NCPE Assessment

Technical Summary

Ivosidenib (Tibsovo®)

HTA ID: 23015

December 2025

Applicant: Servier Laboratories (Ireland) Ltd.

Ivosidenib, in combination with azacitidine, for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of ivosidenib (Tibsovo®), when given in combination with azacitidine, for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy.

Following assessment of the Applicant's submission, the NCPE recommends that ivosidenib (Tibsovo®) not be considered for reimbursement (when given in combination with azacitidine for this indication).*

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 August 2024, Servier Laboratories (Ireland) Ltd. submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of ivosidenib (Tibsovo®) in combination with azacitidine for the treatment of adult patients with newly diagnosed AML with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy.

Servier Laboratories (Ireland) Ltd. is seeking reimbursement of ivosidenib on the High-Tech Drug Arrangement. IDH1 is an enzyme that is mutated and overexpressed in some cancers, leading to abnormal cell growth and proliferation. Ivosidenib is an inhibitor of the mutant IDH1 R132 enzyme. Ivosidenib, 500mg orally once daily, is given on Days 1 to 28 in combination with azacitidine 75mg/m^2 body surface area (BSA) (subcutaneously (SC) or intravenously (IV)) given on Days 1 to 7 of each 28-day cycle (hereafter referred to as IvoAZA). Patients should be treated with IvoAZA for a minimum of six cycles and continued until disease progression or until no longer tolerated. The current standard of care for the treatment of patients with newly diagnosed AML, with a IDH1 R132 mutation who are ineligible to receive standard induction chemotherapy, is venetoclax in combination with azacitidine (VenAZA). Approximately 40% to 60% of patients with newly diagnosed AML are considered ineligible for standard induction chemotherapy, in Ireland, due to age-related factors, ECOG performance status and/ or comorbidities. The Applicant included VenAZA and azacitidine monotherapy as comparators in their submission The Applicant considers VenAZA to be the main comparator which the Review Group considers appropriate. This aligns with international clinical guidelines and clinical opinion in Ireland. The Review Group do not consider azacitidine monotherapy to be a relevant comparator, as azacitidine monotherapy is only considered in certain circumstances for a small number of patients who are not candidates for VenAZA.

1. Comparative effectiveness of ivosidenib

The efficacy and safety of IvoAZA versus placebo plus azacitidine (PboAZA) was assessed in the AGILE trial (n=146). AGILE is a phase III, multicentre, randomised (1:1), placebo-controlled trial of adult participants with newly diagnosed AML, with an IDH1 mutation, who

are ineligible for standard induction chemotherapy. Participants were randomised to oral ivosidenib (500mg once daily) on Day 1 to 28 plus azacitidine or matched placebo plus azacitidine. Azacitidine (75mg/m^2 BSA) was administered subcutaneously or intravenously on Days 1 to 7 of each 28-day cycle. In the original trial protocol, 392 participants were planned to be randomised with overall survival (OS) as the primary endpoint. Amendments in the trial protocol resulted in a change in the primary endpoint to Event Free Survival (EFS), leading to a reduction to 200 participants. OS became a secondary endpoint. The AGILE study was prematurely discontinued, as recommended by the Independent Data Monitoring Committee following a request for an unplanned efficacy analysis. The unplanned analysis became the primary analysis for EFS (data cut off 18 March 2021; median follow up of 12.4 months). The primary efficacy endpoint was met with an improvement in EFS demonstrated for IvoAZA versus PboAZA; (hazard ratio [HR] = 0.33; 95% confidence interval [CI], 0.16 to 0.69; P = 0.0011). Improvement in EFS was driven by the difference in the proportion of participants with treatment failure (assigned an event time of the date of randomization). At the time of the primary analysis, an improvement in OS was shown for IvoAZA versus PboAZA (HR = 0.44; 95% CI, 0.27 to 0.73; P = 0.0005) with median follow up of 15.0 months. In an updated analysis of OS (data cut-off 30 June 2022; median follow-up of 28.6 months), median OS was 29.3 months (IvoAZA) versus 7.9 months (PboAZA) (HR = 0.42; 95% CI, 0.27 to 0.65; P = 0.0005). Secondary endpoints also included complete remission (CR) and complete remission with incomplete haematologic recovery (CRi) rates. Improvement in CR/CRi rate was seen for IvoAZA versus PboAZA (odds ratio (OR) = 5.90; 95% CI, 2.69 to 12.97; P < 0.0001). Health related quality of life (HRQoL) was a secondary outcome measured using EORTC QLQ-C30 questionnaires. No statistically significant or clinically meaningful differences were observed between arms. HRQoL assessments were not adjusted for multiplicity and are considered descriptive only.

Key limitations, identified by the Review Group, include early discontinuation of the trial (based on efficacy) which may result in overestimated treatment effects. In addition, the criteria used to define ineligibility for standard induction chemotherapy may not be aligned with criteria used in clinical practice in Ireland. Thus, generalisability of the AGILE results to the Irish setting is uncertain.

A Bayesian network meta-analysis (NMA) compared IvoAZA and VenAZA for the outcomes of

EFS, OS, and CR/CRi. AGILE and VIALE-A (an international, randomised, double-blinded, phase III study comparing VenAZA and PboAZA) informed the NMA. The Review Group note a key limitation of the NMA was that enrolment in VIALE-A was not restricted to patients with AML with an IDH1 mutation. Subgroup analysis, from VIALE-A, showed a numerically greater relative OS benefit of VenAZA over PboAZA in participants with IDH1 mutation compared to those without the mutation. Thus, use of data from the entire population of VIALE-A, in the NMA, may introduce bias in favour of IvoAZA if this difference in OS benefit is a result of genuine effect-modification. However, results from the subgroup analysis should be interpreted with caution due to small sample size and that IDH1 mutation was not a stratification factor in VIALE-A. Other methodological concerns noted, with the NMA, included the use of a fixed-effects model and the assumption of proportional hazards for OS. The NMA hazard ratio (HR) outputs were numerically favourable towards IvoAZA versus VenAZA for all outcomes considered, however, the effect estimates were not statistically significant. Given the NMA limitations, it is not possible to make a definitive conclusion regarding the relative effectiveness of IvoAZ versus VenAZA.

2. Safety of ivosidenib

Treatment emergent adverse event (TEAE) reported in each arm of AGILE were comparable, occurring in 70 of 71 participants (99%) on IvoAZA and 73 of 73 participants (100%) on PboAZA. Grade ≥3 adverse events (AEs) occurred in 66 of 71 (93%) on IvoAZA and 69 of 73 (94.5%) in PboAZA. An increased incidence in AEs of special interest was observed with IvoAZA versus PboAZA and were included in the EMA's Risk Management Plan for ivosidenib; incidence of QT prolongation 19.7% versus 6.8%, leucocytosis 11.3% versus 1.4% and differentiation syndrome 14.1% versus 8.2%. There is the potential for drug-drug interactions (DDIs) with ivosidenib due to its metabolism through CYP450 isoenzymes, specifically CYP3A4. This is of relevance for concomitant prescribing of antifungal azoles for prophylaxis and treatment in AML. The SmPC states that the dose of ivosidenib should be reduced to 250mg once daily if co-prescribed with moderate to strong azole antifungals to avoid an increased risk of QT prolongation. Conversely, there is a risk that concomitant ivosidenib may result in decreased serum concentrations of selected azoles, increasing the risk of fungal infections. The AGILE protocol did not recommend dose adjustments for ivosidenib despite over half of the participants receiving concomitant azoles.

Cost effectiveness of ivosidenib

Methods

The Applicant investigated the cost-effectiveness of IvoAZA versus VenAZA and IvoAZA versus azacitidine monotherapy in the base case. The Review Group do not consider azacitidine monotherapy to be a relevant comparator, so the comparison with azacitidine monotherapy was instead explored in a scenario analysis in the NCPE adjusted base case. The Applicant's model included a hybrid partitioned-survival analysis (PartSA) and Markov model with three mutually exclusive health states; Event-Free (EF), Progressed Disease or Relapse (PD/RL) and Death. The EF state is further partitioned into an estimated proportion of patients with or without CR/CRi, and a parallel Long-Term Survival (LTS) state for patients that remain in CR/CRi from Year 3 onwards. Patients entering the LTS state are assumed to discontinue treatment, are no longer at risk of relapse and experience no increased risk in mortality compared with the general population. Clinical opinion obtained, by the Review Group, did not align with the Applicant's cure assumption in the absence of transplant. Instead, patients are expected to continue with IvoAZA or VenAZA until disease progression or unacceptable toxicity as per the respective SmPCs. The treatment effects captured by the cost-effectiveness model were the delay of disease progression and death. The key efficacy inputs to the model were OS, EFS, time on treatment (ToT) and CR/CRi rates, which were derived from the AGILE trial and the Applicant's NMA.

The Review Group identified limitations in the Applicant's cost-effectiveness model, which were explored in the NCPE-adjusted base case. These included the use of alternative parametric models for EFS, ToT and OS, the removal of a cure assumption; use of alternative utility values based on pooled data from VIALE-A and VIALE-C (phase III, double-blind, international study comparing venetoclax plus low-dose cytarabine (LDAC) with placebo plus LDAC in newly diagnosed AML patients ineligible for induction chemotherapy), revised estimates for end-of-life costs; implementation of the dosing regimen and relative dose intensity of VenAZA and IvoAZA as per the VIALE-A and AGILE trials respectively; implementation of the proportions treated with azole antifungals as per the AGILE and VIALE-A trials, adjustment of the number of bed days associated with VenAZA in the first cycle to align with clinical practice in Ireland.

Scenario analyses were conducted by the NCPE Review Group, including investigation of the impact of dose reductions of venetoclax and ivosidenib, in line with the respective SmPCs, due to concomitant azoles for the entire modelled population. A scenario analysis of the NCPE adjusted base case, comparing IvoAZA with azacitidine monotherapy, and using the same parametric distributions to extrapolate outcomes in both the azacitidine monotherapy arm and the IvoAZA arm, was also explored.

Results

The results of the Applicant's base case deterministic analysis for IvoAZA versus VenAZA and IvoAZA versus azacitidine monotherapy are presented in Table 1 and 2. The NCPE adjusted base case deterministic analysis, comparing IvoAZA with VenAZA, is presented in Table 3. The probabilities of cost-effectiveness for IvoAZA versus VenAZA, in the NCPE adjusted base case, was 0% at both thresholds of €20,000/QALY and €45,000/QALY. The most influential change, made in the NCPE adjusted base case, was the removal of the cure assumption.

Table 1: Applicant base case incremental cost-effectiveness results for IvoAZA versus VenAZA and IvoAZA versus azacitidine monotherapy [a,b,]

Treatments	Total costs (€)	Total LYG	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
IvoAza	497,841	5.75	3.04	-	-	-
VenAza	422,391	4.08	2.05	75,450	0.99	76,262 [c]
Aza	277,429	1.62	0.83	220,412	2.21	99,621 [c]

Abbreviations **ICER:** Incremental Cost-Effectiveness Ratio; **AZA**: azacitidine monotherapy; **IvoAZA:** Ivosidenib plus azacitidine; **QALY:** Quality-Adjusted Life Year; **VenAZA:** Venetoclax plus azacitidine. Figures in the table are rounded, and so calculations may not be directly replicable. Costs are discounted at 4%

[a] Corresponding probabilistic ICER for IvoAZA versus VenAZA using 5,000 iterations = €79,355/ QALY and versus azacitidine monotherapy = €103,783/QALY.

[b] A commercial in confidence (CIC) PAS has been proposed for ivosidenib, not included here. A CIC PAS is in place for venetoclax, not presented here.

[c] The Review Group were informed in the final stages of the NCPE assessment (post Factual Accuracy Check) that there had been a price realignment. Effective 01 October 2025, the price to wholesaler of ivosidenib is €10,962 for one pack (60 x 250mg); associated deterministic ICER versus VenAZA is €53,289/QALY and versus azacitidine monotherapy is €89,349/QALY.

Table 2: NCPE adjusted base case incremental cost-effectiveness results for IvoAZA vs VenAZA [a, b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
IvoAZA	794,921	2.45	-	-	-
VenAZA	405,367	1.69	389,554	0.76	511,575 [c]

IvoAZA: Ivosidenib plus azacitidine, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years, VenAZA: venetoclax plus azacitidine. Figures in the table are rounded, and so calculations may not be directly replicable

[a] Corresponding probabilistic ICER using 5,000 iterations = €518,119/QALY.

[b] A CIC PAS has been proposed for ivosidenib, not included here. A CIC PAS is in place for venetoclax, not presented here.

[c] The Review Group were informed in the final stages of the NCPE assessment (post Factual Accuracy Check) that there had been a price realignment. Effective 01 October 2025, the price to wholesaler of ivosidenib is €10,962 for one pack (60 x 250mg); the deterministic ICER is €408,128/QALY

Sensitivity analyses

Sensitivity analyses indicated that the most influential parameters in the Applicant base case were the NMA HR outputs for OS and EFS, and the number of bed days for VenAZA. For the NCPE adjusted base case, the most influential parameters were the HR outputs for OS and EFS, and the health state utility value for EF with CR/CRi.

A Price-ICER analysis, on the NCPE adjusted base case, indicated that cost effectiveness could not be achieved at the €45,000/QALY and €20,000/QALY thresholds at any discount.

3. Budget impact of ivosidenib

Following a recent price realignment, the price to wholesaler of ivosidenib is €10,962 for one pack (60 x 250mg). The NCPE were informed of the price realignment in the final stages of the assessment. All cost-effectiveness and budget impact analyses, conducted and presented, in this document, were informed by the original price to wholesaler of €13,800 for one pack. At this original price, the estimated cost per-patient, per-treatment course with IvoAZA is €688,883 (including VAT). This assumes that ivosidenib is administered at the licensed dose (500mg once daily), for a mean treatment duration of 41.6 cycles (28-day cycles) informed by the cost-effective model (CEM), and no wastage. The Applicant estimated that approximately six patients would be newly diagnosed with AML with an IDH1 mutation and would be eligible for treatment with either IvoAZA or VenAZA or azacitidine monotherapy annually. The Applicant assumes a market share of 70% for IvoAZA in Year one, rising to 90% for Year three and beyond, a market share of 20% in Year one for VenAZA decreasing to 10% for Year two and beyond, and a market share of 10% for azacitidine monotherapy in Year one and two only. There is considerable uncertainty associated with the Applicant's budget impact estimates. The Review Group made several amendments to the Applicant's budget impact estimates including updating the ToT for VenAZA and IvoAZA to align with the NCPE-adjusted CEM base case assumptions, correcting drug costs, allowing for costs to accrue in the year in which they are administered. The resultant cumulative five-year gross drug budget impact was €14.63 million (including VAT) and the cumulative net drug budget impact was €10.77 million (including VAT). A scenario analysis was conducted, where it is assumed that patients received either ivosidenib 250mg once daily or venetoclax

100mg once daily due to concomitant azoles. The resultant five-year cumulative gross drug budget impact was €8.59 million (including VAT); the five-year cumulative net drug budget impact was €6.59 million (including VAT). As noted, the NCPE were informed of a price realignment of ivosidenib at the final stages of the NCPE assessment process. The budget impact estimates here do not reflect the realigned price.

4. Patient Organisation Submission

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

5. Conclusion

The NCPE recommends that ivosidenib not be considered for reimbursement (when given in combination with azacitidine for this indication)*.

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