

NCPE Assessment

Summary

Vorasidenib (Voranigo®)

HTA ID: 25059

October 2026

Applicant: Servier Laboratories

Vorasidenib, as monotherapy, for the treatment of predominantly non-enhancing grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients.*

* aged 12 years and older and weighing at least 40 kg who only had surgical intervention and who are not in immediate need of radiotherapy or chemotherapy

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of vorasidenib (Vorango®), as monotherapy, for the treatment of predominantly non-enhancing grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients.

Following assessment of the Applicant's submission, the NCPE recommends that vorasidenib (Vorango®) be considered for reimbursement, for this indication, if cost-effectiveness can be improved relative to existing treatment*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Servier Laboratories) Health Technology Assessment of vorasidenib (Vorango®). 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 March 2026, Servier Laboratories submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of vorasidenib (Vorango®) for the treatment of predominantly non-enhancing grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients aged 12 years and older and weighing at least 40 kg who only had surgical intervention and who are not in immediate need of radiotherapy or chemotherapy. Servier Laboratories is seeking reimbursement of vorasidenib on the High-Tech Drug Arrangement.

Vorasidenib is an inhibitor that targets the mutant IDH1 and IDH2 enzymes. In patients with astrocytoma or oligodendroglioma, IDH1 and IDH2 mutations lead to overproduction of the oncogenic metabolite 2-hydroxyglutarate (2-HG), resulting in impaired cellular differentiation contributing to oncogenesis. Inhibition of the IDH1- and IDH2-mutated proteins by vorasidenib blocks the abnormal production of 2-HG leading to differentiation of malignant cells and a reduction in their proliferation. The recommended dose of vorasidenib is a 40mg tablet once daily for as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

The standard of care for the treatment of predominantly non-enhancing grade 2 astrocytoma or oligodendroglioma with an IDH1 or IDH2 mutation in patients who only had surgical intervention, and who are not in immediate need of radiotherapy or chemotherapy, is active observation (also known as 'active surveillance' or 'watch-and-wait'). There are no relevant pharmaceutical comparators.

1. Comparative effectiveness of vorasidenib

The efficacy and safety of vorasidenib was assessed in the INDIGO trial (n = 336). INDIGO is a randomised (1:1), placebo-controlled, double blinded phase III trial of vorasidenib for the treatment of participants with residual or recurrent grade 2 glioma (astrocytoma or oligodendroglioma) with an IDH1 or IDH2 mutation. Participants weighing at least 40kg received either vorasidenib 40mg or placebo orally, once daily, until radiographic disease progression. Median age in the vorasidenib arm was 40.5 (range 21-71) and in the placebo arm it was 39.0 (range 16-65). There was only one participant aged less than 18 (randomised

to placebo). Slightly over half of participants had oligodendroglioma, with no significant difference in the proportion between arms (vorasidenib arm 52.4%, placebo arm 51.5%). Tumour subtype was a pre-planned stratification factor. The trial was discontinued early in March 2023 on the recommendation of the data and safety monitoring committee based on early demonstration of efficacy of vorasidenib. After unblinding, patients on placebo were given the option of cross-over to vorasidenib. The primary endpoint was radiographic progression-free survival (PFS) assessed by blinded independent central review (BIRC). The key secondary endpoint was time to next intervention (TTNI).

At the final pre-planned data cut (September 2022), median PFS was 27.7 months (95% CI, 17.0, non-estimable (NE)) in the vorasidenib arm versus 11.1 months (95% CI, 11.0, 13.7) in the placebo arm. The hazard ratio for PFS was 0.39 (95% CI, 0.27, 0.56). Median TTNI was not reached in the vorasidenib arm and was 17.8 months (95% CI, 15.0, NE) in the placebo arm. The Applicant performed a follow-up analysis of PFS of the blinded data collected after September 2022 until 07 March 2023. PFS by BIRC was improved in the vorasidenib arm compared with that in the placebo arm, with a hazard ratio of 0.35 (95% CI, 0.25, 0.49). A further data cut from January 2025 showed that the median PFS in the vorasidenib arm was 44.1 months (95% CI, 27.7, NE) and median TTNI was NE (95% CI, 52.0 months, NE). Due to unblinding and potential crossover in the placebo arm to vorasidenib, PFS in the placebo arm is potentially underestimated, therefore favouring the intervention. However, this is mitigated by the fact that the majority of patients in the placebo arm had already experienced progression at the time of study unblinding. The high rate of crossover to vorasidenib in the placebo arm may confound TTNI results, as patients in the placebo arm may have initiated their next intervention quicker than they would otherwise have had crossover not being permitted.

2. Safety of vorasidenib

The most frequent treatment-related adverse events (TEAEs) reported in the vorasidenib arm, of the INDIGO trial, were nervous system disorders (55.7%), alanine aminotransferase (ALT) increase (38.9%), aspartate aminotransferase (AST) increase (28.7%), gammaglutamyltransferase (γGT) increase (15.6%), gastrointestinal disorders (50.9%), infections and infestations (47.3%). TEAEs leading to treatment discontinuation were

reported in six (3.6%) participants in the vorasidenib arm. The summary of product characteristics (SmPC) for vorasidenib details special warnings and precautions of use in relation to hepatotoxicity and recommends it should be withheld, dose reduced or permanently discontinued based on the severity of the liver enzyme abnormalities. Clinical opinion and real-world data indicate that protocol-led dose interruptions and dose reductions would be expected in clinical practice.

3. Cost effectiveness of vorasidenib

Methods

The Applicant used an individual patient state transition model with up to nine health states. Each health state in the model denotes a different treatment and progression status stage. Patients were simulated based on the distributions of baseline characteristics observed in the INDIGO trial. Patients enter the model in a progression-free (PF) state with IDH1- or IDH2-Mutant Low-Grade Glioma (either astrocytoma or oligodendroglioma); those treated with vorasidenib in State 1, while patients under Active Observation (the placebo arm of INDIGO is considered a proxy for Active Observation) in State 2. States 1 to 4 inclusive precede initiation of next treatment (radiotherapy/chemotherapy or surgery), while States 5 to 9 inclusive denote initiation of next treatment to death. Patients could transition to other health states or remain in the same health state at each model cycle. In general, following disease progression, backward transitions are not allowed. However, for patients with surgery as next treatment it is possible to transition from State 5 to State 2 once.

The cost-effectiveness model (CEM) structure adopted by the Applicant is not common in oncology HTA submissions, where typically a (cohort) 3-state partitioned survival model is used. This was justified with the complexity of the disease pathway for this condition. The model had some limitations, namely, that progression on treatment modelled in the CEM does not necessarily imply progression to higher grade glioma and hence, the impact on survival and quality of life of each health state transition is unclear. Additionally, distinct rates of progression and survival for astrocytoma and oligodendroglioma are only considered in a single health state, which could limit the model accuracy.

The key efficacy inputs are PFS and TTNI|P (time to next intervention following progression). PFS in both arms and TTNI|P for the vorasidenib arm were informed by the INDIGO trial. In the Active Observation arm of the INDIGO trial there was crossover to vorasidenib upon progression of disease. This is not generalisable to the Irish setting and could bias the TTNI|P in favour of the intervention. For this reason, TTNI|P in the CEM was informed by an external data cohort and clinical opinion. The Review Group considers that the benefit of vorasidenib, compared to Active Observation, in increasing the TTNI|P, estimated in the CEM, to be very uncertain.

Health Related Quality of Life (HRQoL) parameters in the model included utilities associated with each model health state. As a limitation, HRQoL were an exploratory endpoint in the INDIGO trial and data was only available to inform States 1 to –4 of the model (i.e., before the start of next treatment). Furthermore, there is limited evidence from the literature to inform health state utilities after initiation of next intervention (States 5-8), and therefore these health state utilities were informed by a vignette study conducted by the Applicant. However, estimated health state utilities in the vignette study, for States 1 to 4, were lower than in the INDIGO trial for States 1 to 4. The Applicant adjusted the utilities from the vignette study for States 5 to 8 upwards based on the relative decrement. The Review Group considers utilities for health States 5 to 8 to be very uncertain.

The model included only drug acquisition costs for vorasidenib as it is presumed to be orally self-administered. Acquisition and administration costs were included for subsequent treatments, where applicable. Other healthcare resources were aggregated as health state-independent costs and included scans, hospital visits, consultant costs and debulking surgery. The cost of seizure management was modelled as health-state specific. A once-off end-of-life cost was applied to all patients entering the death state. The Review Group considered the end-of-life cost applied in the Applicant base case to be over-estimated.

Results

An incremental analysis of the costs and benefits of vorasidenib, versus Active Observation,

was presented by the Applicant. Results of the analysis are presented in Table 1. The probabilistic results, which were estimated for 500 simulations, are stable and similar to the deterministic results. The Applicant base case uses the January 2025 data cut from INDIGO which is shown in Table 1.

Table 1: Applicant base case (as presented by the NCPE, using January 2025 INDIGO data cut) incremental cost-effectiveness results^{a,b,c,d}

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
AO	296,006	5.71			
Vorasidenib	1,099,762	9.72	803,756	4.02	200,182

AO: Active observation; **ICER:** Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year

^a Corresponding probabilistic ICER using 500 iterations = €195,701/QALY. Discount rate of 4% on costs and outcomes. Figures in the table are rounded, and so calculations may not be directly replicable.

^b A commercial in confidence PAS is in place for vorasidenib, not reflected in this table.

^c The Review Group corrected the omission of the 9% Framework Agreement rebate.

^d Based on the pricing application form (PAF) submitted to the HSE-CPU on 30/09/2025

The Review Group assessment identified a number of limitations in the Applicant's base case which were addressed in the NCPE adjusted base case. These included the calculation of the hazard rate of TTNI for the Active Observation arm compared with vorasidenib, the choice of the adjustment made to utility values, the ability of patients to return to a PF State in the model following surgery, and the calculation of end-of-life costs. The NCPE adjusted base case incorporating the resulting changes is presented in Table 2.

Table 2: NCPE adjusted base case incremental cost-effectiveness results^{a,b,c}

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
AO	279,871	6.61			
Vorasidenib	1,088,190	9.90	808,319	3.28	246,256

AO: Active observation; **ICER:** Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year

^a Corresponding probabilistic ICER using 500 iterations = €249,226/QALY. Discount rate of 4% on costs and outcomes. Figures in the table are rounded, and so calculations may not be directly replicable

^b A commercial in confidence PAS is in place for vorasidenib, not reflected in this table.

^c Based on the pricing application form (PAF) submitted to the HSE-CPU on 30/09/2025

Sensitivity analysis

An analysis of the Price-ICER relationship on the price to wholesaler (PtW) for vorasidenib was conducted. This indicated that a reduction of 89.2% and 80.3% on the PtW of vorasidenib would be required to achieve an ICER of €20,000 and €45,000 per QALY, respectively.

4. Budget impact of vorasidenib

The PtW of vorasidenib is €15,000 per pack (30 x 40 mg tablets). The estimated cost of vorasidenib, per year, per patient is €181,543 (VAT not applicable). The Applicant omitted a prevalent population in year one of the drug budget. The Review Group corrected this error in the NCPE adjusted drug-budget impact analysis. This yielded an eligible population of 17 patients in year one, increasing to 50 patients in year five. The NCPE adjusted drug budget model is presented in Table 3.

Table 3: NCPE adjusted drug-budget impact analysis^{a,b,c,d}

Population	Year 1	Year 2	Year 3	Year 4	Year 5	5-year cumulative
Eligible population ^e	17	25	33	42	50	-
Proportion treated (%)	75	80	85	90	95	-
Treated population	12	20	28	38	48	-
Net/Gross drug-budget impact ^{f,g}	2,219,765	3,565,863	5,075,674	6,751,391	8,595,172	26,207,866

^aIncluding all relevant fees and a 9% Framework Agreement rebate

^bVAT does not apply to vorasidenib

^cA CIC PAS has been proposed for vorasidenib, not included in this table. The PtW for vorasidenib is €15,000 for one pack of 40 mg tablets, as per the PAF submitted to the CPU on 30/09/2025

^dThe Review Group amended the Applicant's BIM to include a prevalent population in Year 1.

^eThe eligible population is adult and adolescent patients aged 12 years and older and weighing at least 40 kg with predominantly non-enhancing grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation, who only had surgical intervention and who are not in immediate need of radiotherapy or chemotherapy

^fThe Applicant applied a 100% RDI in the BIM which the Review Group retained; however, the Applicant applied a 93.6% RDI in the CEM

^gGross equals net drug budget

Many of the Applicant's budget impact estimates were considered uncertain. The Applicant assumed that 37% of patients would not be in immediate need of chemotherapy or radiotherapy and therefore would be eligible for vorasidenib. This was sourced from a Korean study. However, clinical opinion, to the Review Group, indicated that the proportion in Ireland could be as low as 25% or as high as 60%. The Review Group explored the impact of varying this estimate in a scenario analysis which yielded a revised five-year cumulative budget impact estimate ranging from €18 million to €45 million. The size of the market share for vorasidenib is also uncertain.

5. Patient Organisation Submission

Patient organisation submissions were received from Brain Tumour Ireland and UCAN Ireland. These submissions will form part of the information that the HSE considers when making their drug funding decision.

6. Conclusion

The NCPE recommends that vorasidenib (Vorango®) be considered for reimbursement, for this indication, if cost-effectiveness can be improved relative to existing treatment*.

*Next steps: The NCPE Assessment Report, recommendation, and Patient Organisation submissions, will be considered by the HSE when making their decision on reimbursement, while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

Further information on this process may be found [here](#).