALY) elafibranor vs OCA	ICER (£/QALY) elafibranor vs UDCA
1	Time horizon	Lifetime	20 years	CIC	£29,809
2	UDCA transition extrapolation beyond 12 months	LOCF for cycle 3 to beyond 4 as basis for extrapolation	Average of all transition matrices in first 4 cycles	CIC	£30,550
3	UDCA extrapolated outcomes	Assume improvement not possible	Allowing improvement over time (after 12 months)	CIC	£30,339
4	Moderate risk to liver disease transitions	Included	Excluded	CIC	£28,172
5	Duration of treatment effect: elafibranor relative to OCA	Lifetime	1 year	CIC	N/A
6	Treatment discontinuation extrapolation for elafibranor	Lognormal	Exponential (best fitting)	CIC	£29,428
7	Source for disutility of pruritis	ELATIVE study (0.01/0.08 mild/CS resp)	Clinical opinion (0.07, 0.20 resp)	CIC	£30,950

8	Utilities source for mild, moderate risk states	Published sources (0.84 for both)	ELATIVE study EQ 5D analysis	CIC	£30,076
9	DCC health state utility	NICE TA330 0.38	Alternative publication (McPhail et al 2021) 0.62	CIC	£29,488
Additional scenarios vs OCA*					
10	UDCA extrapolation assumptions		Combining scenarios 2 and 3 (Average of all transition matrices, and allowing UDCA improvement)	CIC	£55,640
11	OR OCA vs elafibranor for all cause treatment discontinuation	OR=CIC value	c) Assume equivalent OR=1	CIC	N/A
12	OR OCA vs elafibranor for cholestasis response	OR=CIC value	c) Assume equivalent OR=1	CIC	N/A
13	ORs OCA vs elafibranor for cholestasis response and treatment discontinuation		Combine scenarios 11 and 12 OR=1	CIC	N/A
14	ORs OCA vs elafibranor for cholestasis response and treatment discontinuation, and pruritis outcomes		Scenario 13 + Exclude pruritis outcomes differences	CIC	N/A

Abbreviations: CIC = commercial in confidence; ICER = incremental cost-effectiveness ratio; OCA: obeticholic acid; PAS = patient access scheme; QALY = quality adjusted life years; UDCA: ursodeoxycholic acid* Scenarios performed by the economic assessor using the company model

6.4. Key strengths

- Appropriate model structure based on a prior model structure used in technology appraisals for PBC. Health states appear to reflect the PBC to liver disease progression pathway.
- Availability of patient level data for elafibranor to inform baseline distribution and transition probabilities for PBC biomarker health states.

6.5. Key uncertainties

- There are uncertainties over bezafibrate as a comparator, and the likely place in therapy of elafibranor. SMC clinical expert feedback was that there is low UDCA use in clinical practice after an inadequate response. However, OCA could be displaced by elafibranor but also

stated off-label bezafibrate would be used second-line ahead of OCA, hence elafibranor or OCA could potentially be used at 3rd line (for which there is no clinical or cost-effectiveness evidence for elafibranor vs OCA).

- Cost-effectiveness of elafibranor in patients intolerant of UDCA compared with OCA is not known as there are too few patients in the ELATIVE study to make this analysis feasible.
- There is uncertainty over the relationship between the PBC biomarkers used in the economic analysis to define progression risk states and longer term clinical and overall survival (life years gained) outcomes. This translates to uncertainty in the robustness of the cost-effectiveness results for elafibranor vs comparators.
- The BM disease progression trajectory for UDCA after 12 months is based on LOCF applied to cycle 4 data from the ELATIVE study which shows worsening outcomes, based on small patient numbers in the placebo arm. This extrapolation approach is uncertain although the company supported the base case assumption based on interim data showing worsening biomarker outcomes evidence at 78 weeks for UDCA from the ELATIVE extension study, however also based on small patient numbers. The results are sensitive to a scenario applying alternative UCDA extrapolation assumptions (Scenario 10, Table 6.3).
- The comparison with OCA is based on an NMA that has limitations, such that there is high uncertainty over the relative treatment discontinuation evidence and the relative effectiveness of elafibranor and OCA based on cholestasis response biomarkers with wide credible intervals for the NMA odds ratios (ORs), and uncertainty in the data for relative pruritus outcomes used in the economic analysis. Uncertainty in the NMA was explored in scenario analyses setting the OR credible intervals to one, assuming equivalence, for efficacy and/or treatment discontinuation (Scenarios 11-13, table 6.3), and also assuming no differences in pruritis outcomes (Scenario14, table 6.3).
- There are several uncertainties with the utilities used for the model health states derived from several published sources rather than the EQ 5D estimates analysed from the ELATIVE study. However, sensitivity and scenario analysis has been performed that has indicated the results are not highly sensitive to varying the utility estimates or using alternative sources or assumptions.

*Other data were also assessed but remain confidential.**

7. Conclusion

After considering all the available evidence, the Committee accepted elafibranor for use in NHSScotland.

8. Guidelines and Protocols

The British Society of Gastroenterology published "The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines" in 2018.[3]

The European Association for the Study of the Liver (EASL) published EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis in 2017.[13]

9. Additional Information

9.1. Product availability date

4 October 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
elafibranor	**80 mg orally once daily**	**34,786**

Costs from eMC Dictionary of Medicines and Devices Browser on 18 December 2024. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 12 February 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.