

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

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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1 Recommendations

- 1.1 Vorasidenib can be used as an option to treat grade 2 astrocytoma or oligodendroglioma in people 12 years and over when:
- the cancer has a susceptible isocitrate dehydrogenase (IDH) 1 or IDH2 mutation
 - the person has had surgery and does not immediately need chemotherapy or radiotherapy, and
 - the company provides vorasidenib according to the [commercial arrangement](#).
- 1.2 Stop vorasidenib if the cancer progresses and in line with the stopping criteria in the marketing authorisation.
- 1.3 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.

What this means in practice

Vorasidenib must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option.

Vorasidenib must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that vorasidenib provides benefits and value for money, so it can be used routinely across the NHS in this population.

Why the committee made these recommendations

Usual care for grade 2 astrocytoma or oligodendroglioma with an IDH1 or IDH2 mutation for people whose cancer has not progressed (got worse) and who do not immediately need chemotherapy or radiotherapy after surgery is active surveillance.

This evaluation included a rule that vorasidenib is stopped if the cancer gets worse. This rule was used in the main clinical trial and is in line with how vorasidenib would be used in practice, but is not part of the marketing authorisation for vorasidenib.

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

The cost-effectiveness estimates for vorasidenib are uncertain. But there are several benefits of vorasidenib that have not been fully captured in the economic model. When considering these, and the severity of the condition and its effect on quality and length of life, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, vorasidenib can be used.

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

- 2.3 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).
- 2.4 The company has a [commercial arrangement](#). This makes vorasidenib available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

- 2.5 For information, Servier Laboratories did not disclose its Carbon Reduction Plan for UK carbon emissions.

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. All LGG tumours eventually progress, with up to 70% transforming to high grade or becoming 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 called a 1p/19q co-deletion. Gliomas with a 1p/19q co-deletion or IDH mutation are thought to grow more slowly than gliomas without these alterations.

Symptoms of the 2 main types of LGG – IDH-mutant astrocytoma and oligodendroglioma (from here, referred to collectively 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, impact daily activities 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. The committee said that 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 main aim of treatment for glioma is to delay progression and improve neurological function and quality of life. [Section 1.2 of NICE's guideline on primary brain tumours and brain metastases in over 16s](#) (from here, referred to as 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 with chemotherapy with or without radiotherapy 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. This should be followed by a maximum of 6 cycles of procarbazine, lomustine 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 best 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. They explained that active surveillance is not a form of treatment but rather a monitoring strategy, which carries a significant psychological burden. Living with a progressively enlarging tumour under this approach can cause considerable anxiety, especially around the time of scans. Chemotherapy and radiotherapy are also associated with debilitating side effects such as cognitive decline, radiation necrosis (permanent tissue damage) and fatigue. These treatments negatively affect fertility and require regular hospital visits, which can limit a person's ability to work. Radiotherapy can also cause secondary malignancies or transformation to HGG. The patient expert said that they would welcome a treatment that could be used after surgery to delay the need for chemotherapy with or without radiotherapy. They said that 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 with or without 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) or
- a gross total or complete resection (where all visible tumour is removed) or
- 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, 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 everyone who was not in need of immediate chemotherapy with or without radiotherapy after surgery would have active surveillance. The committee noted that the summary of product characteristics for vorasidenib stated that it should be continued until cessation of observed clinical benefit or until it is no longer tolerated. The clinical experts confirmed that people whose disease progressed on vorasidenib would have active observation or chemotherapy with or without radiotherapy. The committee noted this aligned with the company's modelled population and clinical trial data (see [section 3.4](#) and [section 3.9](#)). The committee concluded that active surveillance was the relevant comparator but the exact population in 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 includes 4 sites in the UK. It enrolled 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 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 treatment 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 20 months). 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 (TTNI)
- 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 to not estimable) in the vorasidenib arm and was 11.4 months (95% CI 11.1 to 13.9) 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 TTNI was not evaluable in the vorasidenib arm and was 20.1 months (95% CI 17.5 to 27.1) 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 happen 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 3.14](#)).

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 for 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 TTNI 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 IDH2 mutation who do not need 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 cm²) 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 cm² would be eligible to have vorasidenib in the NHS according to its marketing authorisation. It said that some people with a supramaximal or complete resection (see [section 3.3](#)) would also be eligible. 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 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 3.14](#)). The clinical experts stated that, because LGG is a slowly progressing condition, progression will generally be identified by gradual radiological changes unless the cancer transitions to HGG. Although some people might start treatment with chemotherapy with or without radiotherapy for seizures that are uncontrolled on antiseizure 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 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) than chemotherapy with or without radiotherapy, which were the only subsequent-treatment options 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 with or without radiotherapy, on treatment
- first-line chemotherapy with or without radiotherapy, off treatment
- second-line chemotherapy with or without radiotherapy onwards, on treatment
- best supportive care
- death.

The model also included a health state for people who remained on treatment with progressed disease, but this was not used in this appraisal. 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's base case after consultation used a 28-day cycle length with a half-cycle correction, a 60-year time horizon and a 3.5% discount rate for both health effects and costs (see [section 3.17](#)). 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 TTNI). 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, TTNI 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 with or without radiotherapy (on and off treatment) came from multiple sources in the literature. Based on a company assumption, 5% of people moved to best supportive care after progression on vorasidenib, active surveillance or first-line subsequent treatment. The clinical experts at the first meeting confirmed this was reasonable. The committee noted that vorasidenib was stopped on progression of disease in the model. It agreed this was appropriate for clinical practice because it aligned with the data from INDIGO (see [section 3.4](#)). The committee also 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 but acceptable for decision making.

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

Parametric curves using INDIGO data

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. In its original submission, 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 original parametric curves lacked face validity and overestimated the proportion of people off treatment after progression on vorasidenib or placebo. The model also predicted a small percentage of people in the vorasidenib arm to be in the progressed-disease, off-treatment health state for the entire model lifetime. This implied a cure. The EAG considered this implausible given the disease characteristics and noted that TTNI-P benefits were modelled to apply in addition to the PFS benefit for vorasidenib seen in INDIGO. The company stated that a long TTNI-P was plausible for 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 with or without radiotherapy to avoid the associated side effects. It thought this was supported by results from INDIGO, which 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 that vorasidenib caused molecular changes in the tumour. One clinical expert explained that, although uncertain, a longer TTNI for people who had vorasidenib was plausible. This was because, by inhibiting the effects of the IDH mutation early, vorasidenib may alter tumour development. This leads to more favourable tumour biology on

progression and less immediate need for chemotherapy with or without radiotherapy. But the EAG noted the bias in the TTNI results for the placebo arm. It said this 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 a higher quality of life in the placebo arm than the vorasidenib arm, which did not support a longer TTNI-P for vorasidenib. So, it preferred to fit the same curve to both arms, using pooled TTNI-P data from INDIGO. It used a log-normal curve to extrapolate the long-term effects because this was the best-fitting curve that was most plausible. This was because the log-normal curve 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 a single or separate curves were applied 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 3.12](#)). The committee also noted that the extrapolations were limited by a small number of events. This was particularly the case in the vorasidenib arm, where most people remained progression free at the last data cut. The clinical experts at the first meeting 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 in clinical practice twice as many people have astrocytoma. So, at the first committee meeting 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. At that meeting, the committee preferred 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 acknowledged that this approach did not assume a TTNI benefit for vorasidenib. It considered a longer TTNI-P for vorasidenib than placebo may be plausible, because of vorasidenib's effect on tumour biology. But it agreed that this was the most plausible method available at the time to remove bias from the placebo-arm data.

At consultation, the company revised its base case to use the log-normal curve for vorasidenib but incorporated a TTNI-P decrement for active surveillance by applying a hazard ratio (see [section 3.11](#)). It considered that, when using the vorasidenib TTNI-P data for active surveillance, the results lacked face validity. This was because the time spent off treatment with progressed disease (2.3 years) was longer than that spent in the progression-free health state (1.4 years). The resulting TTNI also exceeded external estimates for active surveillance in a mix of grade 2 and 3 glioma. The EAG also used the log-normal curve for vorasidenib in its base case. But it provided scenarios using the exponential and generalised gamma distributions for the vorasidenib arm (with and without a TTNI-P benefit for vorasidenib). At the first meeting the committee noted that applying a log-normal curve for vorasidenib produced a TTNI-P estimate that fell between the EAG and the company's base-case curves. So, this approach was likely to better reflect outcomes in the population with LGG in the NHS. The committee concluded that a log-normal curve should be used to extrapolate the data from the vorasidenib arm of INDIGO and that a TTNI-P benefit for vorasidenib was plausible. But the size of this benefit was uncertain because of bias in the TTNI-P results from the placebo arm of INDIGO.

Modelling a TTNI-P benefit for vorasidenib

3.11 At consultation, the company submitted additional evidence to support a longer TTNI-P in the vorasidenib arm, including:

- A Cox regression model based on data from the vorasidenib arm of INDIGO, which suggested a 56% increase in the risk of a TTNI event for every 1-unit increase in log tumour volume. The company stated this supported a longer TTNI-P for vorasidenib, because around 50% of people in the vorasidenib arm of INDIGO had tumour shrinkage at progression.
- Data from the Brain tumour Registry Australia INnovation and translation registry (BRAIN; resubmitted from clarification) in a similar population to INDIGO (IDH-mutant grade 2 glioma with at least 1 surgery 'between 1 and 5 years prior' and recurrent or residual disease). This indicated a median TTNI-P of 6 months for active surveillance based on the difference between

the median time from surgery to next intervention (48.4 months) and the median PFS (42.7 months).

- Updated health-related quality-of-life data from March 2023, which showed a narrower difference than previously reported between vorasidenib and placebo for people with progressed disease.
- Clinical-expert advice that people whose disease had progressed on active surveillance would typically begin chemotherapy with or without radiotherapy after a further scan assessing post-progression tumour growth, which would be undertaken around 6 months after progression. For vorasidenib, a TTNI-P of about 2 years was considered plausible because of its impact on the molecular biology of LGG.

The company stated that the above data supported a TTNI-P for active surveillance of around 6 months. So, its revised base case applied a hazard ratio of 3 for active surveillance to the TTNI-P curve for vorasidenib, using a log-normal distribution. This produced an average TTNI-P of 5.12 months for active surveillance, compared with 2.19 years for vorasidenib. The company also provided scenarios with hazard ratios of 2.5 and 3.5 for active surveillance. This resulted in average TTNI-P estimates of 6.53 months when a hazard ratio of 2.5 was used and 4.11 months when a hazard ratio of 3.5 was used.

The EAG observed that the population in the BRAIN registry may not be generalisable to the population in INDIGO, because:

- The cohorts were not matched or adjusted for prognostic factors. Notably, more people in the INDIGO study had a chromosomal 1p/19q co-deletion (52%) than in the BRAIN study (32%, although status was unavailable for 43% of the population). This suggests a poorer prognosis for people in the BRAIN study.
- There were potential differences between cohorts in disease duration at study inclusion and whether people needing immediate treatment were included.
- 40% of people in the BRAIN study had surgery as their next intervention. Because of this, the EAG was concerned that the results may not be

generalisable to the modelled time to chemotherapy with or without radiotherapy.

The EAG also thought that analyses that suggest that a reduction in tumour volume increased TTNI-P should be interpreted with caution. This was because the tumour shrinkage from baseline was already modelled through direct correlation with PFS and the number informing the analyses was small. Also, the INDIGO results did not support a link between tumour volume and risk of malignant transformation. They also still suggested a higher quality of life post-progression for placebo than for vorasidenib. The mean log tumour volume at progressed disease was also similar for vorasidenib and placebo. The EAG agreed that some TTNI-P benefit was plausible for vorasidenib. But it considered that applying a hazard ratio of 3 may underestimate the TTNI-P for active surveillance. The EAG was unclear about which hazard ratio to apply in its base case. So, it provided additional scenarios varying the hazard ratio for active surveillance to 1.5 and 2.0 applied to different parametric distributions. When using the log-normal distribution for vorasidenib, the average time off treatment with progressed disease was:

- 1.18 years with the 1.5 hazard ratio, and
- 0.75 years with the 2.0 hazard ratio.

At the second committee meeting, clinical experts confirmed that 6-monthly MRIs are generally used to monitor tumour growth in people with LGG. Since oligodendrogliomas and astrocytomas are slow-growing tumours, progression is often observed relative to the baseline scan rather than the most recent one. In many cases, this tumour growth does not impact wellbeing, so people choose to stay on active surveillance to avoid the side effects of chemotherapy and radiotherapy. Further treatment options would be discussed with these people, who may have additional advanced scans. The clinical experts stated that the decision to start chemotherapy with or without radiotherapy depends on many factors. These include patient preference, the time from diagnosis, tumour location and an assessment of risks and benefits of starting treatment compared with remaining off treatment. The clinical experts noted that practice may vary between centres but, generally, only around 20% of people with LGG start treatment within 6 months of confirmed tumour progression. This is most likely people:

- who develop symptoms such as seizures, or
- whose most recent scan shows:
 - changes that suggest a transformation to HGG (such as contrast enhancement) or
 - significant growth or change from the previous scan.

One clinical expert explained that a further 20% of people having active surveillance would be expected to start chemotherapy with or without radiotherapy between 6 months and 2 years from disease progression. The remaining 60% would remain off treatment until between 2 years and 7 years from progression. The committee noted that these estimates were considerably longer than the average TTNI-P of 5.12 months in the company's base case for active surveillance. So, the company base case likely overestimated any TTNI-P benefit for vorasidenib. The committee noted the generalisability issues with the BRAIN cohort. To inform the TTNI-P for active surveillance, it would have preferred to see registry data in a UK cohort. Or, alternatively, structured clinical-expert input with specific questions on TTNI-P rather than solely on imaging intervals. But, given the options available, it agreed that a 1.5 hazard ratio applied to the log-normal extrapolation of the vorasidenib arm (giving an average TTNI-P of 1.18 years off treatment after progression) aligned better with clinical-expert advice at the second meeting. The committee concluded that the company's modelling of a TTNI-P benefit for vorasidenib was uncertain because it was not informed by robust UK data. It noted that this uncertainty carried through to the overall-survival estimates (see [section 3.12](#)). But it concluded that a TTNI-P benefit for vorasidenib should be modelled by applying a hazard ratio of 1.5 to the vorasidenib arm for active surveillance.

Overall survival

- 3.12 There was no mature overall-survival data available from INDIGO, and no deaths reported before disease progression on vorasidenib and placebo. So, the company 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 in the best supportive care health state. 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 data suggested that delaying the time to first and second progression improved overall survival. The clinical experts at the first committee meeting 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.

At consultation, stakeholders emphasised that delaying disease progression is highly likely to increase survival, because progression is the primary driver of mortality. The company also submitted additional data to support a surrogacy relationship between PFS and overall survival, including data from:

- [Han et al. \(2014\)](#), which reported a strong correlation between hazard ratios for PFS and overall survival in HGG.
- [Bhatia et al. \(2024\)](#), which showed that a 1-unit increase in natural logarithm of tumour volume increased the risk of death 3-fold in IDH-mutant gliomas under active surveillance after surgery.
- New post-hoc analyses from INDIGO, which included:
 - a subgroup analysis showing a longer PFS in people whose tumours grew more slowly or decreased in volume, and
 - a Cox regression model showing that a 1-unit increase in log tumour volume increased the risk of progression by 22%.

But the EAG thought that the applicability of these benefits to grade-2 glioma was uncertain. It noted that much of the company's new data linked overall survival to tumour volume and growth rate rather than PFS.

The EAG was also concerned about using TTNI-P as an effective surrogate marker for overall survival, because it was highly uncertain and was likely confounded by crossover (see [section 3.10](#)). At consultation, the company maintained that TTNI-P was an appropriate surrogate for overall survival. It considered that TTNI is mechanistically linked to overall survival through its dependence on disease progression. It also submitted further evidence to support a link between TTNI-P and overall survival, including data from:

- [EORTC 22845](#) and [RTOG 9802](#), which suggested comparable overall-survival benefits when using radiotherapy (alone or with chemotherapy) early or later after progression
- [Blonski et al. \(2022\)](#), which reported that 42% (5 out of 12) of deaths in 20 people having PCV with radiotherapy for diffuse LGG were caused by treatment-related neurotoxicity, not tumour progression.

The EAG acknowledged that a link between TTNI-P and overall survival was plausible. But it was concerned that this relationship was not directly addressed in the company's new evidence, some of which was in small populations. It also noted that no association between PFS or TTNI-P and overall survival had been seen in INDIGO. This is because only 1 death had occurred despite a statistically significant PFS advantage for vorasidenib compared with active surveillance. There was also no data to suggest a delayed transition to HGG or malignant glioma with vorasidenib compared with active surveillance. 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 uncertain. This was because of the uncertainty in the modelled inputs, especially the TTNI-P from INDIGO. The committee considered this uncertainty in its decision making.

Subsequent treatments

Distribution of subsequent treatments in the model

3.13 In the company's model, the chemotherapy regimens and the proportion having radiotherapy differed by treatment line. In the original company submission, 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. The company then 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 first meeting, the company highlighted that some people in England and Wales self-fund bevacizumab because it 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 had PCV, 33% had temozolomide and 33% had lomustine 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 temozolomide use was limited by [NICE's technology appraisal guidance on temozolomide for the treatment of recurrent malignant glioma](#) (from here, referred to as TA23) and so PCV may be more accessible in the NHS. It acknowledged the uncertainty in the modelling of subsequent treatments. But it agreed that it preferred the EAG's base-case distributions because they better reflected NHS practice. At consultation, the company updated its base case to include the committee's preferred distributions for subsequent treatments.

Utility values

INDIGO utility values

3.14 In its original submission, 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 EAG 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. The company explained that the quality-of-life data in INDIGO was collected relatively close to disease progression and was based on a very small number of people. So, by the time people started chemotherapy with or without radiotherapy they would likely have a poorer quality of life than was recorded in the trial. At consultation, the company updated its base case to include health-related quality-of-life data from a more recent data cut of INDIGO (March 2023). This showed a larger drop between the progression-free and progressed-disease

health states. The EAG included the new utilities in its base case but cautioned they still showed a higher quality of life for progressed disease in people having placebo than vorasidenib. The committee also recalled that active surveillance is associated with a considerable psychological burden that can affect quality of life (see [section 3.2](#)). Stakeholders at consultation highlighted that this may not be captured in the company's model, which used the same progression-free utilities for people having vorasidenib and active surveillance. The committee was also concerned that the INDIGO utilities may not fully capture the quality-of-life impact for people having seizures. It noted that a separate disutility for seizures had not been applied in the modelling. The committee acknowledged the uncertainty in the utility values from INDIGO but accepted them for decision making.

Vignette utility values

3.15 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 EAG highlighted that a vignette study is the lowest quality of evidence for utility values according to [NICE's technology appraisal and highly specialised technologies guidance manual](#). It also said that the description of health states in the vignette did not differentiate by glioma type or grade. The utility values derived from the vignette study were higher for people who had stopped chemotherapy with or without radiotherapy than for people who were having this treatment. The company thought this implausible. So, it 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 original base case. The EAG preferred the unadjusted EQ-5D values. This was based on clinical-expert advice that quality of life would likely increase after chemotherapy with or without radiotherapy because the side effects of these treatments would stop. The clinical experts at the meeting 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 later. This was supported by stakeholders during consultation. The clinical experts noted that the impact of long-term side effects, especially those from radiotherapy (such as radiation necrosis), and transformation to HGG or secondary malignancies, were not fully captured in the model (see [section 3.2](#)). 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 with or without radiotherapy.

The EAG was also concerned that when people moved from progressed disease, off treatment to first-line chemotherapy with or without 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 (0.32). The EAG thought that using different sources resulted in utilities that lacked face validity. 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. It also recalled that people in the company's base case having active surveillance spent 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 was uncertain and was amplifying the impact of the TTNI-P difference between arms.

At consultation, the company updated its preferred approach to use the unadjusted EQ-5D utility values from the vignette in its base case. It also submitted scenarios based on a value of 0.60 that was used for glioma recurrence in TA23, as requested by the committee at the first meeting. It noted that the committee's preferred method of applying a utility of 0.60 for first-line chemotherapy with or without radiotherapy, then adjusting later health states using relative differences from unadjusted EQ-5D vignettes, lacked face validity. This was because the resulting utility for people off treatment with progressed disease after chemotherapy with or without radiotherapy was higher than the baseline utilities from INDIGO. To address this, the company proposed a scenario using the value from TA23 (0.60) for people who were off treatment after chemotherapy with or without radiotherapy. It then applied relative differences from the EQ-5D vignette for the other subsequent-treatment health states. It also

provided a scenario using new utilities for all health states based on those reported in [NICE's technology appraisal guidance on dabrafenib with trametinib for treating BRAF V600E mutation-positive glioma](#) (from here, referred to as TA977). The EAG concluded that the company's alternative approaches did not resolve uncertainty around utility values for subsequent treatments. It noted that utilities based on TA23 and TA977 were similar to those in the unadjusted EQ-5D vignette and still resulted in a substantial drop in quality of life when people started chemotherapy with or without radiotherapy. It was also concerned that the utilities from TA977 may not be transferable to an NHS population because they were derived from a US cohort of both LGG and HGG. They were also based on progression events rather than treatment lines, as used in the company's model. So, at the second committee meeting, the EAG maintained its preference for the vignette-based values. The committee noted that seizures were reflected in the health-state descriptions used for the company's vignette so would likely be captured for later health states. It also recalled the high burden on carers of people with LGG and noted that the company had not included a disutility to capture this. The committee concluded that the vignette-based utility values were highly uncertain because they were not anchored to those derived from INDIGO. It noted that some utility-related uncertainties favoured vorasidenib, such as the high progressed-disease utility from INDIGO. But it noted that there were also uncertainties that worked against vorasidenib. These included that the full impact of seizures, caregiver burden, and long-term effects of chemotherapy with or without radiotherapy may not have been fully captured in the modelling. But it agreed it was appropriate to apply flexibility in accepting the analyses using the unadjusted EQ-5D vignette utilities for its decision making.

Costs

Monitoring costs

- 3.16 The company base case at the first committee meeting 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. At consultation, the

company updated its base case to include only the cost of 6-monthly MRI scans. The committee concluded that the cost of CT scans should be excluded from the modelling in line with clinical practice.

Discount rate

3.17 The [section on economic evaluation in NICE's technology appraisal and highly specialised technologies guidance](#) states that 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 the committee when it is highly likely that, based on 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
- treatment's benefit will be sustained over a very long period.

In its original base case, rather than present the reference-case discount rate (3.5%), 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 considered:

- 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 that does not need immediate further systemic treatment. This was evidenced by the relevant comparator being active surveillance (see [section 3.3](#)). The EAG highlighted that there was also only a small decrease in quality of life between the general population 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 18 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.
- 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.

- That the long-term benefits for vorasidenib including overall survival are unknown. This is 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 to 3.12](#)). 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.

After consultation, the company updated its base case to include a 3.5% discount rate for costs and benefits. The committee agreed that a 3.5% discount rate was appropriate and aligned with the reference-case analysis.

Severity

- 3.18 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 technology appraisal and highly specialised technologies guidance manual](#). In its original base case, the company applied a severity weighting of 1.7 to the QALYs. This was driven by its use of a discount rate of 1.5% for health benefits and costs. After consultation, the company base case (which included a 3.5% discount rate for costs and benefits) applied a severity weighting of 1.2 to the QALYs. The absolute QALY shortfall was 13.32 and the proportional QALY shortfall was 0.71. The committee noted that all EAG scenarios using the preferred log-normal distribution to extrapolate the INDIGO vorasidenib data met the criteria for a QALY weighting of 1.2 (see [section 3.10](#)). The committee concluded that a severity weighting of 1.2 applied to the QALYs was appropriate.

Cost-effectiveness estimates

Uncaptured benefits

3.19 The committee noted that some potential benefits of vorasidenib may not have been included in the company's model, such as:

- The psychological impact of LGG (see [section 3.1](#)). A patient expert at the first 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. At consultation, stakeholders emphasised the significant anxiety caused by active surveillance, limiting quality of life and ability to plan for the future (see [section 3.2](#)). The committee acknowledged this but considered that the extent of this uncaptured benefit was uncertain.
- The effect of seizures associated with LGG. The clinical experts explained that seizures can stop people from driving, which can limit their independence (see [section 3.1](#)). They highlighted that people needed to have not had a seizure for 12 months to restore driving eligibility. At consultation, the company suggested that some people in the vorasidenib arm could meet this criterion, supported by the fact that median PFS in this arm was not reached at the latest data cut (see [section 3.5](#)). The committee accepted that some people having vorasidenib may be seizure free for 1 year. But it thought that the number of people was unknown, given the median follow up of 20 months in INDIGO. Stakeholders emphasised during consultation that seizures also affect daily functioning, parenting, and employment, not just driving eligibility. The committee acknowledged the large impact of seizures on people with LGG. But it said that, although there was no separate disutility included for seizures in the company's model, some of this impact was captured because:
 - it included lower seizure-related costs and resource use for vorasidenib than active surveillance, based on seizure rates from INDIGO (see [section 3.5](#)), and
 - seizures were likely captured for later health states but may not be fully captured in the utility values derived from INDIGO (see [sections 3.14 and](#)

3.15).

The committee concluded that the size of any uncaptured benefit for vorasidenib from reducing the rate of seizures was unknown.

- 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 starting vorasidenib, the level of care needed had reduced considerably because of improvements in their mental health. At consultation, the company submitted a burden-of-care study that also highlighted the practical challenges of caring for people with LGG. This included managing increased household responsibilities and adjusting work hours to provide constant care and mitigate financial burden. But, it explained that it had not included a utility decrement for carer quality of life in the model because of an absence of robust data to inform any decrement (see [section 3.15](#)). The committee thought that LGG has a considerable impact on carers, which is not captured in the economic modelling.
- The socioeconomic benefits of increasing the time before people with LGG have chemotherapy with or without radiotherapy, as highlighted by patient experts. 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. But it noted that considering a societal perspective generally fell outside the remit for NICE committees.
- That diffuse astrocytomas always leave residual tumour even if radiologically undetectable. This was highlighted by a stakeholder at consultation, who explained that they expected vorasidenib to have some benefit for these people. The committee noted that this was not supported by evidence because people with no radiological disease were excluded from the INDIGO trial (see [section 3.6](#)). So, the extent of any benefit for vorasidenib in this population was unclear.

- That vorasidenib is an innovative treatment because it is the first targeted treatment for LGG that crosses the blood–brain barrier, which was noted by stakeholders. The clinical experts at the second committee meeting also highlighted the lack of progress in treatments for LGG over recent years and the high unmet need for new treatments (see section 3.2). During consultation stakeholders also highlighted that vorasidenib offers hope to people with LGG, which may positively impact their mental health and that of their families. The committee agreed that vorasidenib was an important advancement in a population with high unmet need and considered this in its decision making.
- That vorasidenib delays the time to chemotherapy with or without radiotherapy, so also delays the side effects associated with those treatments. Stakeholders and the company said that this benefit is greater in people with young families. The committee acknowledged that much of this benefit would be reflected in the model because adverse events were included in the radiotherapy and chemotherapy health-state descriptions in the vignette (see section 3.15). So, the extent of any additional benefit was uncertain.
- That tumour shrinkage for people having vorasidenib was not considered in the model. This was raised by stakeholders. The committee acknowledged that some tumours treated with vorasidenib in INDIGO had some shrinkage (see [section 3.11](#)). But it considered this likely captured in the PFS benefit, making any additional uncaptured benefit uncertain.
- Additional benefits for young people (12 to 17 years). At consultation the company highlighted that vorasidenib's marketing authorisation includes this population and that they may experience benefits from delaying radiotherapy and chemotherapy, such as:
 - avoiding cognitive side effects and supporting normal brain and skull development during adolescence
 - preventing educational disruption that carries significant long-term societal and economic consequences.

Clinical experts at the second meeting explained that developing brains are highly vulnerable to damage so radiotherapy is generally avoided in

young people. So, delaying toxic treatments until brain maturation offers additional benefits. The committee recognised significant potential benefits of using vorasidenib in young people, which were not reflected in the company's modelling. But it noted that childhood diagnoses of astrocytoma and oligodendroglioma are rare because these tumours typically grow slowly. So, the overall impact on the entire LGG population was uncertain.

- An underestimation of vorasidenib's effect in the licensed population, caused by using the older WHO classification in INDIGO, likely causing some people with HGG to be included in the trial (see [section 3.6](#)). This was highlighted by the company during consultation. The committee acknowledged this but recalled that the size of the population with HGG and the impact on the results was unknown. It considered this uncertainty to have been addressed by accepting the generalisability of the INDIGO trial to NHS clinical practice.

The committee considered that some benefits highlighted by the company and stakeholders may already have been, or could be, included in the modelling. But it considered that the remaining uncaptured benefits for vorasidenib could be taken into account in its decision making by accepting a higher level of uncertainty (see [section 3.20](#)).

Acceptable ICER

3.20 The [introduction on health technology evaluations in NICE's technology appraisal and highly specialised technologies guidance manual](#) notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £25,000 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 in the model.

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 said that it had already applied flexibility for rarity by accepting the generalisability of the INDIGO population to the NHS (see [section 3.6](#)). It also noted the high number of uncaptured benefits for vorasidenib (see [section 3.19](#)). At the first meeting, the committee's preferred threshold was at the lower end of the range NICE considers a cost-effective use of NHS resources. This was because it thought that the level of uncertainty around the key issues was higher than in many other NICE evaluations. Because it accepted this higher level of uncertainty, it agreed that any potential uncaptured benefits did not justify a higher threshold. At the second committee meeting, the committee considered additional benefits identified during consultation that were not fully captured in the economic model. Specifically, it noted:

- the benefits of vorasidenib from:
 - a reduced rate of seizures
 - delaying the effects of radiotherapy and chemotherapy in younger people
- the positive impact on carers.

It also acknowledged that vorasidenib addresses an unmet clinical need in this population. Although uncertainty remained around key model inputs, particularly TTNI-P, the committee concluded that these uncaptured benefits justified accepting some additional uncertainty in the economic modelling. So, it agreed that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£25,000 to £35,000 per QALY gained).

Company and EAG cost-effectiveness estimates

3.21 Because of confidential commercial arrangements for vorasidenib, 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 within the committee's acceptable ICER range (see [section 3.20](#)). The committee recalled that the EAG agreed that a hazard ratio should be applied to the log-normal vorasidenib curve for active surveillance but was unclear exactly what this hazard ratio should be (see [section 3.11](#)). It noted that the EAG's scenarios using a lower hazard ratio for active surveillance increased the company's base-case ICER but were within the committee's preferred range. So, the committee concluded that the ICER using the company's and EAG's preferred assumptions was within the committee's preferred range.

Committee's preferred ICER

3.22 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 with a log-normal distribution (see [section 3.9](#))
- use the TTNI-P data from INDIGO for vorasidenib with a log-normal distribution to model the time off treatment with progression for vorasidenib (see [section 3.10](#))
- apply a hazard ratio of 1.5 to the vorasidenib TTNI-P curve for time off treatment with progressed disease on active surveillance (see [section 3.11](#))
- use the company's modelling of overall survival while noting the uncertainty in this approach (see [section 3.12](#))
- use the distribution of subsequent treatments informed by clinical experts and [NG99](#) (see [section 3.13](#))
- exclude the cost for using bevacizumab as a subsequent treatment (see [section 3.13](#))
- use the INDIGO values for progression-free and progressed-disease health states and unadjusted EQ-5D vignette utilities for subsequent-treatment

health states (see [section 3.14](#) and [3.15](#))

- exclude the cost of using CT scans for monitoring for vorasidenib and placebo (see [section 3.16](#))
- use a discount rate of 3.5% for health benefits and costs (see [section 3.17](#))
- add a severity weighting of 1.2 to the QALYs (see [section 3.18](#)).

When considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates were within the committee's preferred range.

Other factors

Equality

- 3.23 The committee noted that many people with LGG with IDH1 or IDH2 mutations are young. The committee recalled that young people may stand to gain most from delaying chemotherapy with or without radiotherapy (see [section 3.19](#)). Stakeholders at consultation also highlighted that some of these people may have young families and face greater socioeconomic impacts compared with an older population. 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 characteristics 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 the treatment cost related to vorasidenib including travel or time away from work. It said that this could disproportionately affect people with lower incomes 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 that, when considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, vorasidenib can be used.

4 Implementation

- 4.1 Section 7 of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.
- 4.2 Chapter 2 of [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The [NHS England Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.
- 4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has grade 2 astrocytoma or oligodendroglioma with susceptible isocitrate dehydrogenase (IDH) 1 or IDH2 mutations, and they do not need immediate chemotherapy with or without radiotherapy after surgery, if the healthcare professional responsible for their care thinks that vorasidenib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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.

Emma Douch

Technical lead

Alan Moore

Technical adviser

Thomas Feist

Project manager

Richard Diaz

Associate director

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