SMC2664

ivosidenib film-coated tablets (Tibsovo®)

Servier Laboratories

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and 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 assessed under the end of life and orphan medicine process

ivosidenib (Tibsovo®) is accepted for use within NHSScotland.

Indication under review: as monotherapy for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who were previously treated by at least one prior line of systemic therapy.

In a double-blind, phase III study, ivosidenib, compared with placebo, significantly improved progression-free survival in adults with locally advanced or metastatic cholangiocarcinoma with IDH1 mutation who were previously treated by one or two prior lines of systemic therapy for advanced disease.

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.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Ivosidenib is an inhibitor of mutant IDH1 enzyme. The mutant IDH1 enzyme converts alpha-ketoglutarate to 2-hydroxyglutarate (2-HG), which impairs cellular differentiation and promotes tumour formation. By inhibiting the mutant IDH1 enzyme, ivosidenib reduces 2-HG overproduction and restores cell differentiation. However, its mechanism of action is not fully understood. It is administered orally at a dose of 500 mg once daily.[1]

1.2. Disease background

Cholangiocarcinoma is a rare aggressive cancer of the biliary tree, often diagnosed at a late stage that is incurable, with patients having symptoms including jaundice, abdominal pain, fatigue, weight loss, fever and abnormal liver function tests. The prognosis is poor, with 5-year survival rates of 9% to 10% and, in those who present with metastasis, 2%. Both IDH1 and IDH2 mutations have been found in varying proportions (up to a quarter) of patients with intrahepatic cholangiocarcinomas, and the impact of these on prognosis is uncertain. These mutations are found in a small proportion (less than 7%) of patients with extrahepatic cholangiocarcinomas, where their presence is associated with a poor prognosis.[2]

1.3. Treatment pathway and relevant comparators

First-line treatment for patients with advanced and metastatic cholangiocarcinoma is durvalumab in combination with cisplatin and gemcitabine. For patients whose disease progresses, second-line treatment with 5-fluorouracil, L-folinic acid and oxaliplatin (FOLFOX) is recommended and has shown a modest survival benefit compared with active symptom control.[3, 4]

1.4. Category for decision-making process (if appropriate)

Eligibility for a PACE meeting
Ivosidenib meets SMC end of life and orphan criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence is from the ClarIDHy study, detailed in Table 2.1 below.[2, 5]

Table 2.1. Overview of relevant study

Criteria	ClarIDHy study[2, 5]
Study design	Double-blind, phase III study
Eligible patients	Adults with unresectable or metastatic cholangiocarcinoma and IDH1 mutation who had disease progression after one or two regimens for advanced disease including one containing gemcitabine or 5-fluorouracil; ECOG performance status 0 or 1; measurable disease on RECIST v1.1
Treatments	Ivosidenib 500 mg or placebo orally once daily until disease progression, death or unacceptable toxicity. Crossover from placebo to ivosidenib was permitted after disease progression.
Randomisation	Equally assigned with stratification by prior therapies for advanced disease (1 or 2)
Primary outcome	Progression-free survival assessed by IRC per RECIST v1.1
Secondary outcomes	Overall survival; overall response rate assessed by IRC per RECIST v1.1

Statistical analysis	Multiplicity controlled for primary and key secondary outcomes at primary analysis and for overall survival at later analysis (after 150 deaths). RPSFT analysis to adjust for crossover at both data cuts.

ECOG = Eastern Cooperative Oncology Group; IDH1 = isocitrate dehydrogenase-1; IRC = independent radiology centre; RECIST = Response Evaluation Criteria in Solid Tumors; RPSFT = rank-preserving structural failure time.

At the primary analysis (cut-off 31 January 2019), median follow-up was 6.9 months, the primary outcome, progression-free survival (PFS) assessed by central independent radiology centre (IRC), was significantly improved with ivosidenib compared with placebo. There were no significant improvements in the key secondary outcomes, overall survival (OS) and overall response rate (ORR) at this cut-off and in the final pre-specified analysis of OS after 150 deaths (cut-off 31 May 2020) in analysis that did not adjust for crossover of patients from placebo to ivosidenib at disease progression. At the later cut-off, rank-preserving structural failure time (RPSFT) analysis adjusted for crossover of 70% of patients from placebo to ivosidenib and indicated improvement in OS with ivosidenib. An updated analysis (21 June 2021) found similar results.[2, 5, 6] Results at the pre-specified primary analysis of PFS and final analysis of OS are detailed in Table 2.2.

Table 2.2 Result of ClarIDHy.[2, 5, 6]

	Ivosidenib (n=124)	**Placebo (n=61)**	**Hazard ratio or odds ratio (95% confidence interval)**
Progression-free survival assessed by IRC per RECIST v1.1 (31 January 2019)			
Events	76	50	HR 0.37 (0.25 to 0.54), p<0.001
Median, months	2.7	1.4	
KM estimated 3-month PFS	45%	12%	
Overall response rate assessed by IRC per RECIST v1.1 (31 January 2019)			
Overall response, n (%)	3 (2.4%)	0	OR NE (0.29 to NE), p=0.299
Partial response, n (%)	3 (2.4%)	0	
Overall survival (31 May 2020)			
Deaths	100	50	HR 0.79 (0.56 to 1.12), p=0.093
Median, months	10.3	7.5	
KM estimated 1-year OS	43%	36%	
RPSFT median, months	10.3	5.1	HR 0.49 (0.34 to 0.70), p<0.001

HR = hazard ratio; IRC = independent radiology centre; KM = Kaplan Meier; OR = odds ratio; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; RPSFT = rank-preserving structural failure time.

2.2. Health-related quality of life outcomes

Health Related Quality of Life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), EORTC QLQ-Cholangiocarcinoma and Gallbladder Cancer (BIL21), and Patient Global Impression of Severity (PGI-S). Post-baseline sample sizes were small, analyses were not adjusted for multiplicity and there are limited data beyond cycle 2. These suggest that within the ivosidenib group compared with placebo, there were benefits on EORTC QLQ-C30 physical function and emotional function at cycle 2 and 3; and benefits in EORTC BIL21 in tiredness symptoms at cycle 2.[7]

2.3. Supportive studies

An open-label, phase I study (AG120-C-002) included 62 patients with advanced cholangiocarcinoma who received the licensed dose of ivosidenib 500 mg once daily. The ORR was 4.8% (3/62), which comprised three partial responses. Median PFS was 3.7 months and estimated PFS was 63% and 20% at 3 and 12 months, respectively. Median OS was 11.9 months and estimated OS was 49% at 12 months.[2]

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

The submitting company presented an indirect treatment comparison (ITC) of ivosidenib versus FOLFOX (intravenously (IV) administered oxaliplatin 85 mg/m², L-folinic acid 175 mg [or folinic acid 350 mg], fluorouracil 400 mg/m², then fluorouracil 2400 mg/m² over 46 hours; administered for 12 two-weekly cycles) based on data from a randomised, open-label, phase III study of FOLFOX versus active symptom control (ABC-06). This is detailed in Table 2.3

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Bucher for OS; naïve for PFS
Population	Adults with advanced cholangiocarcinoma
Comparators	Ivosidenib versus FOLFOX (5-fluorouracil, L-folinic acid and oxaliplatin)
Studies included	ClarIDHy[5] and ABC-06[8]
Outcomes	OS and PFS
Results	OS: ivosidenib versus FOLFOX, HR suggested possible benefit in the analysis that was adjusted for crossover, despite the statistical testing of this result not being not definitive. PFS: ivosidenib versus FOLFOX, comparison of curves with median 2.7 versus 4.0 months.

CI = confidence interval; HR = hazard ratio; FOLFOX = intravenous oxaliplatin 85 mg/m², L-folinic acid 175 mg [or folinic acid 350 mg], fluorouracil 400 mg/m² then 2,400 mg/m² over 46 hours - administered for 12 two-weekly cycles; OS = overall survival; PFS = progression-free survival.

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

3. Summary of Safety Evidence

A regulatory review concluded the safety profile of ivosidenib in the treatment of advanced cholangiocarcinoma is manageable and adverse events of special interest include QT interval prolongation, with information included in the summary of product characteristics (SPC).[2]

In the ClarIDHy study (at data cut-off 21 June 2021), median duration of treatment with ivosidenib and placebo (prior to crossover) was 2.8 and 1.6 months, respectively. The incidence of adverse events was 98% (120/123) and 97% (57/59) and these were treatment-related in 66% and 39%, respectively. Adverse events with grade ≥3 severity were reported by 51% and 37% of patients (treatment-related in 6.8% and 0) and serious adverse events occurred in 35% and 24% of patients (treatment-related in 2.4% and 0). Adverse events led to study drug discontinuation in 7.3% and 8.5% of patients (treatment-related 1.6% and 0), respectively.[2]

In the ClarIDHy study (at data cut-off 21 June 2021), within the ivosidenib group, compared with placebo (pre-crossover), there were higher rates of gastrointestinal adverse events, including nausea (42% versus 29%), diarrhoea (35% versus 17%) and abdominal pain (24% versus 15%), with higher rates of other adverse events, including ascites (23% versus 15%), fatigue (31% versus 17%), cough (25% versus 8.5%), hypertension (8.9% versus 3.4%), headache (13% versus 6.8%), QT

interval prolongation (9.8% versus 3.4%), peripheral neuropathy (6.5% versus 0), rash (8.1% versus 0), hyperglycaemia (7.3% versus 1.7%), hyperbilirubinaemia (11% versus 6.8%), elevated aspartate aminotransferase (11% versus 5.1%) and anaemia (19% versus 5.1%).[2]

To mitigate the risks of QT prolongation, patients have an electrocardiogram (ECG) prior to initiating treatment, weekly for the first three weeks and monthly thereafter to detect abnormalities and allow prompt action.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In a double-blind, phase III study, ivosidenib, compared with placebo, significantly improved PFS by about 1.3 months, with a HR of 0.37 (95% CI: 0.25 to 0.54), in adults who received one or two prior lines of therapy for advanced cholangiocarcinoma with an IDH1 mutation.[2]
- Ivosidenib is the first IDH1 inhibitor licensed for treatment of cholangiocarcinoma, and it is the first medicine targeting the mutant enzyme that characterises cholangiocarcinoma with IDH1 mutations.[2]

4.2. Key uncertainties

- The RPSFT analysis of OS adjusted for crossover of patients from placebo to ivosidenib and may better estimate expected benefit in practice. This suggests median improvement of around 5 months, with a HR of 0.49 (95% CI: 0.34 to 0.70). However, the RPSFT estimate does not account for any subsequent anti-cancer therapy that may have been given in the placebo group in the absence of crossover.[2, 6]
- Ivosidenib may be used in the second-line setting and data from the sub-group of ClarIDHy that had received one prior line of therapy may be most relevant. Pre-specified sub-group analysis in 57% (106/185) and 43% (79/185) of patients who had received one and two prior lines of therapy, respectively, indicated similar results for IRC-assessed PFS, HR 0.37 (95% CI: 0.22 to 0.61) and 0.41 (95% CI: 0.23 to 0.73). In pre-specified sub-group analysis of OS (31 May 2020), HR were similar in the groups that had received one and two prior lines of therapy, 0.83 and 0.75, respectively.[2]
- ClarIDHy was not actively-controlled. There are no direct comparative data versus the current second-line treatment, FOLFOX, and the indirect comparison to it has limitations. The point estimate for the OS HR has been applied to the economic model to suggest a benefit, despite not achieving statistical significance. This has been applied in a way that assumes proportional hazards, but statistical advice indicates uncertainty around this. The ClarIDHy[5] and ABC-06[8] studies included in the indirect comparison differed in design (double-blind primarily assessing PFS versus open-label primarily assessing OS, respectively); inclusion criteria (advanced cholangiocarcinoma with IDH1 mutation versus any advanced biliary tract cancer); and in methods of assessing and analysing PFS. Crossover from control to active treatment was permitted at disease progression in the ClarIDHy study (with at least 70% of patients crossing over to ivosidenib), but only 10% of the control group in ABC-06 were noted to have received chemotherapy (such as FOLFOX)

after disease progression. The proportion of patients receiving treatment in the second-line setting was 53% and 100% in the respective studies. However, data from patients in ClarIDHy who had received one prior therapy were used in the OS base case. Sample sizes were small. The comparison of PFS was naïve, with limitations characteristic of this type of analysis. Due to these limitations, the results of the indirect comparisons are uncertain.

4.3. Clinical expert input

Clinical experts consulted by SMC noted that ivosidenib is a therapeutic advance in this setting due to its targeted mechanism of action, efficacy and convenient oral administration. They believe that it would be used in place of the current standard of care, FOLFOX or CAPOX (capecitabine plus 5-fluorouracil).

4.4. Service implications

Clinical experts consulted by SMC noted that current timeframes for the return of IDH1 mutation test results may require service development to facilitate use of ivosidenib. Ivosidenib requires regular ECG monitoring, which may have service implications. However, patient numbers are expected to be small.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of ivosidenib, as an orphan and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Cholangiocarcinoma is a rare cancer and the subset of patients with IDH mutations is small, comprising about 15 to 20 patients in Scotland annually.
- Patients with locally advanced or metastatic IDH1 R132 mutated cholangiocarcinoma and previously treated with one prior line of therapy have a poor prognosis with median overall survival of around six months with standard FOLFOX chemotherapy. This requires many hospital visits for administration and for management of frequent serious adverse events, such as infection.
- Patients with IDH1 mutations tend to be younger (often in their 30s and 40s) and struggle to accept their dismal situation. They often feel isolated, anxious, and afraid. There is an unmet need for more effective treatment options with acceptable tolerability.
- Ivosidenib acts on the mutated enzyme that characterises the patient's cancer and accessing this targeted therapy would provide the patient and their family with reassurance that they are receiving optimal treatment. This may relieve some of the anxiety associated with their poor prognosis. It may also provide hope that improved survival may bridge to a time when other new therapies become available.
- By prolonging progression-free survival, ivosidenib may extend the period when the patient's disease is controlled, their quality of life is improved, and they are relatively well and able to spend time with their family and friends. Some patients experience progression-free and overall survival much greater than the average in the clinical studies.

- As ivosidenib may have fewer adverse events requiring hospital treatment and is orally administered in contrast with the burden of the alternative, intravenous chemotherapy regimen, patients benefit from fewer visits to hospital and improved quality of life.
- Overall, ivosidenib may provide the patient and their family with more time to make memories and to come to terms with what is happening in their family, which may be particularly beneficial for younger patients ('in the prime of their life') in the context of a limited life expectancy.
- Clinicians note that ivosidenib could be managed within existing infrastructure and would replace the current second-line chemotherapy, FOLFOX.

Additional Patient and Carer Involvement

We received a patient group submission from AMMF - The Cholangiocarcinoma Charity, which is a charitable incorporated organisation. AMMF has received 15.5% pharmaceutical company funding in the past two years, including from the submitting company. A representative from AMMF participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

A summary of the economic analysis performed is provided in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis
Time horizon	Lifetime (20 years, baseline start age of 61 years)
Population	Adult patients with locally advanced or metastatic cholangiocarcinoma (CCA) with an IDH1 mutation, who were previously treated with at least one prior line of systemic therapy
Comparators	FOLFOX; Best Supportive Care (BSC)
Model description	A partitioned survival model with health states of progression free, progressed disease and death. Within progression free and progressed disease states, patients could be on or off treatment. Model cycle length was 7 days.
Clinical data	Individual patient-level data (IPD) from the ClarlDHy study[5] for ivosidenib vs placebo (representing BSC comparator outcomes). This provided the PFS, progressed disease, OS, adverse event, time on treatment (ToT) and utility data for ivosidenib and BSC in the economic analysis. Relative OS outcomes for ivosidenib vs FOLFOX were derived from a Bucher indirect comparison utilising data for the sub-group of patients from the ClarlDHy study who had one prior therapy, and from the ITT population who all had one prior therapy in the ABC-06 study[8] for FOLFOX plus active symptom control (ASC) versus ASC. Adverse events of grade 3+ occurring in ≥5% of patients were included in the economic analysis.
Extrapolation	Extrapolation of PFS and OS for ivosidenib and BSC was performed by fitting independent parametric functions to the Kaplan-Meier data from the ClarlDHy study. The base case function selected for ivosidenib PFS and OS extrapolation was the log-normal based on goodness of fit statistics and plausibility of the projections, and the Weibull for BSC based primarily on clinical plausibility relating to the poor prognosis of

	patients with CCA after first line treatment. Other functions had similar goodness of fit and were explored in scenario analysis. As patients in the placebo arm of the ClarlDHy study were permitted to cross over to receive ivosidenib on disease progression, for placebo/BSC OS extrapolation was adjusted for the confounding effects of ~70% cross- over using the RPSFT method. Extrapolation of OS for FOLFOX was based on applying to the ivosidenib log normal reference curve the Hazard Ratio (HR) for ivosidenib versus FOLFOX estimated from a Bucher indirect comparison. Relative PFS was based on a naïve comparison, and the log normal function was used in the base case for FOLFOX PFS extrapolation based on best statistical fit to the pseudo patient level data generated from the PFS KM curve recreated for FOLFOX. ToT extrapolation was performed by fitting a log-normal function to the ivosidenib data in ClarlDHy, to be consistent with OS extrapolation (as the ToT data were mature and there was little difference in fit between functions). The ToT for ivosidenib was capped at PFS based on expert opinion and the SPC that treatment is up to disease progression. ToT for FOLFOX was assumed to be to progression (or death) up to a maximum of 24 weeks (as the regimen is twice weekly for 12 cycles).
Quality of life	Health state utility values were informed via regression analysis of EQ-5D-5L data collected in the ClarlDHY study, and mapped to the UK 3L value set. The estimated utilities used in the base case varied according to whether a patient was on or off-treatment in either the PFS or progressed disease states. Adverse event and IV administration disutilities were applied based on prior published technology appraisal (TA) estimates.
Costs and resource use	Medicine acquisition costs have been estimated for ivosidenib, and FOLFOX. Medicines administration costs, including continuous infusion, were estimated for the oxaliplatin and fluorouracil components of FOLFOX. Relative dose intensity (RDI) was assumed for ivosidenib, from the ClarlDHy study. Vial and oral tablet wastage was also accounted for. Subsequent therapies were only assumed for the ivosidenib arm consisting of FOLFOX in a proportion of patients (as representative of chemotherapy that might be used third line after ivosidenib). Health state resource use and one-off costs for adverse event management were based on estimates used in prior NICE TA's (themselves based on expert clinical opinion). A further cost was applied to ivosidenib for additional 3 monthly ECG monitoring due to potential risk of QC prolongation. End of life care costs were included based on a published source. IDH1 mutation testing costs were not included in the company base case on the grounds that it is routine clinical practice in Scotland, but included in a scenario analysis.
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 NHSScotland. Under the PAS, a discount was offered on the list price of ivosidenib. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

6.2. Results

The base case results are presented in Table 6.2 below at list prices.

Table 6.2 Base case results at list prices

Technologies	ICER
Ivosidenib versus:	
FOLFOX	£136,650
BSC	£136,824

Abbreviations: BSC, best supportive care; FOLFOX, folinic acid + fluorouracil + oxaliplatin; ICER, incremental cost-effectiveness ratio.

The key driver of cost-effectiveness for ivosidenib was the incremental life years and QALYs associated with greater survival time in the post progressive state versus FOLFOX, and in both the pre and post progressive disease states versus BSC. Incremental costs estimated for ivosidenib versus each comparator were driven primarily by additional medicine acquisition costs, with additional health state resource use and subsequent costs, but with partial cost offsets associated with lower medicine administration costs versus FOLFOX (zero for ivosidenib and approximately doubled the costs of FOLFOX relative to medicine acquisition costs alone).

6.3. Sensitivity analyses

In one- way sensitivity analysis the results were particularly sensitive to varying the HR for OS for the comparison with FOLFOX. The company presented a range of scenario analyses covering time horizon, discounting, OS, PFS and ToT extrapolations and assumptions, health state utility scenarios, and including IDHG1 mutation testing costs. Further scenario analyses were requested from the company, including using the one prior therapy sub-group data from ClarIDHy study for all extrapolations. Results for selected scenarios with greatest ICER impact versus FOLFOX and/or BSC, or of particular interest, are presented in Table 6.3 below. This shows ICER sensitivity to exploratory scenarios for the HR for OS in the comparison with FOLFOX (Scenario 2), the function used for ivosidenib OS extrapolation (scenario 3), or allowing treatment beyond progression for ivosidenib (scenario 6), and combined scenario analyses (Scenario 11)

Table 6.3 Selected scenario analyses, at list prices

	Parameter	Base case	Scenarios	ICER (£/QALY) Ivosidenib vs FOLFOX	ICER (£/QALY) Ivosidenib vs BSC
	Base case			***£136,650***	***£136,824***
1	Time horizon	20 years	5 years	£163,091	£166,964
2	Ivosidenib OS HR from the Bucher indirect comparison	HR from ITC versus FOLFOX	a.1.0	£4,430,624	N/A
			b. 0.9	£478,901	N/A
			c. 0.8	£259,894	N/A
3	Ivosidenib OS extrapolation	Log normal	a.Log-logistic	£125,159	£125,649
			b.Generalized gamma	£160,832	£163,397
			c.Exponential	£179,450	£182,680
4	Ivosidenib PFS	Log-normal	Generalised gamma	£157,730	£161,980

5	BSC OS extrapolation	Weibull	a.Gompertz	£137,659	£136,650
			b.Exponential	£140,858	£136,650
			c. Generalised gamma	£149,483	£136,650
			d.Log-normal	£159,514	£136,650
6	Ivosidenib ToT	Treat to PFS	Treat beyond progression	£165,413	£171,186
7	ClarlDHy study patient population	1 prior therapy sub-group used only for ivosidenib OS estimation in indirect comparison vs FOLFOX	Using 1 prior therapy sub-group from ClarlDHy study for PFS, OS and ToT estimates ivosidenib and BSC	£151,100	£167,603
8	Utility source	Utility difference associated with on-off treatment (same utility for pre and post progression)	Utility by heath state	£139,587	£138,779
9	IDH1 testing costs	Not included	Included	£137,203	£137,110
10	% of ivosidenib patients receiving subsequent treatment with FOLFOX	Company assumption from ClarylDHy	20%	£139,105	£139,419
11	Combined scenario analysis*	All base case settings	a.Combined scenario for FOLFOX OS HR of 0.8, exponential OS extrapolation for ivosidenib, Treat to progression, 1 prior therapy sub-group, utility by health state (Scenarios 2c+3c+6+7+8)	£208,878	£464,922
			b.Combined scenario 11a with assumed FOLFOX OS HR of 0.9	£208,883	£878,847
			c.Combined scenario 11a but using gen gamma BSC OS extrapolation replacing exponential OS extrapolation for ivosidenib (Scenarios 2c+5c+6+7+8)	£166,817	£356,058
		-	d. Combined scenario 11c with assumed FOLFOX OS HR of 0.9	£166,817	£667,374

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years BSC, best supportive care; FOLFOX, folinic acid + fluorouracil + oxaliplatin; PFS, progression-free survival; OS, overall survival; ToT, time on treatment; HR, Hazard Ratio; PAS,; N/A, Not Applicable

6.4. Key strengths

- Comparators are appropriate for the second line positioning of ivosidenib.
- Individual patient level data from the ClarlDHy study with reasonable mature observed PFS and OS data so enabling reasonably robust PFS/OS extrapolation for ivosidenib and placebo/BSC (although BSC OS was crossover adjusted so potentially adds a level of uncertainty).
- The regression analysis of EQ 5D-5L data from the ClarlDHy study appears robust.

6.5. Key uncertainties

- There is uncertainty over the survival benefit for ivosidenib versus FOLFOX associated with limitations of the Bucher indirect comparison for estimating relative OS (summarised in section 4.2), including differences in CalrlDHy and ABC-06 study design, patient inclusion criteria and in the validity of the proportional hazards (PH) assumption for applying a constant HR for ivosidenib vs FOLFOX OS in the economic analysis. Hence, it is uncertain if the estimated treatment benefit can be assumed to apply over the whole time horizon. The company stated that evidence presented in the Zhu et al publication[6] reporting constant OS HRs by line of therapy sub-groups supported that an assumption of PH is reasonable. However, there remains some uncertainty over this assumption for the economic analysis.
- The results were sensitive to the OS hazard ratio resulting from the indirect comparison. Scenario analyses applying exploratory HRs of 0.8, 0.9 and one produces potentially large increases in the ICER (Scenario 2, Table 6.3), and coupled with uncertainties over the robustness of the indirect comparison, demonstrated the sensitivity of the ICER to whether a survival benefit may exist for ivosidenib over FOLFOX, and if so the magnitude of that survival benefit.
- The comparison of PFS outcomes for ivosidenib and FOLFOX was based on a naïve comparison in the base case so has limitations for use in the economic analysis. With extrapolation this estimated only a very small PFS difference, with the vast majority of the incremental QALY gains for ivosidenib vs FOLFOX estimated to be generated post-progression (i.e. associated with highly uncertain extrapolated OS estimates).
- The Weibull function has been used in the base case to extrapolate OS outcomes for BSC based on expert opinion, which produces the most pessimistic outcomes for BSC of the functions tested (2.9% at 2 years, 0% at 5 years), and the Gompertz and exponential functions tested in scenario analysis also estimated very low survival prognosis (3.6%/4.9% at 2 years, 0%/0.1% respectively at 5 years). There is little difference in goodness of fit and visual fit between all functions tested, hence further scenario analysis was requested to explore the impact of applying functions that produce slightly better 2 and 5 years OS projections for BSC (i.e. generalised gamma and log normal with 2 and 5 year survival estimated at 6.6%/8.8% and 0.6%/1.2% respectively). Applying these produced higher ICERs for the comparison with BSC using generalised gamma and log normal distributions (Scenarios 5c and 5d in Table 6.3).
- In addition, applying the exponential function to ivosidenib OS extrapolation (also a good fitting function) produces a less optimistic 5 year OS estimate for ivosidenib of

1.9% compared to 5.6% with the base case log normal extrapolation, with a consequent upward impact on the ICERs vs FOLFOX and BSC (see scenario 3c, Table 6.3).

- The adjustment for crossover to ivosidenib from placebo/BSC in the ClarlDHy study adds to uncertainty regarding the relative OS benefit vs BSC estimated in the economic analysis, although the adjustment has been handled in an appropriate way.
- A 20-year base case time horizon is long given the poor prognosis – it is applied as some patients with ivosidenib OS extrapolation are assumed to be alive at 20 years. However, a shorter time horizon such as 5 years is likely more realistic to apply (see scenario 1 in Table 6.3)
- Time on treatment (ToT) has been estimated for ivosidenib with a cap on no further treatment beyond disease progression that may underestimate treatment duration for ivosidenib in clinical practice. Scenario analysis without capping ToT demonstrates higher ICERs versus FOLFOX and BSC (Scenario 6, Table 6.3).
- Assuming the same pre- and post- progression utilities (but differentiating by on-off treatment status instead in both states) in the base case lacks face validity. The scenarios applying differential utilities by health state are more realistic (scenario 8, Table 6.3). Using this analysis had only a small impact on the ICER but would represent a more plausible base case setting and was therefore incorporated into the combined scenarios in Table 6.3.
- Subsequent treatment with FOLFOX after progression with ivosidenib was assumed for a proportion of patients estimated from the CarlDHy study. There is uncertainty over whether this estimate would apply in Scottish clinical practice, and assuming a higher proportion would increase the ICER (Scenario 10, Table 6.3).
- As described above, there are a number of areas of parameter uncertainty in the comparisons with FOLFOX and BSC. Exploratory combined scenario analysis using the company economic model has been performed demonstrating ICER sensitivity to these scenarios, presented as Scenarios 11 in Table 6.3.

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

7. Conclusion

The Committee considered the benefits of ivosidenib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as ivosidenib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted ivosidenib for use in NHSScotland.

8. Guidelines and Protocols

The British Society of Gastroenterology (BSG) guidelines for the diagnosis and management of cholangiocarcinoma were published in September 2023.

The European Society of Medical Oncology (ESMO) Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up was published in 2022.[4]

9. Additional Information

9.1. Product availability date

5 July 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28-day cycle (£)
Ivosidenib	**500 mg orally once daily**	**11,667**

Costs from BNF online on 25 April 2024. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The company estimates that there will be around 38 patients eligible for treatment with ivosidenib each year. The uptake rate was estimated to be 39% (15 patients) each year.

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.

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

References

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5. Abou-Alfa Gk MTJMMKRKLSJAJ, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21(6):796-807.
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7. Agios Pharmaceuticals. Clinical study report for AG120-C-005, 20 February 2020.
8. Lamarca A PDHWHSRPJMYTAA, et al. .Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021;22(5):690-701.

This assessment is based on data submitted by the applicant company up to and including 11 June 2024.

**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.