NCPE Assessment

Technical Summary

Ivosidenib (Tibsovo®)

HTA ID 23016

07 March 2025

Applicant: Servier Laboratories (Ireland) Ltd

Ivosidenib as monotherapy for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated with at least one prior line of systemic therapy.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of ivosidenib (Tibsovo®).

Following assessment of the Applicant's submission, the NCPE recommends that ivosidenib (Tibsovo®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.*

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Servier Laboratories (Ireland) Ltd) Health Technology Assessment of ivosidenib (Tibsovo®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health-related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In February 2024, Servier Laboratories (Ireland) Ltd submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of ivosidenib (Tibsovo®) for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma (CCA) with an isocitrate dehydrogenase 1 (IDH1) R132 mutation who were previously treated with at least one prior line of systemic therapy. CCA affects an estimated 230 people in Ireland each year, mainly occurring in those aged 65 years and older. The majority of CCA cases are diagnosed at an advanced stage and consequently, prognosis is poor, with five-year survival ranging from 7% to 20%.

Servier Laboratories (Ireland) Ltd is seeking reimbursement of ivosidenib on the High Tech Drug Arrangement. Ivosidenib is a first-in-class IDH1 inhibitor. IDH1 is an enzyme that is mutated and overexpressed in some cancers, leading to abnormal cell growth and proliferation. Ivosidenib inhibits mutated IDH1, blocking the enzymatic activity and further differentiation of cancer cells. The recommended dose is 500mg (two x 250mg tablets) taken orally once daily. Treatment is recommended until disease progression or until no longer tolerated by the patient as per the summary of product characteristics (SmPC).

The current standard of care for the treatment of patients with CCA at second-line, in Ireland, includes chemotherapy (primarily FOLFOX, which is the 'preferred' treatment in international clinical guidelines) in those able for treatment, and best supportive care (BSC) in those unable for treatment. The Review Group note that FOLFIRI has not been included as a comparator but is a 'recommended' treatment in international clinical guidelines and used in the Irish setting, although less frequently than FOLFOX based on clinical opinion. The Review Group considers recently reimbursed treatments larotrectinib and entrectinib (for advanced or metastatic neurotrophic tyrosine receptor kinase gene fusion displaying cancer to be potential comparators in a very small subpopulation of patients (reported to be <1%)). In addition, pemigatinib may be a relevant comparator in the future in a subset of patients with locally advanced or metastatic CCA that have progressed after at least one prior line of systemic therapy (if reimbursed).

1. Comparative effectiveness of ivosidenib

The efficacy and safety of ivosidenib was assessed in the ClarIDHy trial (n=187). ClarIDHy is a randomised, double-blind, placebo-controlled, phase III trial of participants with

unresectable or metastatic CCA and an IDH1 mutation, following disease progression after prior therapy with at least one gemcitabine or 5-Fluorouracil containing regimen. Ivosidenib was administered at a dose of 500mg orally once daily until disease progression or unacceptable toxicity. The primary endpoint of ClarIDHy was progression-free survival (PFS) as assessed by an Independent Radiology Committee, and key secondary endpoints included overall survival (OS), objective response rate and duration of response. Participants in the placebo arm were permitted to crossover to active treatment upon disease progression, of which 70.5% (n=43) crossed over. As a result of crossover, an analysis of OS adjusted for treatment switching was required. The Applicant presented the rank preserving structural failure time (RPSFT) method, based on a common treatment effect assumption (i.e., that the treatment effect of ivosidenib is the same for all participants, regardless of whether treatment is received before or after progression). Median PFS was 2.7 months (95% confidence interval [CI] 1.6, 4.2) in the ivosidenib arm and 1.4 months (95% CI 1.4, 1.6) in the placebo arm. The hazard ratio [HR] was 0.37 (95% CI 0.25, 0.54, p<0.0001). Median OS was 10.3 months (95% CI 7.8, 12.4) in the ivosidenib arm and 7.5 months in the placebo arm (95% CI 4.8, 11.1). The HR was 0.79 (95% CI 0.56, 1.12, p=0.09). The RPSFT-adjusted median OS was 5.1 months (95% CI 3.8, 7.6) in the placebo arm. The HR was 0.49 (95% CI 0.34, 0.70, p<0.01).

A key limitation of the ClarIDHy trial includes the trial design. At Early Scientific Advice, the CHMP recommended OS as a primary endpoint (rather than PFS which is considered a surrogate endpoint) and suggested an Investigator's choice active control arm (rather than placebo) to facilitate clinical applicability and recruitment and eliminate the need for crossover. Neither approaches were taken by the trial investigators. Further, the RPSFT method is based on a common treatment effect assumption, however an RPSFT analysis does not account for subsequent anticancer therapies that would have been started in the placebo arm in the absence of crossover. Therefore, the only period contributing to the placebo efficacy and safety data is before the participant crossing over, which is not expected to include much data (if any) after the start of subsequent anticancer therapies.

ClarIDHy provided head-to-head comparative evidence for ivosidenib versus placebo. Placebo was considered to be a proxy for BSC. The Review Group consider placebo to be a reasonable proxy for BSC. However, trial participants were fit for active treatment; in the

real-world setting, it is those patients who are unfit for treatment that would be considered for BSC. Indirect comparative methods were required to inform the comparison between ivosidenib and FOLFOX as the comparator of relevance to the decision problem. The Applicant conducted a Bucher indirect treatment comparison (ITC) to compare OS between ivosidenib (from ClarIDHy), and FOLFOX (from ABC-06), assuming that active symptom control (ASC) and placebo can be considered to be a common comparator. The ABC-06 trial, was a randomised, phase III, multicentre, open label study assessing the efficacy of ASC alone compared to FOLFOX plus ASC in participants with locally advanced or metastatic biliary tract cancer. A subgroup of the ClarIDHy trial (n=65) with up to one prior line of therapy and with Eastern Cooperative Oncology Group performance score 0 or 1 informed the ITC to align with the population of the ABC-06 trial. However, the Applicant used the overall population of the ABC-06 trial in the ITC, including participants with different cancer types (gallbladder and ampullary carcinoma). A Bucher comparison of PFS was not presented by the Applicant, as neither PFS data for ASC nor a PFS HR for FOLFOX plus ASC versus ASC were reported within ABC-06.

In the Bucher ITC, an OS benefit for ivosidenib over FOLFOX was not demonstrated (HR 0.58, 95% CI 0.31, 1.09). Limitations of the Bucher ITC include heterogeneity of included trials (differences in trial design and patient demographics including cancer site), which may bias results and leads to uncertainty in the ITC analyses. A naïve comparison for ivosidenib versus FOLFOX for PFS was presented as an ITC was not possible. The Review Group highlight the challenges associated with naïve comparisons, including the inability to adjust for prognostic factors which subjects the analyses to significant confounding and bias owing to the lack of control for systematic differences between trials.

2. Safety of ivosidenib

Treatment-emergent adverse events (TEAEs) were reported in 97.6% of ivosidenib-treated participants versus 96.0% in the placebo arm. The rate of Grade ≥3 TEAEs were higher in the ivosidenib arm (51.2% vs. 37.3%). The most common TEAEs in participants exposed to ivosidenib were fatigue (30.9%), decreased appetite (24.4%), cough (25.2%), gastrointestinal symptoms: nausea (42.3%), diarrhoea (35.0%), abdominal pain (24.4%), vomiting (22.8%), and ascites (22.8%). Compared to placebo, ivosidenib showed higher incidence rates (≥5%)

of gastrointestinal adverse events (78% vs 64.4%), anaemia (18.7% vs. 5.1%), hypertension, QT prolongation (9.8% vs. 3.4%), peripheral neuropathy (6.5% vs. 0%), rash, hyperglycaemia, and various laboratory abnormalities (e.g., aminotransferase increased and white blood cell count decreased). The incidence of serious adverse events was higher in the ivosidenib arm (35.0% vs 23.7%). QT prolongation was an adverse event of special interest due to its risk of life-threatening arrhythmias in the SmPC.

3. Cost effectiveness of ivosidenib

Methods

The Applicant has compared the cost-effectiveness of ivosidenib to FOLFOX and to BSC in the base case.

A three-state partitioned survival model was submitted by the Applicant, comprising three mutually exclusive Health States: Progression-Free (PF), Progressed Disease (PD) and Death. The PF and PD Health States are further divided into on- and off-treatment periods to account for treatment discontinuation prior to disease progression. Key efficacy inputs were PFS and OS. The population was based on the ClarIDHy trial. Treatment duration for ivosidenib was informed by time-to-treatment discontinuation data from ClarIDHy, capped by disease progression. OS and PFS were modelled independently. The proportion of patients in each health state over time was derived directly from the OS and PFS area under the curve, using treatment group-specific parametric distributions fitted to time-to-event data. PFS and OS data from the ClarIDHy trial were used to inform the treatment effects of ivosidenib in the model. OS data for the BSC arm (from ClarIDHy) used in the model was adjusted using the RPSFT method to account for crossover. Comparator treatment effects for FOLFOX were informed by data from the ABC-06 trial. OS for FOLFOX was derived using a Bucher ITC. For PFS, pseudo individual patient-level (IPD)-data were reconstructed from digitised ABC-06 Kaplan Meier data, to enable a naïve comparison for FOLFOX, as PFS data were not reported for the ASC arm in the ABC-06 trial. In each cycle, patients accrue quality adjusted life years (QALYs) and incur costs based on the utilities and costs specified for the Health State occupied, the relevant treatment arm, and the time on treatment (ToT). Utility values were derived from EQ-5D-5L data collected in ClarIDHy, mapped to EQ-5D-3L. The Review Group highlighted concerns that the utilities used in the Applicant base case were

derived from a model which included only treatment status and TRAEs. The Review Group do not consider the stepwise model selection approach taken appropriate, as the analysis model should be consistent with the cost-effectiveness model structure and assumptions made. In addition, the utility values used in the Applicant's base case lack face-validity because utility values are linked to treatment status only ('on treatment' or 'off treatment'), and not disease progression (i.e., disease progression is assumed to have no effect on Health State utility). The HSE perspective was taken.

The Review Group identified a number of limitations in the Applicant's base case, which were explored through changes in the NCPE adjusted base case. These changes included: 1) choice of OS extrapolation curves; 2) ToT for FOLFOX (Applicant base case: capped by PFS; NCPE adjusted base case: ToT as observed in ABC-06; 3) wastage (Applicant base case: no wastage; NCPE adjusted base case: wastage; 4) relative dose intensity (Applicant base case: 96%; NCPE adjusted base case: 100%); and 5) utilities (Applicant base case: treatment-status specific utilities; NCPE adjusted base case: progression-status specific utilities).

Results

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1 (versus FOLFOX) and Table 2 (versus BSC). Respective results of the NCPE adjusted base case are presented in Table 3 and Table 4. The probabilities of cost-effectiveness, for ivosidenib versus FOLFOX and versus BSC, in the NCPE adjusted base case was 0% at both thresholds of €20,000/QALY and €45,000/QALY.

Table 1 Applicant base case incremental cost-effectiveness results [a, b] (FOLFOX)

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
FOLFOX	60,837	0.51	-	-	-
Ivosidenib	135,948	0.95	75,111	0.44	170,243

FOLFOX: *Oxaliplatin, leucovorin and 5-fuorouracil;* ***ICER:*** *incremental cost-effectiveness ratio;* ***QALY****: quality adjusted life year*

[a] Corresponding probabilistic ICER using 5,000 iterations =€183,578/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% on costs and outcomes.

[b] A CIC PAS has been proposed for ivosidenib, not included here.

Table 2 Applicant base case incremental cost-effectiveness results [a, b] (BSC)

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BSC	52,910	0.41	-	-	-
Ivosidenib	135,948	0.95	83,038	0.54	154,546

BSC: *best supportive care;* ***ICER:*** *incremental cost-effectiveness ratio;* ***QALY****: quality adjusted life year*

[a] Corresponding probabilistic ICER using 5,000 iterations =€153,057/QALY. Figures in the table are rounded, and so calculations may

not be directly replicable. Discount rate of 4% on costs and outcomes.
[b] A CIC PAS has been proposed for ivosidenib, not included here.

Table 3 NCPE adjusted base case incremental cost-effectiveness results[a,b] (FOLFOX)

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
FOLFOX	57,035	0.51	-	-	-
Ivosidenib	144,472	0.87	87,436	0.36	242,529

FOLFOX: *Oxaliplatin, leucovorin and 5-fuorouracil;* ***ICER:*** *incremental cost-effectiveness ratio;* ***QALY****: quality adjusted life year*
[a] Corresponding probabilistic ICER using 5,000 iterations =€247,190/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% on costs and outcomes.
[b] A CIC PAS has been proposed for ivosidenib, not included here.

Table 4 NCPE adjusted base case incremental cost-effectiveness results [a, b] (BSC)

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BSC	53,752	0.47	-	-	-
Ivosidenib	144,472	0.87	90,720	0.40	228,276

BSC: *best supportive care;* ***ICER:*** *incremental cost-effectiveness ratio;* ***QALY****: quality adjusted life year*
[a] Corresponding probabilistic ICER using 5,000 iterations =€241,232/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% on costs and outcomes.
[b] A CIC PAS has been proposed for ivosidenib, not included here.

Sensitivity analysis

Sensitivity analyses indicated that the main drivers of cost-effectiveness in the Applicant base case related to the choice of OS extrapolation curves for ivosidenib and BSC. A Price-ICER analysis, under the NCPE adjusted base case assumptions, indicates that a reduction of about 84.54% and 95.24%, in the price-to-wholesaler (PtW) of ivosidenib (versus FOLFOX), would be required to meet the €45,000/QALY and €20,000/QALY thresholds respectively. A reduction of about 86.46% and 98.26%, in the PtW of ivosidenib (versus BSC), would be required to meet the €45,000/QALY and €20,000/QALY thresholds respectively.

4. Budget impact of ivosidenib

The PtW of ivosidenib is €13,800 for one pack (60 x 250mg tablets). The estimated cost of ivosidenib per-patient, per-treatment course is €79,998 (VAT not applicable), assuming a mean treatment duration derived from the ToT curve in the cost-effectiveness model (6.25 x 28-day cycles).

The Applicant estimated that 42 patients would receive treatment with ivosidenib over five years. The Applicant's estimated five-year cumulative gross drug budget impact for ivosidenib is €3.39 million (VAT not applicable). The estimated five-year cumulative net drug budget impact is €3.34 million including VAT (€3.35 million excluding VAT). There is considerable uncertainty associated with the budget impact estimates. In particular, the

Review Group considers that the true number of patients expected to receive treatment may be higher given ivosidenib is a first-in-class targeted treatment, and thus the Applicant's budget impact estimates may be underestimated.

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

The NCPE recommends that ivosidenib not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.