NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using vorasidenib in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: October 2025

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using vorasidenib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 4 November 2025
- Second evaluation committee meeting: 20 November 2025
- Details of membership of the evaluation committee are given in section 4.

1 Recommendations

1.1 Vorasidenib should not be used to treat grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase (IDH) 1 or IDH2 mutation in people 12 years and over who do not need immediate chemotherapy or radiotherapy after surgery.

1.2 This recommendation is not intended to affect treatment with vorasidenib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For young people, this decision should be made jointly by the healthcare professional, the young person, and their parents or carers.

Update – Please note that section 1.2 of the guidance refers to treatment started in the NHS funded by the NHS, not treatment started as part of the company's named patient programme. The terms of that programme apply if this treatment is not recommended at the conclusion of this evaluation.

What this means in practice

Vorasidenib is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because the available evidence does not suggest that vorasidenib is value for money in this population.

Why the committee made these recommendations

Usual care for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations for people who do not need immediate chemotherapy or radiotherapy after surgery is active surveillance.

Clinical trial evidence shows that vorasidenib increases how long people have before their cancer gets worse compared with placebo. But it is unclear if vorasidenib affects how long people with the condition live.

There are uncertainties in the economic model, including assumptions on:

- how long people who had vorasidenib or placebo wait before starting a new treatment after their cancer gets worse
- if vorasidenib extends how long people live
- the quality of life of people in the model.

Because of the uncertainties in the economic model it is not possible to determine the most likely cost-effectiveness estimates for vorasidenib. So, vorasidenib should not be used routinely in the NHS.

Collecting more evidence during a managed access period is unlikely to resolve the key uncertainties in the evidence. So, vorasidenib cannot be used with managed access.

2 Information about vorasidenib

Marketing authorisation indication

2.1 Vorasidenib (Voranigo, Servier Laboratories) is indicated for 'the treatment of Grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation or isocitrate dehydrogenase-2 (IDH2) mutation in adults and paediatric patients 12 years and older, who are not in need of immediate chemotherapy or radiotherapy following surgical intervention'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for vorasidenib.

Price

2.4 The list price of a 30-tablet pack of vorasidenib is £15,000 for 40-mg tablets and £7,500 for 10-mg tablets (excluding VAT; company submission).

2.5 The company has a commercial arrangement. This makes vorasidenib available to the NHS with a discount and it would have also applied to this indication if vorasidenib had been recommended. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.6 Information on the Carbon Reduction Plan for UK carbon emissions for Servier Laboratories will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Servier Laboratories, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Gliomas are the most common type of brain tumour. They develop from the glial cells that support the nerve cells of the brain and spinal cord. Gliomas are classified by how quickly they grow. Most gliomas are grade 1 or 2 at diagnosis, referred to as low-grade glioma (LGG), and do not grow or only grow slowly. Grade 3 and 4 gliomas, referred to as high-grade glioma (HGG), grow quickly. Consequently, HGG is associated with worse outcomes than LGG. Up to 70% of LGGs may progress to high grade or become malignant within 10 years. The 3 main types of glioma in adults are astrocytoma, oligodendroglioma and ependymoma. Key genetic alterations in gliomas include mutations in the isocitrate dehydrogenase (IDH) 1 and 2 genes, which are involved in cell

metabolism, and a chromosome alteration known as a 1p/19q codeletion. Gliomas with a 1p/19q codeletion or IDH mutation are thought to grow more slowly than gliomas without these alterations.

Symptoms of IDH-mutant astrocytoma and oligodendroglioma (from here, referred to as LGG) include headaches, seizures, difficulty thinking or remembering and changes in vision. Patient-organisation submissions highlighted the large impact on quality of life of living with LGG, which affects social life, education and work. The physical symptoms of the condition can be challenging, especially seizures, which can cause anxiety and affect independence by limiting the ability to drive. Living with an incurable and slowly progressing condition can also have a large mental impact on people with the condition, their families and carers. The patient expert at the meeting explained that the fear of inevitable progression of the disease can considerably affect quality of life. The committee noted that some people are diagnosed with LGG in their 20s, 30s, and 40s and so may have young families. This can increase the burden on carers who are often the sole financial provider. There are also practical challenges in providing support for people with LGG, which can lead to exhaustion for carers. The committee concluded that LGGs are slowly progressing conditions that significantly impact the lives of people affected, their families and carers.

Clinical management

Treatment options

3.2 The clinical experts explained that the aims of treatment for glioma include delaying progression and improving neurological function and quality of life. Section 1.2 of NICE's guideline on primary brain tumours and brain metastases in over 16s (NG99) recommends maximal safe surgical resection as first-line treatment for LGG. The clinical experts at the meeting explained that post-surgical outcomes determine the next treatment offered. People whose tumour is not considered at immediate

risk of progression after surgery will usually have active surveillance. The clinical experts explained that people having active surveillance in the NHS have minimal residual disease volume after surgery. They said that these people are likely to have slow-growing disease that is appropriate to monitor using regular scans. They explained that the need for further treatment after surgery was based on a multidisciplinary team discussion instead of defined eligibility criteria. But they said that treatment was more likely to be offered to people whose tumour had a higher risk of progression because they:

- were older
- had post-surgical histology results that suggested transformation to HGG
- had a substantial amount of residual tumour after surgery
- had residual tumour volume around the areas of the brain responsible for motor, visual or speech control that was likely to cause a neurological defect
- had astrocytoma, which is generally more aggressive and progresses faster than oligodendroglioma
- preferred to have adjuvant treatment after discussion with their healthcare professional.

Based on NG99, people whose tumours need immediate treatment after surgery or whose disease has progressed during active surveillance should have radiotherapy followed by a maximum of 6 cycles of procarbazine, lomustine (CCNU) and vincristine (PCV) chemotherapy. If the disease progresses further, additional treatments can be used. These could include another round of chemotherapy, more radiotherapy, surgery, or supportive care. The clinical experts at the meeting agreed that this pathway broadly represented the treatments used in the NHS but highlighted that treatment for LGG varies across centres. The patient expert explained that treatments for LGG have a large effect on quality of life. The psychological burden of

active surveillance for a progressively enlarging tumour can lead to substantial anxiety. Chemotherapy and radiotherapy are also associated with debilitating side effects such as cognitive decline and fatigue. They can also negatively affect fertility and need regular hospital visits which can limit the ability to work. The patient expert highlighted that they would welcome a treatment that could be used after surgery to delay the need for chemotherapy or radiotherapy. This would also relieve the anxiety linked to having a progressing disease that is not being actively treated. The committee concluded that treatment for LGG includes chemotherapy or radiotherapy, active surveillance, surgery and best supportive care.

Pathway and comparators

3.3 Vorasidenib is licensed for people who do not need immediate chemotherapy or radiotherapy after surgery. The company explained that the marketing authorisation for vorasidenib included people with:

- a supramaximal resection (where all the tumour and some surrounding tissue is removed)
- a gross total or complete resection (where all visible tumour is removed)
- some residual disease not at immediate risk of progression.

But, the clinical experts stated that they may not recommend adjuvant therapy after complete or supramaximal resection so as to reduce the treatment burden and avoid side effects. They also highlighted the lack of evidence to support the use of vorasidenib in this population (see section 3.6). But they said that using an IDH inhibitor may positively affect the biology of the condition, so there may be potential long-term benefits for these people (see section 3.10). They highlighted that the proportion of people who have a supramaximal resection is increasing because of improvements in surgical techniques. The committee agreed that vorasidenib may be used for people who have had a

supramaximal or complete resection but that this would be determined on a case-by-case basis. It thought that all people who were not in need of immediate chemotherapy or radiotherapy after surgery would have active surveillance. So, the committee concluded that active surveillance was the relevant comparator but the exact population for which vorasidenib would be used in clinical practice was unclear.

Clinical effectiveness

Data sources

3.4 The clinical-effectiveness evidence for vorasidenib came from INDIGO, an ongoing, multicentre, randomised, placebo-controlled trial, which included 4 sites in the UK. It included people with IDH-mutant grade 2 oligodendroglioma or astrocytoma who:

- were 12 years and over
- had measurable, non-enhancing LGG, defined by having at least 1 target lesion of 1 cm or over in both width and diameter, confirmed on MRI by blinded review
- had at least 1 surgery for glioma as their only treatment, the latest of which was within 1 to 5 years from screening
- had no high-risk features such as uncontrolled seizures, brain-stem involvement, or tumour-related functional or neurocognitive deficits.

In the trial, 168 people had a daily 40-mg vorasidenib tablet, and a control group of 163 people had a daily placebo tablet. The trial stratified people by 1p/19q deletion status and baseline tumour size. People had trial treatment until disease progression (as confirmed by a blinded independent review committee), at which point their treatment was unblinded. After progression, people could have subsequent treatments with radiotherapy and chemotherapy or, for the placebo arm, they could have vorasidenib. The company submitted results from a data cut in September 2022 (median follow up 14 months) and an ad-hoc analysis in March 2023 (median follow up unknown). The primary outcome in

INDIGO was progression-free survival (PFS). Progression was assessed by investigators and by blinded independent review. Secondary outcomes were time to next intervention, tumour growth rate, response rates, overall survival, health-related quality of life and adverse events. The committee concluded that the relevant evidence for vorasidenib came from the INDIGO trial.

Results

3.5 At the most recent data cut (March 2023), 54 people (32%) in the vorasidenib arm and 104 people (64%) in the placebo arm had progressed disease. Median PFS was not reached (95% confidence interval [CI] 22.1 months to not estimable) in the vorasidenib arm and was 11.4 months (95% CI 11.1 months to 13.9 months) in the placebo arm. A benefit in PFS was seen across all prespecified subgroups for vorasidenib compared with placebo. The key results for the secondary endpoints as of the March 2023 data cut were as follows:

- The median time to next intervention was not evaluable in the vorasidenib arm and was 20.1 months (95% CI 17.5 months to 27.1 months) in the placebo arm. Twenty eight people in the vorasidenib arm and 78 people in the placebo arm had further treatment after their disease progressed. Of these, 70 people in the placebo arm crossed over to vorasidenib. This was 90% of the people who had subsequent treatment. The committee noted that this would not occur in NHS clinical practice because vorasidenib is not available.
- There were no significant improvements in neurological function or health-related quality of life between arms (see section 3.13).

Data from the March 2022 data cut showed a 64% lower rate of seizures in the vorasidenib arm than the placebo arm (ratio of rates 0.36 [95% CI 0.14 to 0.89]). Malignant transformation was recorded in 6 people (4%) in the vorasidenib arm and 2 people (1%) in the placebo arm. There was only 1 death in INDIGO, which occurred in the placebo arm after disease

progression. The committee said that the INDIGO trial demonstrated improved PFS with vorasidenib. But it concluded that the high rate of crossover to vorasidenib in the placebo arm introduced significant uncertainty into the post-progression results, including the time to next intervention and overall survival.

Generalisability

Generalisability of the INDIGO population

3.6 The UK marketing authorisation for vorasidenib includes all people 12 years and over with grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or 2 mutation who are not in need of immediate chemotherapy or radiotherapy after surgery. The committee noted that this was wider than the population included in INDIGO because:

- INDIGO only included people who had surgery between 1 and 5 years before screening for the clinical trial. The committee noted that this restriction would not apply in clinical practice. So, vorasidenib could be used immediately after surgery in some people who may not have met the criteria to enter INDIGO 1 year later. But the clinical experts explained that LGG would be unlikely to progress within this time so this would likely be few people.
- INDIGO excluded people who had little to no residual disease (tumour area less than 1 cm^2) after surgery. The company explained that this was to ensure that disease was measurable radiologically. The committee noted that subgroup analyses from INDIGO suggested a smaller treatment effect in smaller tumours. It agreed that people with a residual tumour area of under 1 cm^2 would be eligible to have vorasidenib in the NHS according to its marketing authorisation, as could some people with a supramaximal or complete resection (see section 3.3). So, it was concerned that INDIGO may overestimate vorasidenib's treatment effect compared with the effect it would have in the NHS. The clinical experts explained that the relative reduction, not

the size of remaining tumour, was a surrogate for the extent of disease. They also highlighted the lack of statistical power in the subgroup analyses. So, the committee agreed that vorasidenib's treatment effect in smaller and completely resected tumours was uncertain.

- INDIGO excluded people with high-risk features such as uncontrolled seizures, brain-stem involvement and tumour-related functional or neurocognitive deficits. Because of this, the EAG highlighted that people in INDIGO were more likely to have stable glioma, which may not reflect the population in which vorasidenib would be used in the NHS.
- The clinical experts explained that the INDIGO trial used an older World Health Organization (WHO) classification criteria for LGG than is used in clinical practice. Because of this, a small proportion of people with astrocytoma in the INDIGO trial would likely be classed as having HGG under the new criteria. The committee noted that these people would not be eligible for vorasidenib in clinical practice and were likely to have disease progression sooner than people with LGG. This might have underestimated the treatment effect for vorasidenib in the full population. But the committee thought that the size of the population with HGG and the impact on the results was unknown.

The committee agreed that there were several issues with how well the population in the INDIGO trial represented people who would be eligible for vorasidenib in the NHS. But the clinical experts thought that, overall, the people in INDIGO represented people who have active surveillance in clinical practice. That is, people with stable or slowly progressing disease as documented on scans after surgery (see section 3.2). The committee recalled that LGG is rare, which may present obstacles to recruiting a clinical trial population that is fully generalisable to the NHS. It concluded that the population with LGG included in the INDIGO trial was narrower than that expected in the NHS and outlined in the UK marketing authorisation. The committee noted the uncertainty in the generalisability

of the population in INDIGO to the NHS population, but it noted the rarity of the condition, and considered it acceptable for decision making.

Generalisability of outcomes in INDIGO

3.7 Progressed disease in the INDIGO trial was assessed using the modified Response Assessment in Neuro-Oncology for LGG (mRANO-LGG) criteria. The company modified the criteria so that disease progression was determined solely by imaging results, excluding clinical deterioration as an indicator. The EAG was concerned that this did not reflect clinical practice. It noted that around 50% of people with progressed disease in INDIGO had no subsequent treatment at the latest data cut, which might be related to a lack of clinical progression. They also queried the clinical relevance of the progressed-disease outcome given the lack of improvement in neurocognitive function or health-related quality of life reported in INDIGO (see section 3.5 and section 3.13). The clinical experts stated that, because LGG is a slowly progressing condition, progression will generally be identified in gradual radiological changes unless the cancer transitions to HGG. Although some people might start treatment for seizures that are uncontrolled on anti-seizure medicines, this was likely for only 5% to 10% of people with LGG. So, the committee agreed that the company's use of radiological outcomes to define progression was likely appropriate.

The EAG was also concerned that the time to next intervention (TTNI) outcome, which was defined as the time from randomisation to starting the first subsequent anticancer treatment, may not be generalisable to the NHS. This was because vorasidenib was available as a subsequent treatment in the placebo arm, which did not reflect clinical practice. The EAG noted that around 90% of people who had a subsequent treatment in the placebo arm crossed over to vorasidenib, which biased the results. It thought that the true TTNI for people whose disease progressed on active surveillance was likely longer. It said that this was because people were more likely to start vorasidenib (an oral tablet with minimal side effects)

rather than chemotherapy or radiotherapy, which was the only subsequent treatment option in the vorasidenib arm. The committee concluded that the definition of progressed disease used in the trial was likely generalisable to clinical practice. But it said that the availability of vorasidenib as a subsequent treatment made the TTNI results in the placebo arm highly uncertain and so not suitable for decision making.

Economic model

Company's modelling approach

3.8 The company developed a microsimulation model based on key treatment milestones to evaluate the cost effectiveness of vorasidenib. The base-case model included 8 health states:

- progression free, on treatment, where people having vorasidenib entered the model
- progression free, off treatment, where people having placebo entered the model
- progressed disease, off treatment
- first-line chemotherapy or radiotherapy, on treatment
- first-line chemotherapy or radiotherapy, off treatment
- second-line chemotherapy or radiotherapy onwards, on treatment
- best supportive care
- death.

Excess mortality associated with LGG applied only to people in the best supportive care health state. The company assumed that a proportion of people moved to best supportive care because they opted out of further treatment after their disease progressed on vorasidenib or first-line subsequent treatment. People could move to death from any health state. The company used a 28-day cycle length with a half cycle correction and a 60-year time horizon. It also incorrectly applied the non-reference discount rate of 1.5% for both health effects and costs in its base case (see section 3.15). The EAG thought that it may be more appropriate to

base the model on progression events over time (for example, transition to HGG or malignant transformation) instead of treatment milestones. But, given the limited data available to inform the modelling, it agreed that the model was conceptually acceptable and broadly reflected the aim of treatment in LGG (to reduce the risk of progression and delay time to next treatment). The committee agreed it would have preferred a model based on disease progression status but concluded that the company's model was acceptable for decision making given the available data.

Clinical-effectiveness data in the model

3.9 The company used data from INDIGO to inform the clinical effectiveness for the following health states:

- The progression-free health states (both on and off treatment) were informed by the time to progression from INDIGO, extrapolated using a log-normal distribution. There were no deaths on treatment in INDIGO so the company assumed that PFS was a proxy for time to progression.
- The progressed disease, off-treatment health state (that is, the time between progression and the start of the next treatment) was informed by a conditional outcome calculated by the company, time to next intervention given progression (TTNI-P). The progressed-disease, off-treatment health state (that is, the time between progression and the start of the next treatment) was informed by a conditional outcome calculated by the company, time to next intervention given progression (TTNI-P). This was calculated using the difference between the PFS (as a proxy for time to progression) and TTNI in INDIGO, which was then extrapolated beyond the trial data (see section 3.10).

Clinical-effectiveness data for the health states associated with chemotherapy and radiotherapy (on and off treatment) came from multiple sources in the literature. Five per cent of people moved to best supportive care after progression on vorasidenib, active surveillance or first-line subsequent treatment, based on a company assumption. The clinical

experts confirmed this was reasonable. The committee recalled the uncertainty around the post-progression data from INDIGO (see section 3.7). It concluded that the company's modelling of clinical-effectiveness data for vorasidenib and placebo was uncertain.

TTNI-P as a proxy for time off treatment with progressed disease

3.10 The company extrapolated the TTNI-P data beyond the clinical trial follow up by fitting separate parametric curves to the Kaplan–Meier data from the vorasidenib and placebo arms of INDIGO. It chose the best-fitting curve, the generalised gamma, for its base case. The EAG was concerned about this approach because the data from the placebo arm was biased by the high levels of crossover to vorasidenib after progression. The committee recalled that this data was not appropriate for decision making (see section 3.7). The EAG was also concerned that the company's chosen parametric curves lacked face validity because:

- Twenty one per cent of people having vorasidenib and 9% having placebo had had no further treatment 20 years after their disease progressed, implying a cure, which they believed to be not plausible given the disease characteristics. The EAG queried whether the large difference in TTNI-P was plausible, given that these benefits were modelled to apply in addition to the PFS benefit for vorasidenib seen in INDIGO.
- A small percentage of people in the vorasidenib arm stayed in the progressed-disease, off-treatment health state for the entire model lifetime. The EAG highlighted that these people never experienced the excess mortality from LGG because they never entered the best supportive care health state.
- People in the vorasidenib and placebo arms spent considerably more time with progressed disease off treatment than in the progression-free health state, which the EAG considered implausible.

The company stated that a long TTNI-P was plausible in people with progressed disease after vorasidenib. This was because these people may have more favourable features on progression than people who had placebo. So, they may choose to delay chemotherapy or radiotherapy to avoid the associated side effects. It thought this was supported by INDIGO results that that showed a:

- higher proportion with tumour shrinkage at progression for vorasidenib compared with placebo, and
- longer TTNI-P in people with a stable or decreased tumour volume on progression than people with tumour growth.

(The exact results are confidential and cannot be reported here.)

A perioperative study also suggested vorasidenib caused molecular changes in the tumour. One clinical expert explained that, although uncertain, a longer time to next treatment for people who had vorasidenib was plausible. This was because, by inhibiting the effects of the IDH mutation early, vorasidenib changes the downstream effects of tumour development, leading to more favourable tumour biology on progression and less immediate need for chemotherapy and radiotherapy. But the EAG thought that the bias in the TTNI results for the placebo arm meant there was no evidence from INDIGO to suggest people having vorasidenib and placebo would be managed differently in clinical practice. It also noted that people with progressed disease in INDIGO reported higher quality-of-life results in the placebo arm than the vorasidenib arm, which did not support a longer TTNI-P for vorasidenib. So, the EAG believed that the company's TTNI-P curves lacked face validity and that using separate curves was likely inappropriate. Because of this, it preferred to fit the same curve to both arms, that is, to assume no benefit in TTNI-P for vorasidenib. In its base case, it pooled TTNI-P data from INDIGO and fitted a log-normal curve to extrapolate the long-term effects. This was because the log-normal curve was the best-fitting curve that also estimated more time in the progression-free than the progressed-disease,

off-treatment health state.

The committee noted that the parametric distribution for long-term extrapolation of TTNI-P and whether to apply a single or separate curves had a large impact on the cost-effectiveness results. This was because these affected overall survival and delayed movement to later health states associated with a lower quality of life (see section 3.11). The committee also noted that the extrapolations were limited by a small number of events, particularly in the vorasidenib arm where most people remained progression free at the last data cut. The clinical experts thought that the EAG's TTNI-P curve represented people with astrocytoma, whose disease is likely to have progressed within 5 years. But they considered that the company's base-case curves better fitted the natural history of oligodendroglioma, which is generally slower growing with a more stable course. The committee noted that the trial had a roughly equal number of people with astrocytoma and oligodendroglioma, but twice as many people have astrocytoma in clinical practice. So, it agreed that the TTNI-P in the full NHS population with current standard care likely lay between the company and EAG's base-case curves. The company and EAG approaches both included data from the placebo arm, which the committee thought was not suitable for decision making (see section 3.7).

The company had done a multiple imputation adjustment to replace TTNI data for people who had vorasidenib as a subsequent treatment in the placebo arm. But it agreed that the results were not robust and could not be used in the model. The company also explained that it had not identified any natural history data that would be appropriate for the placebo arm. The committee noted an EAG scenario that applied a log-normal curve using the vorasidenib TTNI-P data for both the vorasidenib and the active surveillance arms in the model. It believed that this removed the bias from the placebo arm data but noted that it had not been provided with alternative parametric curves using this approach. The

committee noted that this approach did not assume a TTNI-P benefit for vorasidenib. It acknowledged that a different time to next treatment after progression on placebo and vorasidenib may be plausible, because of vorasidenib's effect on tumour biology. But the size of this difference was uncertain. It agreed that using the vorasidenib data for both arms may overestimate the TTNI-P for people having active surveillance but considered that it had not seen any plausible ways to accurately capture the TTNI-P in the placebo arm. Because of this, it preferred to apply the INDIGO vorasidenib data to both arms in the model. The committee agreed that the company should provide a full exploration of the best-fitting parametric curve using this approach at consultation. The committee also requested that the company explore alternative ways to plausibly model a TTNI-P benefit for vorasidenib as a scenario. It concluded that the time off treatment after disease progression for people having vorasidenib and active surveillance was highly uncertain. But, given the analyses available, the analyses based on parametric curves derived from the vorasidenib arm of INDIGO should be used in the modelling.

Overall survival

3.11 There was no mature overall-survival data available from INDIGO, and no deaths reported before disease progression on vorasidenib and placebo. Because of this, the company model assumed in its base case that there was a benefit in overall survival for vorasidenib compared with placebo, driven by benefits in PFS and TTNI-P. The company also only applied excess mortality for LGG to people having best supportive care. It used data from Ma et al. (2021) to extrapolate the long-term mortality rates. The clinical experts confirmed that this reflected clinical practice, where excess mortality generally occurs at the end of the treatment pathway. But the EAG was concerned that the surrogacy relationship between PFS, TTNI-P and overall survival was uncertain and not supported by data. It noted that the company submitted data from Miller et al. (2019), a retrospective analysis of 275 people with IDH-mutant glioma who had treatment in the

US between 1991 and 2007. This suggested that delaying the time to first and second progression improved overall survival. The clinical experts explained that it was difficult to directly translate improvements in PFS to overall survival without further evidence, but that this might be plausible. They noted that treatment options for LGG are limited, so a poorer overall survival would be expected in people whose disease progressed quickly through treatments. They noted that the transformation to HGG is associated with a known mortality risk and so would be a better surrogate marker for overall survival than those in the company's model.

The committee noted that there was no data to suggest a delayed transition to HGG or malignant glioma with vorasidenib compared with active surveillance. It was also concerned about the use of TTNI-P as a surrogate marker for overall survival, because it was highly uncertain and was likely confounded by crossover (see section 3.7). It recalled that its preferred extrapolation did not have a TTNI-P benefit for vorasidenib (see section 3.10). But it noted that in the company's base case, the more optimistic TTNI-P curves and the substantial benefit for vorasidenib had a significant positive impact on overall survival. The company explained that an additional data cut from INDIGO was expected in May 2028. The EAG thought that this would reduce the uncertainty around PFS and TTNI for vorasidenib. But it thought that any overall-survival data would be difficult to interpret because of the high number of people who crossed over to vorasidenib in the placebo arm. It considered that the only alternative approach would be to model survival hazards based on progression events over time. But it acknowledged that collecting data to inform a progression-based model would be challenging given the rarity of LGG and the lack of published evidence on the condition. The committee agreed that any overall-survival benefit for vorasidenib was highly uncertain because of the uncertainty in the modelled inputs, especially the TTNI-P from INDIGO. The committee noted that the company's overall-survival modelling method may be suitable for decision-making, although

it was highly uncertain, but that it would evaluate any overall-survival outputs from updated analyses presented during consultation.

Subsequent treatments

Distribution of subsequent treatments in the model

3.12 In the company's model, the chemotherapy regimens and the proportion having radiotherapy differed by treatment line. The distribution of chemotherapy treatments was based on a French periodic synthesis report for ivosidenib. This included people with IDH1-mutant LGG who could not have surgery. The percentage of people having radiotherapy with chemotherapy at first line was based on the rates in the INDIGO trial, and the company assumed a 50% reduction in radiotherapy use at each successive line. The EAG's clinical advisers suggested there were differences in the use of subsequent treatments between Europe and the NHS. Specifically, subsequent treatments in the NHS:

- include higher use of PCV at first line than in the company's model
- do not include bevacizumab, which was included as a third- and fifth-line chemotherapy in the French review.

At the meeting, the company highlighted that some people in England and Wales self-fund bevacizumab because is not funded by the NHS. But the clinical experts agreed that any use of bevacizumab would be negligible because it is not the preferred treatment for LGG. The EAG's clinical advisers also considered that the proportion of people having radiotherapy in the NHS was likely to be higher at first line and lower at subsequent lines than was modelled by the company. Based on clinical-expert advice and NG99, the EAG's base case assumed that:

- 100% of people had PCV with radiotherapy as the first subsequent treatment
- 100% of people had temozolomide and 50% of people had radiotherapy as their second subsequent treatment

- 33% of people each had PCV, temozolomide and lomustine (CCNU) as their third subsequent treatment; no one had radiotherapy.

The clinical experts supported the EAG's modelling of subsequent treatments. The committee also noted that use of temozolomide was limited by NICE's technology appraisal guidance on temozolomide for treating recurrent malignant glioma (TA23) and so PCV may be more accessible in the NHS. The committee acknowledged the uncertainty in the modelling of subsequent treatments. But it concluded that it preferred the EAG's base-case distributions because they better reflected NHS practice.

Utility values

Source of utility values

3.13 The company derived health-state utility values for the progression-free and progressed-disease health states from EQ-5D-5L data collected in the INDIGO trial. It mapped the EQ-5D-5L data to the EQ-5D-3L value set, using the average utility across arms. The company did a vignette study to inform utility values for people who had subsequent treatments in the model. This was because INDIGO did not collect this data and the company had not identified any appropriate utility values in the literature. The vignette study asked members of the public to estimate health-related quality of life based on descriptions of the hypothetical health states using EQ-5D and time trade-off approaches. The utility values derived from the vignette study were higher for people who had stopped chemotherapy or radiotherapy than for people who were having this treatment. The company thought this implausible, so applied the average utility value between on and off treatment for each subsequent treatment line in the model using the EQ-5D values in its base case.

The EAG had several concerns about the company's utilities. It noted that the progression-free utility values from INDIGO were relatively high,

supporting that the trial cohort was stable compared with the wider LGG population (see section 3.6). Also, moving from progression free to progressed disease resulted in a small utility decrease (0.009), which the EAG thought was an implausibly small drop. It was also concerned about the utility values derived from the vignette study. It highlighted that a vignette study is the lowest quality of evidence for utility values according to NICE's health technology evaluations manual. It also said that the description of health states in the vignette did not differentiate by glioma type or grade. Firstly, the EAG thought it inappropriate to average the on- and off-treatment utility values from the vignette study. This was based on clinical-expert advice that quality of life would likely increase after chemotherapy and radiotherapy because the side effects of these treatments would stop. So, the EAG used the unadjusted EQ-5D vignette utilities in its base case. The clinical experts supported this. They reiterated that chemotherapy and radiotherapy cause major, short-term side effects that disrupt daily life and work. Though quality of life is likely to improve after treatment, the experts stressed that long-term side effects like cognitive decline and fatigue can still emerge years down the line. The EAG explained that the description used in the vignette study for the off-treatment health states assumed no adverse events from treatment. So, the committee thought that the unadjusted vignette utilities may not have captured the long-term impacts of chemotherapy or radiotherapy.

The EAG was also concerned that when people moved from progressed disease, off treatment to first-line chemotherapy or radiotherapy (that is, from the utility values derived from the INDIGO study to the values derived from the vignette study), there was a very large drop in health-related quality of life (0.328). The company explained that the quality-of-life data in INDIGO was collected relatively close to disease progression and was based on very small numbers. So, by the time people started chemotherapy or radiotherapy they would be expected to have a poorer quality of life than was recorded in the trial. The committee recalled that,

in the company's base case, people spent a long time in the progressed-disease, off-treatment health state. The company explained that during this time, people got older and there would likely be some progressive deterioration in their LGG. The committee also recalled that people having active surveillance spent considerably less time off treatment with progressed disease (that is, less time in the health states with higher quality of life) than people having vorasidenib. So, the committee agreed with the EAG that the large drop between the INDIGO and vignette utility values may not be plausible and noted it was amplifying the impact of the TTNI-P difference between arms. The EAG thought that using different sources resulted in utilities that lacked face validity. It also noted a big difference between the off-treatment health states before and after having first-line chemotherapy or radiotherapy. It noted that the vignette study had not included descriptions of progression-free and progressed-disease health states that could be used to anchor them to the vignette and INDIGO utilities.

The committee thought both the company's and the EAG's preferred utility values were highly uncertain because they used 2 different unanchored sources. It noted that the company's literature search had identified a utility value of 0.60 that was used for glioma recurrence in TA23. It thought that using the utility value of 0.60 for first-line chemotherapy and radiotherapy in the model, and applying the relative difference between health-state utilities in the unadjusted EQ-5D vignette applied for later health states, would result in a more plausible set of utility values. This was because it would capture the burden of treatment from subsequent treatments but remove the implausible drop in utility when moving to subsequent treatments. The committee also requested further analysis to consider the quality-of-life decrement of moving from progression-free to progressed-disease health states, because of the uncertainty around time spent in the progressed-disease state without treatment (see section 3.10). The committee agreed that these analyses, including the approach

outlined, should be provided at consultation. It concluded that the utility values from the vignette study were highly uncertain, and that further analyses should be presented at consultation.

Costs

Monitoring costs

3.14 The company base case included monitoring costs for 3-monthly MRI and CT scans for people having vorasidenib and placebo. Based on clinical-expert advice, the EAG only included an imaging cost for monitoring with MRIs in its base case. This was supported by the clinical experts who stated that CT scans are rarely used to monitor LGG. The committee concluded that the cost of CT scans should be excluded from the modelling in line with clinical practice.

Discount rate

3.15 NICE's health technology evaluations manual states alternative analyses using rates of 1.5% for both costs and health effects may be presented alongside the reference-case analysis. This may be considered by committee when it is highly likely that, on the basis of the evidence presented, the treatment is likely to restore people to full or near-full health when they would otherwise die or have a very severely impaired life, and when this is sustained over a very long period. Rather than present the reference case discount rate (3.5%) in its base case, the company used a discount rate of 1.5% for health benefits and costs. The EAG used a 3.5% discount rate, stating that the criteria for applying a lower discount rate were not met. The committee thought that:

- Although people with LGG have severely impaired quality of life as the disease progresses, the population having vorasidenib in clinical practice would have stable disease not in immediate need of further systemic treatment. This was evidenced by the relevant comparator being active surveillance (see section 3.3). The EAG also highlighted that there was also only a small decrease in quality of life between the

public and people in INDIGO whose glioma was progression free after surgery. The committee noted that the company's base-case analyses predicted an overall survival for people having active surveillance of around 20 years after entering the model. So, the committee agreed that people would not have a severely impaired quality of life or otherwise die at the point in the treatment pathway where vorasidenib would be used.

- The committee next considered whether vorasidenib restored people to full or near-full health. They noted that it aims to delay time to progression and next treatment but was not a cure for the condition. There was also better health-related quality of life in the placebo arm in INDIGO after progression than the vorasidenib arm. A patient expert explained that vorasidenib helped greatly lower the anxiety of living with an inevitably progressive disease, but did not eliminate this completely. So, the committee agreed that vorasidenib does not restore people to full or near-full health.
- The long-term benefits for vorasidenib including overall survival are unknown because of the high level of uncertainty about the benefit in TTNI-P and overall survival for vorasidenib in the model (see sections 3.10 and 3.11). Because of this, the committee agreed that it could not be confident that there was a plausible case for the maintenance of benefits over time.

The committee concluded that a 3.5% discount rate should be used for health benefits and costs in the model.

Severity

3.16 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight (a severity modifier) to quality-adjusted life years (QALYs) if technologies are indicated for conditions with a high degree of severity. The company provided absolute

and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. In its base case, the company applied a severity weighting of 1.7 to the QALYs. But the committee recalled that this included a discount rate of 1.5% for health benefits and costs. It noted that the NICE health technology evaluations manual states that absolute and proportional shortfall calculations should include discounting at the reference-case rate. When using a 3.5% discount rate for health benefits and costs, the absolute QALY shortfall was 12.39 in the company's base case and 12.96 in the EAG's base case. The proportional QALY shortfall was 0.66 in the company's base case and 0.69 in the EAG's base case. So, based on the absolute QALY shortfall, both the EAG and company base cases applied a weight of 1.2 to the QALYs. The committee noted that several of the EAG's scenarios did not meet the criteria for applying a QALY weighting, including when applying the utility values from the time trade-off vignette study for subsequent treatments. But it concluded that, based on the current analysis, a severity weight of 1.2 applied to the QALYs was appropriate. The committee said that any changes to the analysis following consultation would be considered in relation to severity weighting.

Cost-effectiveness estimates

Uncaptured benefits

3.17 The committee noted that some potential benefits of vorasidenib may not have been included in company's model:

- The committee recalled the psychological impact of LGG (see section 3.1). A patient expert at the meeting explained that, since starting vorasidenib, their mental health had improved considerably, to the point where they could live a close-to-normal life and had returned to work and social events. The committee thought that the full impact of vorasidenib on mental health may not be captured in the model.

- The committee recalled that the seizures associated with LGG stop people from driving, which can limit their independence (see section 3.1). The clinical experts explained that people needed to have not had a seizure for 12 months to restore driving eligibility. It noted that the INDIGO trial reported a reduction in the number of seizures compared with placebo, and that this reduction had been included in the model (see section 3.5). But, given the median PFS of 22.1 months in the vorasidenib arm, it considered it unlikely that many people having vorasidenib would be seizure-free for an entire year to allow them to return to driving. It concluded that it was uncertain whether the full quality-of-life benefit from reducing seizures had been captured in the model.
- The committee recalled the large physical and psychological impact on carers and family members of people with LGG (see section 3.1). The patient expert explained that family members often have to take time off work to provide physical and emotional care, and transport to regular hospital visits. They explained that, since taking vorasidenib, the level of care needed had reduced considerably because of improvements in their mental health. The committee considered that the impact on carers may not be captured in the economic modelling.
- The patient experts highlighted the socioeconomic benefits of increasing the time before people have chemotherapy and radiotherapy for people with LGG. Postponing the associated debilitating side effects extends the time people can function at their best, both professionally and personally. The committee recalled that people who would have vorasidenib are often in the middle of their careers and have young families to support (see section 3.1). It agreed that the socioeconomic benefits of vorasidenib may not be captured in the modelling.

  The committee considered the uncaptured benefits of vorasidenib in its decision making by accepting a higher level of uncertainty (see section 3.18).

Acceptable ICER

3.18 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically the:

- time off treatment with progressed disease
- overall-survival benefit for vorasidenib compared with active surveillance
- utility values for health states and subsequent treatments.

It considered whether other factors should be included in its decision making. It recalled that astrocytoma and oligodendroglioma are rare conditions, which may present specific challenges in data collection. But it felt that it had already applied flexibility for rarity by accepting the generalisability of the INDIGO population to that in the NHS (see section 3.6). It also noted the uncaptured benefits for vorasidenib including the impact on carers and the wider socioeconomic benefits (see section 3.17). Because of this, the committee agreed that it was appropriate to accept some of the extra uncertainty in the economic modelling, as it considered the uncertainties in key issues such as overall survival, time to next intervention given progression and utility values, were higher than in many other evaluations. But it determined that based on the evidence presented, the level of uncertainty surrounding the data was significant enough that any potential uncaptured benefits did not justify a higher threshold. So, the

committee concluded that an acceptable ICER would be around £20,000 per QALY.

Company and EAG cost-effectiveness estimates

3.19 Because of confidential commercial arrangements for vorasidenib and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. The company's base-case ICER for vorasidenib compared with active surveillance was just above the committee's acceptable ICER (see section 3.18). The EAG's base-case ICER for vorasidenib compared with active surveillance was considerably above this range. The committee noted that using its preferred 3.5% discount rate (see section 3.15) increased the company's base-case ICER considerably, as did using pooled data from INDIGO to inform the TTNI-P curve (see section 3.10). The committee concluded that, when using its preferred discount rate, both the company's and EAG's base-case ICERs were considerably above the range normally considered a cost-effective use of NHS resources.

Committee's preferred ICER

3.20 For the model assumptions, the committee preferred to:

- use the baseline characteristics for the population from INDIGO (see section 3.6)
- use the PFS data from INDIGO for vorasidenib and placebo, using a log-normal distribution (see section 3.9)
- use the vorasidenib TTNI-P data to model the time off treatment with progression for both vorasidenib and placebo but exploring alternative approaches (see section 3.10)
- use the company's modelling of overall survival while noting the uncertainty in this approach, but would assess outputs from updated analyses (see section 3.11)
- use the EAG's preferred distribution of subsequent treatments, informed by clinical experts and NG99 (see section 3.12)

- exclude the cost for using bevacizumab as a subsequent treatment (see section 3.12)
- exclude the cost of using CT scans for monitoring for vorasidenib and placebo (see section 3.14)
- use a discount rate of 3.5% for health benefits and costs (see section 3.15)
- add a severity weight of 1.2 to the QALYs (see section 3.16).

The committee could not establish a plausible ICER because of the modelling of relative effectiveness and utilities. It noted that all of the scenarios provided by the EAG that included a 3.5% discount rate were above the threshold considered a cost-effective use of NHS resources. So, vorasidenib was unlikely to be cost effective using its preferred assumptions. It agreed that it could not recommend vorasidenib for treating LGG with IDH1 or IDH2 mutations after surgery in people 12 years and over.

Uncertainties to explore further in the modelling

3.21 The committee noted that there was considerable uncertainty surrounding the cost effectiveness of vorasidenib for LGG. It agreed that the company's model after consultation should:

- explore alternative ways to model TTNI-P, including but not limited to:
  - providing full parametric distributions for TTNI-P, applying data from the INDIGO vorasidenib arm to both vorasidenib and active surveillance in the model
  - exploring alternative ways to plausibly model a benefit in TTNI-P for vorasidenib without using data from the placebo arm of INDIGO as a scenario (see section 3.10)
- model the quality-of-life burden for subsequent treatments by applying the relative difference between health-state utilities in the unadjusted EQ-5D vignette study to the value for glioma recurrence from TA23,

and consider alternative quality-of-life decrements moving from progression-free disease to progressed disease (see section 3.13).

Managed access

3.22 Having concluded that vorasidenib could not be recommended for routine use in the NHS, the committee then considered if it could be recommended for use during a managed access period for treating LGG with IDH1 or IDH2 mutations. The committee considered whether a recommendation with managed access could be made, given the following:

- Its preferred ICER threshold was £20,000 per QALY gained (see section 3.18). It had not been presented with analyses that included its preferred assumptions, but its preferred ICER likely lay above the range considered an acceptable use of NHS resources. So, there was currently no plausible potential for cost effectiveness.
- The key uncertainties in the data were the TTNI-P and overall-survival benefits for vorasidenib compared with placebo and the utility values for subsequent treatments. The committee considered potential sources of new evidence that could become available within the timeframe of a managed access agreement:
  - The INDIGO trial has a planned data cut in May 2028. The committee agreed that this could provide useful information on the generalisability of the population having vorasidenib in the trial to the expected population in the NHS. But this data would be unlikely to resolve the existing uncertainty because:
    - The post-progression data was biased by the high proportion of people who crossed over to vorasidenib from the placebo arm (see section 3.7). The committee was concerned that, even with further data from INDIGO, it would not be possible to adjust for this bias.
    - An overall-survival benefit would likely not be demonstrated within the available period of managed access.

- The company explained that there was also an early access scheme that could provide real-world evidence on people having vorasidenib in the NHS. The NHS England representative thought that it would be possible to collect data on the size of tumour and time of surgery that would resolve some uncertainty about the generalisability of the population to that in the NHS.
- The committee considered whether it would be possible to collect data from existing cancer registries. It noted that surgery and radiotherapy data were not captured in the Systemic Anti-Cancer Therapy (SACT) dataset. But it noted that it may be possible to get information on subsequent treatments by linking data on chemotherapy regimens from SACT with data on radiotherapy from NHS England's National Radiotherapy Data Set database.

The committee judged that, although there was information that could be collected to resolve some of the uncertainty as part of a managed access agreement, the key issues and uncertainties around those would not be resolved. There was also no plausible potential for cost effectiveness. So, it concluded that, based on the evidence presented, vorasidenib did not meet the criteria to be considered for managed access.

Other factors

Equality

3.23 The committee noted that many people with LGG with IDH1 or IDH2 mutations may be young. A patient-organisation submission also highlighted that vorasidenib is not licensed for use in pregnancy and treatment is expected to continue until progression which affects the ability to have children. Age and pregnancy are protected under the Equality Act 2010. But because its recommendation does not restrict access to treatment for some people over others, the committee agreed these were not potential equalities issues that could be addressed by this

evaluation. A patient organisation also highlighted that treatment cost related to vorasidenib including travel or time away from work could disproportionately affect poeple from lower-income backgrounds if additional monitoring was needed for vorasidenib. But a patient expert explained that there was no significant additional monitoring compared with active surveillance because vorasidenib was an oral treatment that could be taken at home. The committee concluded that there were no equality issues relevant to the recommendations.

Conclusion

Recommendation

3.24 The committee noted the important uncertainties in the cost-effectiveness evidence. This meant it was not possible to reliably estimate the cost effectiveness of vorasidenib. So, it should not be used. The committee concluded that the company should provide additional information for consideration at the next evaluation committee meeting.

4 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Paul Arundel

Chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

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