5.15 VORASIDENIB, Tablet 10 mg, Tablet 40 mg, Voranigo®, SERVIER LABORATORIES (AUST.) PTY. LTD.

1 Purpose of submission

1.1 The Category 1 submission requested a General Schedule Authority Required (Streamlined) listing of vorasidenib, for the treatment of patients with isocitrate dehydrogenase (IDH)-mutant astrocytoma or oligodendroglioma.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus active surveillance.

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Patients with WHO Grade 2 IDH-mutant astrocytoma or oligodendroglioma who have residual or recurrent disease after at least one prior surgery for glioma, an ECOG performance score ≤1, and who are not in immediate need of radiotherapy or chemotherapy.
Intervention	Vorasidenib 40 mg once daily in addition to active surveillance.
Comparator	Active surveillance alone.
Outcomes	Radiographic progression-free survival; overall survival.
Clinical claim	Vorasidenib in conjunction with active surveillance is superior in terms of effectiveness and inferior in terms of safety, compared to placebo, as a proxy for active surveillance alone.

Source: Table 1.1, p2 of the submission; Section 2.7.2, p71 of the submission.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IDH, isocitrate dehydrogenase; WHO, World Health Organization.

2 Background

Registration status

2.1 Vorasidenib was registered on the Australian Register of Therapeutic Goods (ARTG) on 11 September 2023 for the treatment of Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 mutation or IDH2 mutation in adults and paediatric patients 12 years and older, who are not in need of immediate chemotherapy or radiotherapy following surgical intervention.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
VORASIDENIB					

Vorasidenib 10 mg tablet, 60	$[redacted] published price $[redacted] effective price	1	60	5	Voranigo
Vorasidenib 40 mg tablet, 30	$[redacted] published price $[redacted] effective price	1	30	5	Voranigo

Category / Program: ☒ GENERAL – General Schedule (Code GE)	
Prescriber type: ☒Medical Practitioners	
Restriction type: ☒Authority Required (Streamlined) [new code]	
+Prescribing rule level	***Administrative Advice:*** *No increase in the maximum quantity or number of units may be authorised.*
	Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
	Administrative Advice: Special Pricing Arrangements apply.
Episodicity: [blank]	
Severity: [blank]	
Condition: Adult-type IDH-mutant astrocytoma or oligodendroglioma	
Indication: Adult-type IDH-mutant astrocytoma or oligodendroglioma	
Restriction Summary [new1] / Treatment of Concept: [new1A]	
Treatment Phase: Initial treatment	
Clinical criteria:	
Patient must have a ~~The condition must be~~ World Health Organisation (WHO) Grade 2 *astrocytoma or oligodendroglioma*,	
AND	
Clinical criteria:	
The ~~condition~~ *patient* must have a *test of tumour tissue confirming the presence of a* susceptible isocitrate dehydrogenase-1 (IDH1) *R132H/C/G/S/L variant* or isocitrate dehydrogenase-2 (IDH2) *R172K/M/W/S/G variant*,	
AND	
Clinical criteria:	
Patient must have residual or recurrent disease after at least one prior surgery (biopsy, sub-total resection, or gross total resection) for this condition,	
~~**AND**~~	
Clinical criteria:	
~~The~~ Patient must not be in immediate need of radiotherapy and/or chemotherapy for this condition,	
AND	
Clinical criteria:	
The condition must not have been previously treated with *systemic* anticancer therapy *or radiotherapy*,	
AND	
Clinical criteria:	
Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 1 or less,	
~~**AND**~~	
~~**Clinical criteria:**~~	
~~Patient must not have developed disease progression while receiving treatment with this drug for this condition~~	
Prescriber instructions: *Confirm that evidence of the presence of a pathogenic variant of the IDH1 or IDH2 gene is documented/retained in the patient's medical records once only with the first PBS prescription.*	
Treatment Phase: Continuing treatment	
Clinical criteria:	

Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria
Patient must not have developed disease progression while receiving treatment with this drug for this condition.
Restriction Summary [new3] / Treatment of Concept: [new3A]
Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment - Grandfather arrangements
Clinical criteria:
Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [date of listing],
AND
Clinical criteria:
Patient must have a World Health Organisation (WHO) Grade 2 astrocytoma or oligodendroglioma
AND
Clinical criteria:
The ~~condition~~ *patient* must have a *test of tumour tissue confirming the presence of a* susceptible isocitrate dehydrogenase-1 (IDH1) *R132H/C/G/S/L variant* or isocitrate dehydrogenase-2 (IDH2) *R172K/M/W/S/G variant*
AND
Clinical criteria:
Patient must have had an Eastern Cooperative Oncology Group (ECOG) performance status score of 1 or less at the time of initiation of non-PBS subsidised treatment with this drug,
AND
Clinical criteria:
Patient must have had residual or recurrent disease after at least one prior surgery (biopsy, sub-total resection, or gross total resection) for this condition at the time of initiation of non-PBS-subsidised treatment with this drug for this condition,
AND
~~**Clinical criteria:**~~
~~The patient must not have been in immediate need of radiotherapy and/or chemotherapy for this condition at the time of initiation of non-PBS subsidised treatment with this drug,~~
~~**AND**~~
Clinical criteria:
The condition must not have been previously treated with *systemic* anticancer therapy *prior to initiation non-PBS subsidised treatment with this drug for this condition*
AND
Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition.
Prescriber instructions: *Confirm that evidence of the presence of a pathogenic variant of the IDH1 or IDH2 gene is documented/retained in the patient's medical records once only with the first PBS prescription.*
~~**Administrative advice:** Special Pricing Arrangements apply~~
Administrative advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
~~**Note:** ***Administrative advice:***~~ Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.

3.1 The submission proposed a special pricing arrangement, with a published dispensed price maximum quantity (DPMQ) price of $ and an effective DPMQ price of $ per

pack of 30 × 40 mg tablets. The same published and effective DPMQ was proposed per pack of 60 x 10 mg tablets.

3.2 The submission proposed an Authority Required (Streamlined) listing for initial and continuing treatment. This differs from the PBS restriction for dabrafenib for the treatment of paediatric glioma, which is an Authority Required (telephone/online) listing for initial and continuing treatment. The Commentary noted that an Authority Required (telephone/online) listing may be more appropriate given the risk of use outside of the proposed restriction. Additionally, it may be reasonable to require documentation of relevant tumour characteristics at the time of treatment initiation.

3.3 The proposed listing is broader than the TGA indication with respect to age, as the TGA indication limits treatment to patients aged 12 years and older. There is a lack of data regarding the effectiveness and safety of vorasidenib in paediatric patients (the youngest patient in the vorasidenib arm of the INDIGO trial was 21 years).

3.4 The proposed listing is narrower than the TGA indication, which does not limit treatment on the basis of previous anticancer therapy, performance status, the presence of residual or recurrent disease, or the occurrence of disease progression while receiving treatment.

3.5 The submission noted that the proposed restriction requires an ECOG score ≤1, whereas eligibility for the INDIGO trial was based on a Karnofsky Performance Status score ≥80% (Lansky Play-Performance Scale score for patients aged <16 years). The submission argued that the Karnofsky Performance Status and Lansky Play-Performance Scale are not routinely assessed in clinical practice, but acknowledged that an ECOG score of ≤1 would encompass a slightly broader population than a Karnofsky Performance Status/Lansky Play-Performance Scale score of ≥80. This may be reasonable given greater familiarity with ECOG scoring in clinical practice and given that the NCCN guidelines include vorasidenib as a recommended treatment for patients with patients a Karnofsky Performance Status score ≥60. However, the PBS restriction for dabrafenib for the treatment of paediatric low grade glioma is based on Karnofsky or Lansky performance scores rather than an ECOG score.

3.6 The submission noted that the proposed restriction does not specify a duration of time since surgery, whereas the INDIGO trial enrolled patients whose most recent surgery was at least one year (and not more than 5 years) prior to randomisation. The submission argued that the impact of surgery on overall health, aggressiveness of disease and tumour growth rate can be determined by imaging and clinical assessment within the 12 months following surgery; and that limiting access during the initial 12 months following surgery would limit access to vorasidenib for patients with residual disease who may be ideal candidates for treatment, and patients with recurrent disease following complete resection. The Commentary noted that while it may be reasonable to allow patients to initiate treatment with vorasidenib within 12 months of surgery, early initiation of vorasidenib may impact the ability to gauge the underlying rate of tumour growth. As a result, some patients with aggressive tumours may receive treatment with vorasidenib rather than

radiotherapy/chemotherapy, and some patients with slow growing tumours who would otherwise have been observed for years may receive upfront treatment with vorasidenib. In general, the optimal time to initiate therapy with vorasidenib is unclear, and will likely require individualisation based on the unique underlying risk profile and patient preferences.

3.7 The submission argued that there is no clinical rationale to exclude patients who had their last surgery more than 5 years ago from accessing vorasidenib, given that these patients would have likely been treated earlier if vorasidenib was available on the PBS. The Pre-Sub-Committee response (PSCR) noted that the sponsor considered that it would be reasonable for the restriction to avoid specifying a fixed time window for initiation of vorasidenib and argued that subgroup analyses indicate that treatment outcomes did not vary meaningfully with earlier or later initiation.

3.8 The proposed restriction requires patients to have residual or recurrent disease. It is unclear how 'residual disease' will be interpreted in clinical practice, given that gross total resection of Grade 2 IDH-mutant gliomas is typically not curative (and therefore all patients could be considered to have residual disease). However, the proposed criterion is consistent with the NCCN guidelines, which recommend observation for patients who do not have evidence of residual disease after surgery.

3.9 The proposed restrictions require that patients not be in need of immediate treatment with radiotherapy/chemotherapy. While this was also an eligibility requirement for the INDIGO trial, there does not appear to be accepted criteria to determine whether a patient should proceed to immediate radiotherapy/chemotherapy. The RTOG 9802 study established that the addition of chemotherapy to radiotherapy was associated with a substantial survival benefit among patients with low grade glioma with high-risk features. A large proportion of patients in the INDIGO trial had subtotal resection or biopsy only and would likely be considered high risk based on the definition used in the RTOG 9802 study. The PSCR noted that the INDIGO trial protocol defined high risk features as including brainstem involvement, clinically relevant functional or neurocognitive deficits due to the tumour or uncontrolled seizures. The Sub-Committees (ESC and DUSC) noted that this restriction was consistent with the INDIGO trial, TGA indication and NCCN guidelines.

3.10 The Commentary considered there is a risk of use outside the proposed restriction among patients with non-Grade 2 disease; patients in immediate need of radiotherapy and/or chemotherapy; patients with previous anticancer therapy use (e.g., patients with recurrent or progressive disease after radiotherapy and chemotherapy); and patients with an ECOG >1. The Sub-Committees considered that clinicians are unlikely to delay initiation of radiotherapy/chemotherapy where patients are symptomatic or have impending symptoms as vorasidenib does not provide a reduction in tumour size (based on tumour growth rate and overall response rate, see also paragraph 6.24). In addition, the Sub-Committees considered that clinicians are unlikely to use vorasidenib in patients with high risk disease (including Grade 3 or 4) or with progression on radiotherapy/chemotherapy as there is no

evidence to suggest it would be effective. The PBAC noted that there may be trials in other treatment settings in the future (e.g. after prior chemotherapy), however the appropriate clinical place based on the INDIGO trial is clear and effectiveness has not been demonstrated for use outside the proposed population.

3.11 The proposed initial and continuing treatment listings do not preclude the use of vorasidenib in combination with other treatments. Concomitant treatment with other anticancer therapies was not permitted in the INDIGO trial.

3.12 The proposed initial and continuing treatment restrictions state that patients must not have developed disease progression while receiving treatment with vorasidenib for this condition. A definition of disease progression was not included in the proposed restriction. The PBAC considered it is unlikely that patients who develop disease progression will discontinue treatment with vorasidenib if there is a possible/perceived benefit associated with ongoing IDH inhibitor therapy. In the INDIGO trial, treatment was continued until centrally confirmed disease progression. The PBAC noted that the cost-effectiveness of ongoing treatment beyond progression was uncertain and could not be assessed.

3.13 The submission requested grandfather provisions for patients enrolled in the sponsor's compassionate access program and estimated that < 500 patients would require grandfathered treatment.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Gliomas are tumours that originate from glial cells in the central nervous system and are the most common form of primary malignant brain tumour. Astrocytomas and oligodendrogliomas are types of IDH-mutant diffuse glioma. The Australian incidence of IDH-mutant astrocytomas in 2020 was 1.0 cases per 100,000 persons (0.8 cases per 100,000 females and 1.1 cases per 100,000 males); and the incidence of IDH-mutant oligodendrogliomas was 0.4 cases per 100,000 persons (0.4 cases per 100,000 in females and males; AIHW, 2025).

4.2 The presence of key molecular markers (mutations in IDH1 or IDH2 and the codeletion of 1p/19q) is used to categorise diffuse gliomas into 3 main groups: IDH-mutant astrocytoma, IDH-mutant and 1p/19q-codeleted oligodendroglioma and IDH-wildtype glioblastoma. In general, the presence of an IDH1 or IDH2 enzyme mutation is associated with a more favourable prognosis compared to IDH-wildtype tumours.

4.3 Symptoms of IDH-mutant glioma vary according to the tumour size, location, and degree of infiltration. Common symptoms include headaches, nausea/vomiting, seizures, drowsiness, visual disturbance, speech/language problems, sensory loss, motor deficits and changes in cognitive and/or functional ability. Impairment of coordination, motor skills, balance and increased seizure activity may lead to loss of independence and increased reliance on carers and family members.

4.4 Initial treatment typically involves maximal safe tumour resection, which also allows for tissue diagnosis and tumour grading. As total resection may not be a feasible option, patients may undergo subtotal resection or biopsy of the tumour only. Following surgery, management of patients with diffuse gliomas is individualised based on the underlying histologic and molecular characteristics of the tumour, the extent of surgical resection, and other patient factors.

4.5 Patients considered to be at high risk of progression (i.e., patients with Grade 3 and Grade 4 IDH-mutant glioma and patients with high-risk Grade 2 IDH-mutant glioma) typically receive treatment with radiotherapy and chemotherapy following surgery. Due to the relatively slow progression of the disease, and side effects associated with radiotherapy/chemotherapy treatment, patients considered to be at lower risk of disease progression may delay the initiation of radiotherapy/chemotherapy until signs of disease progression become apparent.

4.6 The submission positioned vorasidenib in combination with active surveillance as an alternative to active surveillance alone for patients with residual or recurrent disease who are not in immediate need of radiotherapy/chemotherapy. The NCCN guidelines do not provide specific recommendations regarding the selection of patients with Grade 2 IDH-mutant glioma who are preferred/not preferred for radiotherapy and chemotherapy, but note that factors associated with a higher risk of progression include age >40 years and/or subtotal tumour resection. The guidelines state that other prognostic factors such as tumour size, presence of neurologic deficits, and the loss of CDKN2A homozygous deletion may also be used to guide treatment choice. The guidelines note that treatment decisions should be based on multidisciplinary input once pathology is available.

4.7 Vorasidenib is also included as a preferred regimen in the NCCN guidelines for the treatment of recurrent or progressive disease after radiotherapy and chemotherapy in patients with WHO Grade 2 disease with a Karnofsky performance score ≥60; and as a preferred regimen for patients with recurrent or progressive WHO Grade 3 disease with a Karnofsky Performance Score ≥60. Vorasidenib is listed as 'useful in certain circumstances' for the adjuvant treatment of WHO Grade 2 or 3 disease for patients with a Karnofsky performance score <60.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated active surveillance as the main comparator. The main argument provided in support of this nomination was that active surveillance is the treatment strategy most likely to be replaced in the target population of patients with WHO Grade 2 IDH-mutant glioma who have residual or recurrent disease after surgery and are not in immediate need of treatment with radiotherapy/chemotherapy. The Sub-Committees agreed with the Commentary that active surveillance is an appropriate comparator. The Sub-Committees agreed with the PSCR that a

comparison with radiotherapy/chemotherapy was not informative as vorasidenib is indicated for a population who would not be treated with radiotherapy/chemotherapy.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (107), health care professionals (13) and organisations (6) via the Consumer Comments facility on the PBS website.

6.3 The comments from health professionals described the current treatment options for IDH mutant gliomas as surgery, radiotherapy and chemotherapy. These treatments can have immediate impacts on independence (e.g. ability to drive), and result in brain fogginess, nausea/vomiting, constipation and increased infection risk; as well as longer term impacts such as memory loss, reduced cognition (ability to think, problem solve etc), fatigue, infertility, and an inability to work. The comments noted that new treatments in this space have been very limited for a long time and vorasidenib has the potential to improve outcomes for patients. The comments stated that vorasidenib may delay the conversion of tumours to high grade, aggressive tumours, which will significantly extend survival, though survival outcomes will not be known for some years. The comments noted that the primary advantage of vorasidenib will be delaying toxic adjuvant therapies, including chemotherapy and high-dose radiation, in a group of patients who are generally healthy, active members of society. The comments noted that vorasidenib provides a more palatable option with less short-term and long-term impacts on patient wellbeing. Comments from one health professional indicated that given these benefits there may be patients who should be having radiotherapy and chemotherapy, but would seek to have lower toxicity vorasidenib, despite this not being an evidence-based approach to use of the drug. These comments suggested that eligibility criteria should ensure that the appropriate setting for vorasidenib is considered.

6.4 The comments from individuals also noted the side effects from surgery, radiation and chemotherapy can include long-term effects that significantly affect memory, cognition, language, energy levels, and emotional wellbeing and the commencement of seizures. Comments from individuals noted that vorasidenib offers a chance to delay radiotherapy or further surgery and so preserve cognitive function and independence for as long as possible. Comments described the potential side effects

of vorasidenib as being manageable. Comments described the quality of life impact of IDH gliomas on family, career, and friends. Input also outlined what impact vorasidenib has had since commencing treatment, offering hope, prolonging life and allowing for a better quality of life. The comments described the current non-PBS listed price of vorasidenib as extremely expensive, with inequality in access deeply concerning, especially considering it is the first targeted therapy specifically developed for low-grade gliomas with IDH mutation. Consumers also noted the high costs of regular MRIs to manage their disease. Those accessing vorasidenib through compassionate means expressed concern that they will be unable to afford to continue treatment if it is not listed on the PBS.

6.5 Consumer groups (Rare Cancers Australia, Cure Brain Cancer Foundation, Brain Tumour Alliance Australia and the Australian Brain Tumour Collaborative) were strongly supportive of the submission for vorasidenib. The comments from consumer groups described the high unmet need for effective treatments for patients with glioma, and the impact of glioma and treatments (surgery, chemotherapy and radiotherapy) on typically relatively young adult patients, and on their families. They also described the potential benefit of vorasidenib in terms of offering patients more time and a better quality of life by slowing disease progression and delaying the need for radiotherapy. The comments noted concerns regarding equity of access to vorasidenib treatment without PBS subsidisation.

6.6 Comments from the medical organisation Cooperative Trial Group for Neuro-Oncology (COGNO) echoed those from consumer groups, and also noted the key trial evidence from the INDIGO trial and ongoing research including a study assessing vorasidenib as maintenance therapy in patients with high risk grade 2 or 3 astrocytoma following chemotherapy.

6.7 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the vorasidenib submission, categorising it as one of the therapies of "highest priority for PBS listing", noting the clinical need, on the basis of the INDIGO trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for vorasidenib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[1], based on a comparison with active surveillance alone.

Clinical trials

6.8 The submission was based on one head-to-head randomised trial comparing vorasidenib to placebo in patients with Grade 2 IDH-mutant astrocytoma or oligodendroglioma (INDIGO).

[1] Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017]

6.9 Details of the INDIGO trial are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/publication title	Publication citation
INDIGO (NCT04164901)	A Phase 3, multicentre, randomised, double-blind, placebo-controlled study of AG-881 in patients with residual or recurrent Grade 2 glioma with an IDH1 or IDH2 mutation. Mellinghoff IK, van den Bent MJ, Blumenthal DT, Touat M, et al. Vorasidenib in IDH1-or IDH2-mutant low-grade glioma.	Primary clinical study report, 29 September 2023 (data cutoff: 6 September 2022). Clinical study report addendum 2, 2 December 2024 (data cutoff: 7 March 2023). Clinical study report Japan addendum, 14 March 2024 (data cutoff: 18 September 2024). *New England Journal of Medicine* 2023; 389(7): 589-601.

Source: Table 2.4, pp21-22 of the submission.
Citations relating to conference abstracts omitted.

6.10 The key features of the INDIGO trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Vorasidenib versus placebo						
INDIGO	331	Phase 3, randomised, double-blind, placebo-controlled trial; median follow-up of 17.3 months.	Low	- Age ≥12 years - Grade 2 oligodendroglioma or astrocytoma (WHO 2016 criteria) - At least one prior surgery for glioma (biopsy, subtotal resection, gross total resection) - Most recent surgery at least 1 year and no more than 5 years prior to randomisation - Confirmed IDH1 or IDH2 gene mutation and available 1p19q status - MRI-evaluable, measurable, non-enhancing disease - No other prior anticancer therapy (including chemotherapy and radiotherapy) - Not in need of immediate chemotherapy or radiotherapy. - Karnofsky performance score or Lansky Play-Performance Scale score ≥80% - Expected survival of ≥12 months.	- Radiographic PFS by blinded independent review (primary) - Time to next intervention (key secondary) - Tumour growth rate - Objective response rate - Time to response - Overall survival - HRQoL (FACT-Brain, EQ-5D-5L, PGI) - Adverse events	- Radiographic PFS by blinded independent review - Adverse events - EQ-5D-5L

Source: Table 2.13, p34; Table 2.16, p36; Table 2.17, pp27-28 of the submission; Section 4.2, pp55-56; Section 4.3, pp57-58 of the INDIGO trial protocol (Amendment 3, Version 4).
Abbreviations: 5L, 5-level; FACT, Functional Assessment of Cancer Therapy; HRQoL, health-related quality of life; IDH, isocitrate dehydrogenase; MRI, magnetic resonance imaging; PGI, Patient Global Impression; PFS, progression-free survival; WHO, World Health Organization.

6.11 The clinical evidence for vorasidenib was derived from the INDIGO trial, an ongoing, Phase 3, multicentre, randomised, double-blind trial of vorasidenib versus placebo conducted at 77 study centres across 10 countries. Three analyses were planned for the INDIGO trial, including an initial interim analysis for futility, a second interim analysis for superiority, and a final analysis. Patients in the placebo arm with radiographic disease progression (confirmed by the blinded independent review committee) could cross over to receive treatment with vorasidenib.

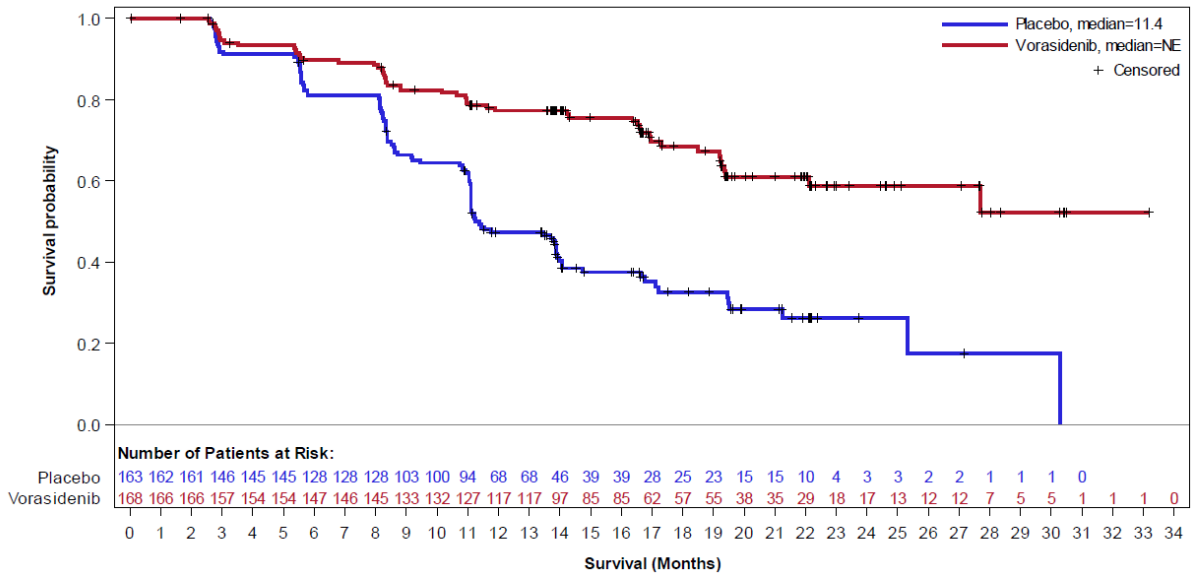
6.12 The trial was unblinded after the second interim analysis based on the recommendation of the independent data and safety monitoring committee due to early demonstration of efficacy. At the time the trial was unblinded (approximately 6 months after the second interim analysis), patients in the placebo arm, including patients who had not yet experienced disease progression, were able to cross over to receive vorasidenib treatment.

6.13 The submission included clinical study reports corresponding to the second interim analysis (September 2022 data cut) and the end of blinded treatment (March 2023 data cut; referred to as extended follow-up herein). The extended follow-up analysis included approximately 6 months of additional blinded follow-up following the second interim analysis.

Comparative effectiveness

6.14 Figure 1 and Table 4 present the results for progression-free survival (PFS) assessed by the blinded independent review committee based on extended follow-up.

Figure 1: Kaplan-Meier plot of progression-free survival assessed by BIRC based on extended follow-up



Source: Figure 2.5, p43 of the submission.
Abbreviations: BIRC, blinded independent review committee; NE, not estimable.

Table 4: PFS assessed by BIRC based on extended follow-up

	Vorasidenib N=168	Placebo N=163
Median duration of follow-up, months (95% CI)	17.7 (16.7, 19.4)	16.7 (16.4, 19.9)
Participants with event, n (%) - Progressive disease, n (%) - Death, n (%)	54 (32.1) 54 (32.1) 0	104 (63.8) 104 (63.8) 0
Number censored, n (%) - Start of subsequent anticancer therapy - No adequate baseline assessment - Withdrawal of consent - Ongoing without an event	114 (67.9) 4 (2.4) 1 (0.6) 5 (3.0) 104 (61.9)	59 (36.2) 2 (1.2) 0 4 (2.5) 53 (32.5)
Median PFS, months (95% CI)	NE (22.1, NE)	11.4 (11.1, 13.9)
Hazard ratio (95% CI)	0.35 (0.25, 0.49)	
KM estimate of proportion remaining event-free - 3 months, % (95% CI) - 6 months, % (95% CI) - 12 months, % (95% CI) - 18 months, % (95% CI) - 24 months, % (95% CI) - 30 months, % (95% CI)	 94.6 (89.8, 97.1) 89.7 (84.0, 93.5) 77.3 (70.1, 83.0) 68.5 (59.9, 75.7) 58.8 (48.4, 67.8) 52.2 (36.6, 65.8)	 91.8 (86.3, 95.2) 81.1 (74.1, 86.4) 47.3 (39.3, 54.9) 32.6 (24.6, 41.0) 26.2 (17.9, 35.3) 17.5 (5.7, 34.6)

Source: Table 2.19, p44 of the submission.

Abbreviations: BIRC, blinded independent review committee; CI, confidence interval; KM, Kaplan-Meier; NE, not estimable; PFS, progression-free survival.

6.15 Based on a median follow-up of 17.7 months for patients in the vorasidenib arm and 16.7 months in the placebo arm, treatment with vorasidenib was associated with a statistically significant improvement in PFS compared to placebo (hazard ratio: 0.35; 95% CI: 0.25, 0.49). All events were disease progression events. There were stepwise decreases in the Kaplan-Meier plots for the vorasidenib and placebo arms, reflecting the timing of scheduled MRI scans in the trial, which were undertaken every 12 weeks during the first 34 months.

6.16 Table 5 presents the results for the time to next intervention based on extended follow-up.

Table 5: Time to next intervention based on extended follow-up

	Vorasidenib N=168	Placebo N=163
Median duration of follow-up, months (95% CI)	17.7 (16.7, 19.4)	16.7 (16.4, 19.9)
Participants with event, n (%) - First subsequent anticancer therapy (except crossover) - Crossover to vorasidenib - Death	28 (16.7) 28 (16.7) 0 (0) 0 (0)	78 (47.9) 8 (4.9) 70 (42.9) 0 (0)
Number censored, n (%) - Ongoing without an event - Withdrawal of consent	140 (83.3) 135 (80.4) 5 (3.0)	85 (52.1) 81 (49.7) 4 (2.5)
Median TTNI, months (95% CI)	NE (NE, NE)	20.1 (17.5, 27.1)
Hazard ratio (95% CI)	0.25 (0.16, 0.40)	
KM estimate of proportion remaining event-free - 6 months, % (95% CI) - 12 months, % (95% CI) - 18 months, % (95% CI) - 24 months, % (95% CI) - 30 months, % (95% CI)	 97.6 (93.7, 99.1) 90.3 (84.6, 93.9) 86.8 (80.5, 91.2) 80.3 (71.6, 86.6) 70.7 (53.0, 82.7)	 97.5 (93.5, 99.1) 74.9 (67.3, 80.9) 54.7 (46.1, 62.5) 41.4 (31.0, 51.5) 34.5 (20.1, 49.3)

Source: Table 2.21, p49 of the submission.
Abbreviations: CI, confidence interval; KM, Kaplan-Meier; NE, not estimable; TTNI, time to next intervention.

6.17 Based on a median follow-up of 17.7 months for patients in the vorasidenib arm and 16.7 months in the placebo arm, treatment with vorasidenib was associated with a statistically significant improvement in the time to next intervention compared to placebo (hazard ratio: 0.25; 95% CI: 0.16, 0.40). The availability of vorasidenib as a crossover treatment for patients in the placebo arm is likely to have influenced the time to next treatment results for the placebo arm.

6.18 Based on extended follow-up, the median duration of follow-up for overall survival (OS) was similar for the vorasidenib (20.2 months) and placebo arms (19.8 months). OS data for the INDIGO trial were immature. One patient (0.6%) in the vorasidenib arm had died due to disease progression, and no patients in the placebo arm had died at the time of extended follow-up analysis, when treatment was unblinded and patients on placebo were crossed over to vorasidenib.

6.19 The PSCR argued that the absence of comparative OS data should not be interpreted as evidence of lack of benefit, but reflects: 1) the biphasic nature of glioma which typically follows a slow then aggressive disease course with median OS 11.4 years, and 2) the ethical considerations of the trial due to the strength of the PFS evidence. The PSCR and pre-PBAC response also noted evidence from trials in similar tumour types; the Radiation Therapy Oncology Group (RTOG) 9802 trial in patients with high risk

grade 2 glioma[2] and Han et al (2014) in patients with glioblastoma[3], which demonstrated a delay in progression that translated to an improvement in OS. The Sub-Committees considered it is unclear whether the improvements in radiographic progression-free survival associated with vorasidenib treatment will translate into improvements in OS, and noted further analyses will not be informative due to the large number of patients who crossed over to receive vorasidenib. The Sub-Committees considered that despite the trial's inability to demonstrate an effect on OS, the PFS benefit shown was substantial and likely to be highly clinically relevant for patients.

6.20 Table 6 presents the results for the tumour growth rate assessed by the blinded independent review committee based on extended follow-up.

Table 6: Tumour growth rate assessed by BIRC based on extended follow-up

	Vorasidenib N=167	Placebo N=161
Median duration of follow-up, months (95% CI)	17.7 (16.7, 19.4)	16.7 (16.4, 19.9)
Mean percent change for every 6 months, % (95% CI)	-1.3 (-3.2, 0.7)	14.4 (12.0, 16.8)
Between group difference, % (95% CI)	15.9 (12.6, 19.3)	

Source: Table 14.2.3.1.1.d, p42 of the March 2023 INDIGO clinical study report tables and figures document provided in the submission.
Abbreviations: BIRC, blinded independent review committee; CI, confidence interval.

6.21 Treatment with vorasidenib was associated with a statistically significant reduction in the mean percent change in the tumour growth rate compared to placebo (between group difference: 15.9%; 95% CI: 12.6, 19.3).

6.22 Table 7 presents the results for the best overall response assessed by the blinded independent review committee based on extended follow-up.

[2] Buckner J.C., Shaw E.G., et al. Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma. N Engl J Med. 2016;374(14):1344-55 https://doi.org/10.1056/nejmoa1500925

[3] Han, K., Ren M., et al. Progression-free survival as a surrogate endpoint for overall survival in glioblastoma: a literature-based meta-analysis from 91 trials. Neuro Oncol. 2014;16(5):696-706 https://doi.org/10.1093/neuonc/not236

Table 7: Best overall response assessed by BIRC based on extended follow-up

	Vorasidenib N=168	Placebo N=163
Best overall response, n (%)		
- Complete response	0	0
- Partial response	2 (1.2)	0
- Minor response	18 (10.7)	4 (2.5)
- Stable disease	137 (81.5)	144 (88.3)
- Progressive disease	10 (6.0)	14 (8.6)
- Not evaluable	1 (0.6)	1 (0.6)
Objective response rate, n (%) [a]	20 (11.9)	4 (2.5)
- Odds ratio (95%) CI	5.45 (1.77, 16.78)	
Complete or partial response, n (%)	2 (1.2)	0
- Odds ratio (95%) CI	NE (0.28, NE)	

Source: Table 14.2.4.1, p47 of the March 2023 INDIGO clinical study report tables and figures document provided in the submission.
Abbreviations: BIRC, blinded independent review committee; CI, confidence interval; NE, not estimable.
[a] The proportion of patients achieving a best response of compete response, partial response or minor response.

6.23 A higher proportion of patients treated with vorasidenib achieved an objective response compared to placebo (11.9% versus 2.5%; odds ratio: 5.45; 95% CI: 1.77, 16.78). There were no complete responses and only 2 (1.2%) partial responses in the vorasidenib arm.

6.24 The Commentary noted the objective response rate and the impact of vorasidenib on the tumour growth rate was modest, suggesting a more tumour-static mode of action. The Sub-Committees agreed with the Commentary that these data suggest that vorasidenib does not provide a reduction in tumour size.

6.25 Quality of life in the INDIGO trial was assessed using the Functional Assessment of Cancer Therapy (FACT)-Brain (total and subscale scores), the EQ-5D-5L, and the Patient Global Impression questionnaire. At baseline, FACT-Brain total score and subscale scores were similar between treatment arms. No improvements in the FACT-Brain total score, and physical well-being and brain cancer subscale scores were observed favouring either arm at any time point up to and including Cycle 13. At later time points, some subscales (total score, functional well-being, trial outcome index) showed improvement in the vorasidenib arm; however, the results were sporadic and the small number of assessments at these time points does not allow for meaningful interpretation.

6.26 Results for the change in EQ-5D-5L index and visual analogue scale scores were not presented in the submission. The clinical study report stated that at baseline, the proportions of patients reporting no problems across mobility, self-care, usual activity, pain/discomfort, and anxiety and depression were consistent between arms. In both arms, no respondents reported experiencing severe or extreme baseline problems with selfcare activities. The proportions of patients reporting no problems, some problems, and extreme problems across the EQ-5D-5L questionnaire were consistent between arms on treatment.

6.27 The PSCR stated that it is highly likely that quality of life (QoL) will reduce post progression due to increasing morbidity and impact of subsequent interventions. Subsequent interventions (after progression) including RT/CT are associated with

toxicity and lead to loss of daily functions. The Sub-Committees noted that the duration of the trial was insufficient to capture the impact of delayed progression on QoL, and agreed with the PSCR that there is potential for significant improvements in QoL where there is a delay in symptomatic progression.

Comparative harms

6.28 Table 8 presents a summary of adverse events among patients in the INDIGO trial, based on extended follow-up.

Table 8: Summary of key adverse events in the INDIGO trial based on extended follow-up

	Vorasidenib N=167	Placebo N=163
Any AE, n (%)	165 (98.8)	155 (95.1)
Grade ≥3 AE, n (%)	45 (26.9)	26 (16.0)
Treatment-related AE, n (%)	115 (68.9)	101 (62.0)
- Grade ≥3 treatment-related AE, n (%)	23 (13.8)	9 (5.5)
Serious AE, n (%)	20 (12.0)	10 (6.1)
- Treatment-related serious AE, n (%)	3 (1.8)	0
AE leading to treatment discontinuation, n (%)	7 (4.2)	2 (1.2)
AE leading to dose reduction, n (%)	19 (11.4)	7 (4.3)
AE leading to treatment interruption, n (%)	55 (32.9)	41 (25.2)
AE leading to death, n (%)	0	0
Any adverse event of special interest, n (%)	35 (21.0)	7 (4.3)
AE associated with COVID-19, n (%)	61 (36.5)	57 (35.0)
Any AE occurring in ≥10%, n (%)		
- ALT increased	72 (43.1)	29 (17.8)
- Fatigue	61 (36.5)	57 (35.0)
- COVID-19	58 (34.7)	54 (33.1)
- AST increased	55 (32.9)	15 (9.2)
- Headache	48 (28.7)	46 (28.2)
- Diarrhoea	45 (26.9)	31 (19.0)
- Nausea	40 (24.0)	42 (25.8)
- GGT increased	31 (18.6)	8 (4.9)
- Dizziness	30 (18.0)	29 (17.8)
- Seizure	26 (15.6)	20 (12.3)
- Constipation	22 (13.2)	20 (12.3)
- Insomnia	18 (10.8)	15 (9.2)
- Paraesthesia	18 (10.8)	14 (8.6)
- Arthralgia	17 (10.2)	19 (11.7)
- Vomiting	16 (9.6)	19 (11.7)
- Abdominal pain	15 (9.0)	17 (10.4)
- Anxiety	13 (7.8)	17 (10.4)
Grade ≥3 AE occurring in ≥2%, n (%)		
- ALT increased	17 (10.2)	2 (1.2)
- AST increased	8 (4.8)	0
- Seizure	7 (4.2)	5 (3.1)
- GGT increased	5 (3.0)	2 (1.2)

Source: Table 2.27, p56; Table 2.28, pp58-59 of the submission.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase; NE, not estimable.

6.29 Almost all patients in each treatment arm of the INDIGO trial experienced at least one adverse event. Treatment-related adverse events were reported for 115 patients

(68.9%) in the vorasidenib arm and 101 patients (62.0%) in the placebo arm. The most commonly occurring adverse events in the vorasidenib arm were increased alanine aminotransferase (43.1% versus 17.8% in the placebo arm), fatigue (36.5% versus 35.0%), COVID-19 (34.7% versus 33.1%), increased aspartate aminotransferase (32.9% versus 9.2%), headache (28.7% versus 28.2%) and diarrhoea (26.9% versus 19.0%).

6.30 Grade ≥3 adverse events occurred in 26.9% of patients in the vorasidenib arm and 16.0% of patients in the placebo arm. The most commonly occurring Grade ≥3 adverse events in the vorasidenib arm were increased alanine aminotransferase (10.2% versus 1.2% in the placebo arm), increased aspartate aminotransferase (4.8% versus 0%), seizure (4.2% versus 3.1%) and increased gamma-glutamyl transferase (3.0% versus 1.2%). There were no reported fatal adverse events.

Benefits/harms

6.31 On the basis of direct evidence presented by the submission, for every 100 patients treated with vorasidenib in comparison with placebo:

- Approximately 33 additional patients will remain progression-free after 24 months.
- Approximately 39 additional patients will not have received a subsequent intervention after 24 months.
- It was not possible to assess any differences in survival from the evidence presented in the submission.
- Approximately 6 additional patients would experience a serious adverse event that is life-threatening or required hospitalisation.

Clinical claim

6.32 The submission described vorasidenib as superior in terms of effectiveness and inferior in terms of safety, compared to placebo.

6.33 The Sub-Committees agreed with the Commentary that the therapeutic conclusion presented in the submission was adequately supported by the evidence presented in the submission. However, the following issues were noted:

- There was effectively no OS data for the INDIGO trial (1 death only) and further analyses will not be informative.
- The Sub-Committees noted that the magnitude of benefit for PFS over a longer time horizon was uncertain given the short follow up of the comparative trial data (~17 months).
- No differences in QoL outcomes between vorasidenib and placebo were demonstrated, however the duration of trial follow-up may be too short to capture differences due to symptomatic progression.
- The optimal timing of initiation of vorasidenib and the optimal duration of therapy for vorasidenib are unclear.
- There is a lack of long-term safety data for vorasidenib. While treatment with vorasidenib appeared to be well tolerated in the INDIGO trial, the impacts of long-

term exposure to IDH inhibitor therapy are unclear. The Sub-Committees agreed long-term safety is uncertain, particularly as some patients may be treated with vorasidenib for an extended time. The Sub-Committees noted that there were no major safety concerns identified in the trial and Grade 3 AEs were predominantly liver enzyme abnormalities that may not have clinical relevance.

6.34 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.35 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.36 The submission presented a modelled economic evaluation comparing vorasidenib with placebo (as a proxy for active surveillance), for the treatment of patients with Grade 2 IDH-mutant astrocytoma or oligodendroglioma. The economic evaluation was based on the results of the INDIGO trial, with additional modelled data. The economic evaluation was presented as a stepped cost-effectiveness/cost-utility analysis.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Vorasidenib versus active surveillance
Time horizon	40 years in the base case versus a median follow-up of 17.3 months in the INDIGO trial.
Outcomes	Quality-adjusted life years; life years; progression-free life years.
Methods used to generate results	Markov cohort model.
Health states	Progression-free, progressed disease, dead.
Cycle length	One month
Transition probabilities	Transition probabilities from the progression-free health state to the progressed disease state were based on PFS results for the vorasidenib and placebo arms of the INDIGO trial, with extrapolation using a lognormal function estimated independently for each treatment arm. Transition probabilities from progression-free to dead were based on Australian life tables. Transitions from the progressed disease state to dead were based on an analysis of post-progression survival among patients in an Australian brain tumour registry (BRAIN), extrapolated using a Gompertz function and Australian life tables.
Health related quality of life	Progression-free health state utility: 0.93; based on a *post hoc* analysis of the INDIGO trial. Progressed disease health state utility: time-varying utility starting at 0.93 and reducing by 0.00919 per cycle, reaching 0 over 8.43 years; based on assumption.

Component	Summary
Costs	Initial treatment costs: Vorasidenib cost based on the proposed effective DPMQ, with the duration of PFS in the model used as a proxy for treatment duration. Active surveillance (placebo) was assumed to have nil cost. Adverse event costs: Grade ≥3 adverse events occurring in ≥2% of patients in the INDIGO trial were included. Costs of management of increased liver enzymes (ALT, AST and GGT) were based on PBS prednisone DPMQ. Costs of seizure management were based on 2021/22 NHCDC data for AR-DRG B76 (seizures). Disease management costs: Liver function test monitoring costs were based on MBS 66512 (specified pathology tests), MBS 23 (general practitioner visit) for initial test and MBS 91790 (telehealth visit) for subsequent tests. MRI costs associated with tumour assessment were based on MBS 63001 (MRI brain), with an MRI scan assumed every 4.5 months for the first 5 years, and every 6 months thereafter. Additional management costs (rehabilitative and support health care services) were based on assumption. Subsequent treatment costs: The distribution of subsequent treatment interventions was based on Australian registry data (BRAIN); assuming 100% of patients experiencing disease progression receive subsequent treatment. Chemotherapy treatment regimen costs were based on the eviQ protocol for temozolomide and the published PBS temozolomide DPMQ. Radiotherapy treatment regimen costs were based on the eviQ protocol with the cost based on 2021/22 NHCDC data. Brain surgery costs were based on 2021/22 NHCDC data for AR-DRG B66 (nervous system neoplastic disorders). Seizure management costs: The frequency of generalised seizure events among patients who are progression-free and patients with progressed disease was based on the INDIGO trial. The proportions of seizures requiring emergency department visits (100%) and hospitalisation (90%), and the proportion of patients brought to hospital by ambulance (90%) were based on assumption. The cost of a hospital admission was based on 2021/2022 NHCDC data for AR DRG B76 (seizures). The cost of an emergency department visit was based on 2021/2022 NHCDC data (emergency department visit for seizure). The cost of an ambulance was based on ambulance fees published by the Victoria health service. End of life costs: Based on the end of life cost included in the July 2022 trastuzumab deruxtecan Public Summary Document (derived from Reeve et al., 2018).
Discount rate	5.0% applied to costs and outcomes
Software package	TreeAge Pro and Microsoft Excel

Source: Table 3.1, p72 of the submission; Section 3 economic model Excel workbook; Section 3 economic model TreeAge Pro file.
Abbreviations: BRAIN, Brain tumour Registry Australia INnovation and translation; PFS, progression free survival; QALY, quality-adjusted life year.

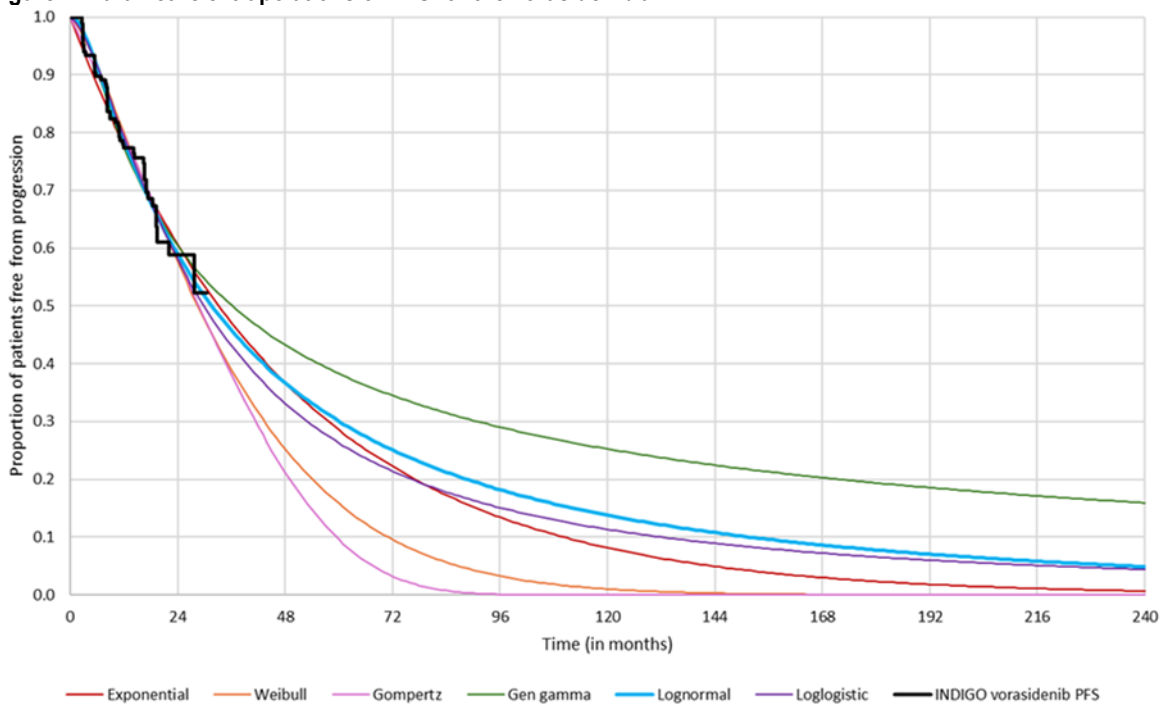
6.37 The economic model was a Markov model with 3 health states (progression-free, progressed disease and dead). The submission claimed that a simple model structure was adopted to avoid introducing additional uncertainty. The assumed model structure may not adequately reflect the natural history of the disease, which is typically associated with slow tumour growth for a number of years prior to a more rapidly progressing phase. The model does not explicitly model the impact of subsequent treatments such as surgery and radiotherapy/chemotherapy, which may be associated with periods of disease remission and symptom reduction. The PSCR acknowledged these limitations but argued that introducing additional health states would have increased the structural complexity and uncertainty without necessarily improving the precision of the incremental estimates. The Sub-Committees considered this resulted in some uncertainty in the modelled costs and outcomes, but noted that there are no clear sources to inform assumptions regarding the timing of

subsequent treatments and their impacts on survival outcomes and quality of life. The Sub-Committees considered that the model structure adopted was reasonable, but that the model should account for the costs and utility impacts of subsequent treatments within the existing model structure, without the need for additional health states.

6.38 The probability of transitioning from the progression-free to the progressed disease state was based on extrapolated results for the vorasidenib and placebo (as a proxy for active surveillance) arms of the INDIGO trial. Parametric functions were fitted to the PFS results reported at the extended follow-up data cut. The submission stated that lognormal functions were selected to extrapolate the PFS data in the base case on the basis of goodness of fit and visual inspection.

6.39 Figure 2 presents the parametric extrapolations of PFS for the vorasidenib arm.

Figure 2: Parametric extrapolations of PFS for the vorasidenib arm



Source: Figure 3.9, p87 of the submission.
Abbreviations: Gen, generalised; PFS, progression-free survival.
Note: The presented figure is based on a 20-year time frame, compared to the model time horizon of 40 years.

6.40 All of the tested functions appeared to fit the Kaplan-Meier data for the vorasidenib arm relatively well, but produced large differences in projected PFS. The longer-term PFS trajectory among patients treated with vorasidenib is unknown. The Commentary considered that given the impact of the selected extrapolation on the ICER, a more conservative option such as a Gompertz or Weibull function may be more appropriate. The Sub-Committees noted that the extrapolation of PFS was a major source of uncertainty in the modelled outcomes, and noted that the difference in PFS directly translated into a difference in OS. The PSCR and pre-PBAC response stated that the lognormal function was chosen based on statistical fit (AIC/BIC), clinical plausibility,

and alignment with observed trial data. The Sub-Committees considered that sensitivity analyses using alternative reasonable functions were informative in highlighting the uncertainty associated with extrapolation of PFS data. In addition, given the lack of OS data available for vorasidenib, the Sub-Committees considered that adoption of a more conservative approach to extrapolation of PFS may also be justified. The pre-PBAC response argued that these Gompertz and Weibull functions provide the most pessimistic projections of PFS outcomes and are not reflective of the most likely clinical trajectory.

6.41 Due to the lack of meaningful OS data in the INDIGO trial, the probability of transitioning from the progressed disease health state to the dead state was derived from an analysis of Australian brain tumour registry data, and was assumed to be the same for the vorasidenib and active surveillance arms. In the model, the longer duration of radiographic PFS associated with vorasidenib resulted in a substantial OS advantage for the vorasidenib arm. However, it is unclear whether the improvement in radiographic PFS demonstrated in the INDIGO trial will translate into a survival benefit in clinical practice and, if so, the magnitude of the OS benefit. The association between radiographic PFS (as defined in the INDIGO trial) and OS among patients with Grade 2 IDH-mutant astrocytoma and oligodendroglioma was not adequately addressed in the submission. The PSCR and pre-PBAC response argued that the INDIGO trial demonstrated a tumour-static effect for vorasidenib, with a marked reduction in tumour growth rate and prolonged PFS compared to placebo, which may translate into improved outcomes beyond progression compared to active surveillance. In addition, evidence presented in the submission from the BRAIN registry suggests longer PFS periods tend towards longer post-progression survival times. As such, the PSCR suggested that assuming equal post-progression survival in both arms is a reasonable (if not conservative) approach. The Sub-Committees considered that it was unclear whether assuming the same probability of transitioning from the progressed disease state to the dead state for both arms was reasonable as no definitive data are available and additional follow-up data from the INDIGO trial are unlikely to provide further certainty. The Sub-Committees noted that this assumption led to a large modelled survival benefit, which was not supported by the available evidence (see also paragraph 6.48). The pre-PBAC response noted that the relatively long survival of patients with IDH-mutant gliomas means that OS data will take many years to mature.

6.42 Health utility in the progression-free health state (0.929) was based on the average reported health state utility among patients remaining progression-free in the INDIGO trial. The resulting utility appeared to overestimate utility in the population, given that the disease is typically incurable, and given that around 30% of patients in the INDIGO trial experienced seizures while in the progression-free state. Additionally, the assumed utility value exceeded Australian population norms for EQ-5D-5L reported by Redwood et al. (2024; 35-44 years: 0.87, 45-54 years: 0.85, 55-64 years: 0.86). The PSCR noted Redwood et al (2024) state that the Australian utility scores they reported are lower than utility scores reported from other countries, as well as those previously

reported from Australia. In addition, the PSCR and pre-PBAC response maintained that deriving this value from the trial data, with Australian weights, is the approach preferred in the PBAC Guidelines and is consistent with precedent[4], and the values used in the submission reflect the actual experience of patients enrolled in the INDIGO trial during the progression free phase of the disease. The Sub-Committees acknowledged that this was an appropriate approach, but noted that alternative approaches may be justified where the utilities appear to lack face value. The Sub-Committees noted that the use of the value derived from the INDIGO trial was favourable to vorasidenib and lower progression-free utility values substantially increased the ICER.

6.43 Health state utility in the progressed disease health state was assumed to decrease linearly over time from 0.93 at the time of disease progression to zero at the time of death. Based on the average duration of post-progression survival of 8.43 years derived from the extrapolated post-progression survival curve, this equated to a utility reduction of 0.00919 per cycle. The assumed progressed disease utilities may not adequately reflect the natural history of the disease, given that disease progression was defined based on radiographic findings (which may not be associated with clinical changes or changes in quality of life), and given that the model does not explicitly model the impact of subsequent treatments such as surgery and radiotherapy/chemotherapy (which may be associated with periods of disease remission and symptom reduction). The Sub-Committees considered that the assumption of a linear decrease in utility is simplistic and does not adequately account for the disease course and subsequent treatments. The pre-PBAC response maintained that the assumption of a linear decline in utility is more appropriate than assuming a constant utility value throughout the progression period, arguing that utility is unlikely to remain stable from the point of radiographic progression until death, therefore a linear decline offers a transparent approximation of gradual deterioration experienced by patients. The PBAC noted that the submission's approach to estimation of utility values in the progressed health state favoured vorasidenib and that alternative approaches increased the ICER by up to %.

6.44 The model assumed that patients in the progression-free health state would receive an MRI scan every 4.5 months for the first 5 years; whereas MRI scans in the INDIGO trial were performed every 12 weeks during the initial 3 years of the trial. However, a lower frequency of MRI scanning in clinical practice is likely to delay the identification of disease progression, resulting in a longer duration of vorasidenib treatment. The PSCR clarified that as per the INDIGO trial protocol, MRI scans occurred in the trial every 3 months for the first 3 years, every 6 months for the next 2 years, and then annually thereafter and the value applied in the model represented the midpoint. The

[4] Durvalumab Public Summary Document, July 2023 PBAC meeting

PSCR also noted that no adjustment to account for potential differences in the identification of disease progression were made as it is not possible to reliably estimate how alternative scan frequencies would affect the precise timing of radiographic progression. The Sub-Committees considered it would be appropriate for the costs for MRI scans to reflect their use in the INDIGO trial, given that adjustment to outcomes to account for the difference is not feasible. The Sub-Committees noted that this adjustment had negligible impact on the ICER.

6.45 The cost per cycle for vorasidenib in the model was derived based on 30.0 days per month. The assumption of 30.0 days per month rather than 30.44 days (i.e., 365.25 ÷ 12) was not appropriate. Correction of this error increased the ICER by %.

6.46 Table 10 summarises the key drivers of the economic model.

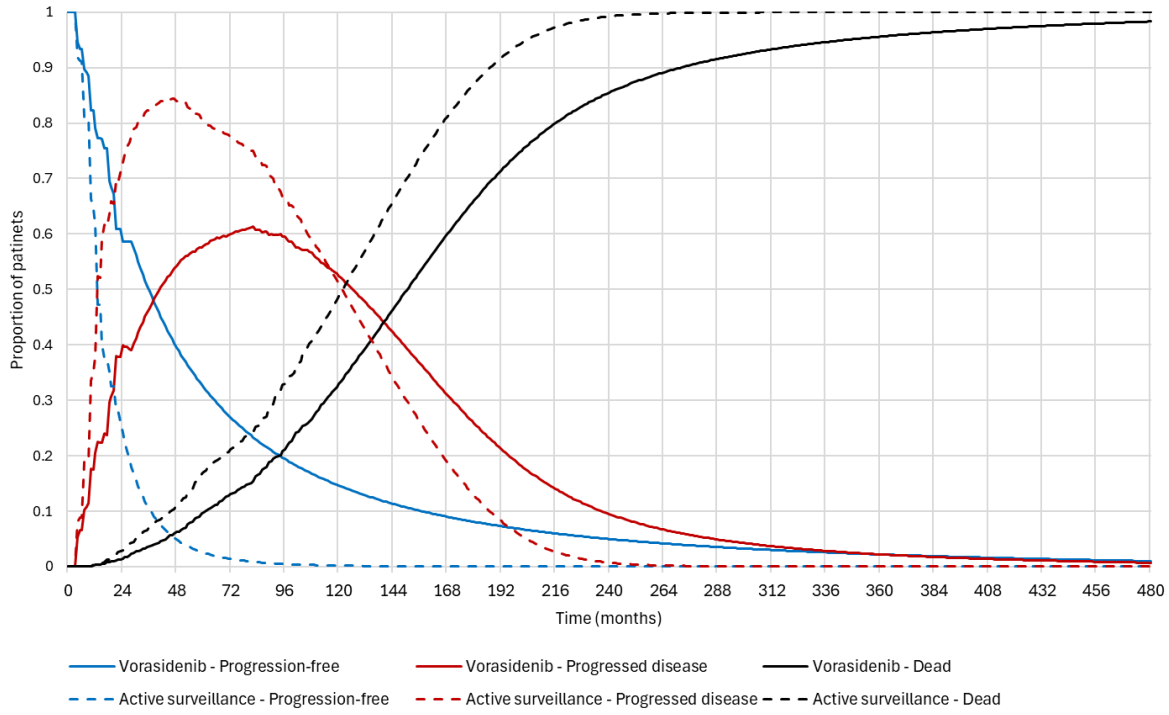
Table 10: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	PFS data for the vorasidenib arm were extrapolated using a lognormal function. The longer-term PFS trajectory among patients treated with vorasidenib is unclear and a more conservative option such as a Gompertz or Weibull function may be more appropriate.	High, favours vorasidenib
Overall survival	The rate of post-progression survival was assumed to be the same in both treatment arms. Differences in PFS resulted in a substantial OS benefit for the vorasidenib arm. However, it is unclear whether the improvement in radiographic PFS demonstrated in the INDIGO trial will translate into a survival benefit in clinical practice and, if so, the magnitude of the overall survival benefit.	High, favours vorasidenib
Utilities	Health utility in the progression-free health state (0.929) was based on the average reported health state utility among patients remaining progression-free in the INDIGO trial. The resulting utility appeared to be an overestimate of utility for patients with Grade 2 IDH-mutant astrocytoma or oligodendroglioma. Health state utility in the progressed disease health state was assumed to decrease linearly by 0.00919 per cycle from 0.93 at the time of disease progression. The assumed progressed disease utilities may not adequately reflect the natural history of the disease.	High, favours vorasidenib
Treatment duration	PFS was used as a proxy for the time to treatment discontinuation. Patients may not receive MRI scanning as frequently as in the INIDIGO trial which may delay the identification of disease progression (resulting in a longer duration of vorasidenib treatment). Additionally, some patients with radiographic disease progression may continue vorasidenib if there is a possible/perceived benefit associated with ongoing IDH inhibitor therapy.	Moderate, favours vorasidenib
Model structure	The assumed model structure may not adequately reflect the natural history of the disease, which is typically associated with slow tumour growth for a number of years prior to a more rapidly progressing phase. The model does not explicitly model the impact of subsequent treatments such as surgery and radiotherapy/chemotherapy, which may be associated with periods of disease remission and symptom reduction.	Unclear impact

Source: Constructed during the evaluation with reference to Section 3, pp72-108 of the submission.
Abbreviations: ICER, incremental cost-effectiveness ratio; IDH, isocitrate dehydrogenase; MRI, magnetic resonance imaging.

6.47 Figure 3 presents model traces for the vorasidenib and active surveillance arms.

Figure 3: Model traces for vorasidenib and active surveillance arms of the model



Source: Constructed using the Section 3 economic model Excel spreadsheet and the Section 3 economic model TreeAge Pro file.

6.48 The proportion of patients remaining alive in the vorasidenib arm at 20 and 40 years were 14.5% and 1.7%, respectively, compared to 0.7% and 0.0%, respectively, in the active surveillance arm. The model traces show a modelled survival benefit for vorasidenib compared to active surveillance that persists over the 40-year model duration. The modelled survival benefit for vorasidenib was inconsistent with the results of the INDIGO trial that did not demonstrate a difference in overall survival between vorasidenib and placebo. The Sub-Committees noted that the modelled difference in PFS translated to a large OS benefit that was highly uncertain and not supported by the evidence presented, as OS data from the INDIGO trial were immature and will be impacted by cross-over to the vorasidenib arm for any further data cuts.

6.49 The traces also show a larger proportion of patients remaining progression free in the vorasidenib arm compared to the active surveillance arm, which persists over the modelled time horizon. A smaller proportion of patients were in the progressed disease state in the vorasidenib arm compared to the active surveillance arm until approximately 10 years, when a higher proportion of vorasidenib patients have progressed disease (due to longer survival).

6.50 Table 11 presents the results of the stepped economic evaluation.

Table 11: Results of the stepped economic evaluation

Step and component	Vorasidenib	Active surveillance	Increment
Step 1: Modelled analysis over 30 months based on the results of the INDIGO trial, including initial treatment costs, adverse event costs, disease management costs and seizure management costs.			
Costs	$	$29,366	$
Progression-free life years	1.903	1.327	0.577
Incremental cost/progression-free life year gained			$[1]
Step 2: Time horizon increased to 40 years, with incorporation of post-progression survival data derived from an Australian brain tumour registry, extrapolated using a parametric function.			
Costs	$	$185,933	$
Life years	13.586	9.961	3.624
Incremental cost per life year gained			$[2]
Step 3: Inclusion of subsequent therapy and end-of-life costs; discounting applied to costs and outcomes.			
Costs	$	$167,634	$
Life years	9.311	7.611	1.699
Incremental cost per life year gained			$[1]
Step 4: Incorporation of health state utilities.			
Costs	$	$167,634	$
QALYs	6.206	4.203	2.003
Incremental cost per QALY gained			**$[1]**

Source: Table 3.12, p106 of the submission.
Abbreviations: QALY, quality-adjusted life year.
The redacted values correspond to the following ranges:
[1] $155,000 to < $255,000
[2] $115,000 to < $135,000

6.51 Based on the economic model, treatment with vorasidenib was associated with an incremental cost per quality-adjusted life year of $155,000 to < $255,000 compared to placebo, as a proxy for active surveillance.

6.52 In the model, 92% of the incremental QALYs and 59% of the incremental costs were accrued in the extrapolated period beyond 30 months.

6.53 For every patient treated with vorasidenib versus active surveillance and followed up for 40 years, the economic evaluation (without discounting) estimated that there would be:

- An additional 3.6 years of life lived.
- An additional 3.5 years of quality-adjusted life lived.
- Additional initial therapy costs of $, additional disease management costs (including seizure management) and adverse event costs of $15,022, a reduction in subsequent anticancer therapy costs of $319 and a reduction in end-of-life costs of $788.

6.54 The results of key sensitivity analyses presented in the resubmission and conducted during the evaluation, and conducted for the ESC are summarised in Table 12.

Table 12: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change
Base case	**$**	**2.003**	**$** [1]	**-**
Time horizon (base case: 40 years)				
10 years	$	1.243	$ [1]	%
20 years	$	1.835	$ [1]	%
30 years	$	1.969	$ [1]	%
Discount rate (base case: 5% for costs and outcomes)				
0%	$	3.515	$ [2]	- %
3.5%	$	2.335	$ [3]	- %
PFS parametric function in vorasidenib arm (base case: lognormal)				
Exponential	$	1.563	$ [1]	%
Weibull	$	1.031	$ [1]	%
Gompertz	$	0.840	$ [1]	%
Generalised gamma	$	3.034	$ [3]	- %
Loglogistic	$	1.842	$ [1]	%
PFS parametric function in active surveillance arm (base case: lognormal)				
Exponential	$	1.962	$ [1]	%
Weibull	$	2.122	$ [3]	- %
Gompertz	$	2.147	$ [3]	- %
Generalised gamma	$	2.003	$ [1]	%
Loglogistic	$	1.957	$ [1]	%
Post-progression survival parametric function (base case: Gompertz)				
Exponential	$	1.840	$ [1]	%
Weibull	$	1.937	$ [1]	%
Generalised gamma	$	2.019	$ [3]	- %
Lognormal	$	1.815	$ [1]	%
Loglogistic	$	1.849	$ [1]	%
Vorasidenib drug cost (base case: $, based on 30.0 days of treatment per month)				
Based on 30.4375 days of treatment per month ($)	$	2.003	$ [1]	%
MRI scan frequency in progression-free state (base case: every 4.5 months for initial 60 months; every 6 months beyond 60 months)				
Every 12 weeks for 3 years; every 6 months for the next 2 years and annually thereafter (as per pre-PBAC response) [a]	$	2.003	$ [1]	%
Health state utilities (base case: progression-free 0.93; progressed disease time-varying from 0.93 to 0 over 8.43 years)				
Progression-free: 0.93; progressed disease: based on Qian et al. (2007) approach, with a reduction of 0.02 per month from progression-free utility for 30 months.	$	2.021	$ [3]	- %
Based on March 2024 dabrafenib submission (progression-free: 0.89; progressed disease: 0.73)	$	1.656	$ [1]	%
Based on Garside et al. (2007; progression-free: 0.86; progressed disease: 0.73) [b]	$	1.578	$ [1]	%
Based on Vera et al. (2018; progression-free: 0.81; progressed disease: 0.70) [c]	$	1.475	$ [1]	%
Additional health state utility analyses requested by the Sub-Committees [d]				
Progression-free based on March 2024 dabrafenib submission (0.89); progressed disease initially 0.89 reducing to 0 over 8.43 years.	$	1.919	$ [1]	%

Analyses	Incremental cost	Incremental QALY	ICER	% change
Progression-free based on March 2024 dabrafenib submission (0.89); progressed disease initially 0.89 reducing to 0 by 0.00919 per cycle.	$[redacted]	1.938	$[redacted][1]	[redacted]%
Progression-free based on Vera et al. (2018; 0.81); progressed disease initially 0.81 reducing to 0 over 8.43 years.	$[redacted]	1.746	$[redacted][1]	[redacted]%
Progression-free based on Vera et al. (2018; 0.81); progressed disease initially 0.81 reducing to 0 by 0.00919 per cycle.	$[redacted]	1.787	$[redacted][1]	[redacted]%
Multivariate sensitivity analyses requested by the Sub-Committees[e]				
PFS extrapolation for vorasidenib arm: Weibull function Utilities based on dabrafenib submission (progression-free: 0.89; progressed disease: 0.73)	$[redacted]	0.858	$[redacted][1]	[redacted]%
PFS extrapolation for vorasidenib arm: Weibull function Utilities based on dabrafenib submission (progression-free: 0.89; progressed disease: 0.73) Vorasidenib drug cost based on 30.4375 days of treatment per month ($[redacted]); MRI scan every 12 weeks during initial 60 months	$[redacted]	0.858	$[redacted][1]	[redacted]%

Source: Table 3.14, p108 of the submission.

Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year.

[a] p24 of the March 2023 INDIGO clinical study report states that disease response assessment by MRI occurred every 12 weeks (84 ±7 days) beginning at Cycle 4, every 6 months beginning at Cycle 37 for 2 years and then annually after that.

[b] Study comparing the cost-effectiveness of adjuvant carmustine wafers or adjuvant and concomitant temozolomide versus surgery with radiotherapy, among patients with newly diagnosed high-grade glioma. Utilities obtained from a panel using the standard gamble method for preference elicitation.

[c] Based on alternative utility values included in the March 2024 dabrafenib submission, derived from Vera et al. (2018), a study assessing quality of life (assessed using the EQ-5D) among 100 patients with malignant glioma undergoing outpatient treatment at a US cancer treatment centre.

d Differences between these analyses and those provided in the pre-PBAC response are due to the assumed timing of the utility change. In the sensitivity analyses, the pre-progression utility was applied in the cycle that disease progression occurs, with the first 0.00919 decrement applied in the first cycle in the progressed disease health state. The sensitivity analysis was based on the application of the exact utility decrement (0.00918561….), whereas the analyses in the pre-PBAC response appear to have used the rounded figure (0.00919).

e In the multivariate sensitivity analyses, the utility in the cycle that disease progression occurs was assumed to be the same as the progression-free utility, with the post-progression value applied from the first cycle in the progressed disease health state onwards. The multivariate analyses provided in the pre-PBAC response include 50% of the progression-free utility and 50% of the post-progression utility in the cycle that the disease progression occurs, and the post-progression utility from the first cycle in the progressed disease health state onwards.

The redacted values correspond to the following ranges:

[1] $155,000 to < $255,000

[2] $115,000 to < $135,000

[3] $135,000 to < $155,000

6.55 The model was most sensitive to the choice of parametric function for the vorasidenib PFS extrapolation, the choice of parametric function for the post-progression survival extrapolation, and the included health state utilities.

6.56 The pre-PBAC response stated that the sponsor was unable to replicate some analyses varying health state utilities in Table 12. There were slight differences in the results provided in the pre-PBAC response due to the assumed timing of the switch from the progression-free to the progressed disease utility and rounding of the utility value applied.

6.57 The Sub-Committees noted that with more conservative assumptions regarding PFS extrapolation, utility values and correction of the vorasidenib drug costs the ICER increased by %, from $155,000 to < $255,000 to $155,000 to < $255,000 per QALY.

Drug cost/patient/course

6.58 Table 13 presents a comparison of drug costs for vorasidenib included in the economic model and financial estimates.

Table 13: Drug cost per patient for vorasidenib

	Vorasidenib		
	Clinical trial	**Economic model**	**Financial estimates**
Dose distribution	40 mg: 90.3% [a] 20 mg: 5.7% [a] 10 mg: 1.9% [a] 0 mg: 2.1% [a]	40 mg: 92.2% [b] 20 mg: 5.8% [b] 10 mg: 2.0% [b]	40 mg: 92.2% [b] 20 mg: 5.8% [b] 10 mg: 2.0% [b]
Treatment adherence	93.3% [c]	97.9% [d]	93.6% [e]
Proposed price	-	40 mg × 30 tablets: $ 10 mg × 60 tablets: $ 10 mg × 30 tablets: $	40 mg × 30 tablets: $ 10 mg × 60 tablets: $ [f] 10 mg × 30 tablets: $ [f]
Cost/patient/month	-	$ [g]	$ [h]
Cost/patient/year	-	$	$
Treatment duration	17.8 months [i]	5.37 years [j]	Y1: 100% [k] Y2: 77% [k] Y3: 59% [k] Y4: 49% [k] Y5: 39% [k] Y6: 32% [k]

Source: Table 14.1.16, pp12-14 of the March 2023 INDIGO clinical study report tables and figures document; Section 3 economic model Excel workbook; Section 4 financial implications Excel workbook.
Abbreviations: NR, not reported.
[a] Based on the mean number of vorasidenib administrations by dose in the INDIGO trial (0 mg: 2,382; 10 mg: 2,169; 20 mg: 6,404; 40 mg: 101,902).
[b] Based on the mean number of vorasidenib administrations by dose in the INDIGO trial, excluding 0 mg doses.
[c] Mean relative dose intensity reported among patients in the vorasidenib arm in the INDIGO trial.
[d] Derived from the vorasidenib dose distribution, assuming 2.1% of patients receive a dose of 0 mg.
[e] Derived by multiplying each dose by the proportion of administrations in the INDIGO trial and dividing by the planned daily dose of 40 mg.
[f] Corrected costs. The cost per pack of 10 mg × 60 tablets and 10 mg × 30 tablets were incorrectly specified in the spreadsheet as $ and $, respectively.
[g] Based on an assumed 30.0 days per month of vorasidenib treatment.
[h] Based on an assumed 30.44 days per month of vorasidenib treatment.
[i] Mean duration of vorasidenib treatment at the time of the extended follow-up analysis.
[j] Modelled duration of vorasidenib treatment. Progression-free survival was used as a proxy for time to treatment discontinuation.
[k] The proportion of patients remaining on treatment at the start of each year was derived from the economic model.

6.59 The PBAC noted that the modelled treatment duration for vorasidenib was uncertain as it was based on extrapolation of PFS from 17.7 months mean follow up for the vorasidenib arm in the INDIGO trial. The PBAC noted that if more conservative extrapolation functions are selected the treatment duration estimated from the model was reduced from 64.5 months to 49.1 months (exponential model), 36.7 months (Weibull model) or 32.7 months (Gompertz model).

Estimated PBS usage & financial implications

6.60 This submission was considered by DUSC at a joint meeting of ESC and DUSC.

6.61 The submission used an epidemiological approach to estimate the utilisation and financial implications of listing vorasidenib for the treatment of patients with Grade 2 IDH-mutant diffuse glioma.

6.62 Table 14 presents the key inputs relied on in the financial estimates.

Table 14: Key inputs for financial estimates

Data	Value	Source	Commentary and sub-committee comments
Eligible population			
Australian population by 10-year age segments in 2016 to 2031.	-	ABS actual (2016-2023) and forecast (2024-2031) population by age segments, obtained from https://www.abs.gov.au/statistics/people/ population/population-clock-pyramid	The Sub-Committees considered this to be reasonable.
Grade 2 IDH-mutant glioma 5-year incidence by age segments	0-11 yrs: 23 12-18 yrs: 23 19-28 yrs: 129 29-38 yrs: 187 39-48 yrs: 177 49-58 yrs: 142 59-68 yrs: 124 69-78 yrs: 97 79-88 yrs: 24 89-99 yrs: 12	Data obtained from the AIHW. Total incident cases of IDH-mutant glioma in 2016 to 2020 based on 10-year age segments for brain tumours with histology codes 9400 ('astrocytoma, IDH-mutant, Grade 2 and astrocytoma, NOS') and 9450 ('oligodendroglioma, IDH-mutant and 1p/19q-codeleted, Grade 2 and oligodendroglioma, NOS').	The histology descriptors for the 9400 and 9450 codes include astrocytomas and oligodendrogliomas that are not otherwise specified. Therefore, it is unclear whether all tumours under this category correspond to Grade 2 tumours. The overall number of incident cases per year matched AIHW data available using the AIHW cancer visualisation (incidence by histology) online tool. The Sub-Committees noted the potential for overestimating incident patients, however overall the Sub-Committees' considered this to be reasonable.
Grade 2 IDH-mutant glioma incidence per 100,000 population for 2016 to 2020 period	0-11 yrs: 0.121 12-18 yrs: 0.222 19-28 yrs: 0.737 29-38 yrs: 1.022 39-48 yrs: 1.079 49-58 yrs: 0.912 59-68 yrs: 0.928 69-78 yrs: 1.041 79-88 yrs: 0.773 89-99 yrs: 0.480	Total incident cases of Grade 2 IDH-mutant glioma over 5 years (2016-2020) by age segments divided by the population by age segments for the corresponding 5-year period (2016-2020) and multiplied by 100,000.	The Commentary and Sub-Committees considered this to be reasonable.
Incident cases of IDH-mutant glioma in Year 1 to Year 6	Y1: 212 Y2: 216 Y3: 219 Y4: 223 Y5: 227 Y6: 230	The derived incidence of Grade 2 IDH-mutant glioma by age segment for 2016 to 2020 was applied to the corresponding projected population (by age segments) in 2025 to 2031.	The submission assumed a stable incidence of IDH-mutant glioma over time. Based on the available incidence data, this appeared reasonable.

Data	Value	Source	Commentary and sub-committee comments
Prevalent cases of IDH-mutant glioma in Year 1 of listing	369	Derived from the incident cases in 2020 to 2025 who are not considered to be in immediate need of radiotherapy/ chemotherapy. Patients receiving treatment under the sponsor's compassionate access program and patients requiring chemotherapy/radiotherapy treatment were removed from the prevalent pool.	Given the relatively long natural history of the disease (as per BRAIN registry), there may be additional prevalent patients arising prior to 2020. The Sub-Committees' advised that prevalent patients prior to 2020 should also be considered in the estimates. An error was identified by the evaluators in the financial worksheet where the persistence rate was applied to each previous year's population rather than the initial population. This error was corrected for the values presented in Table 16.
Proportion of incident patients not in immediate need of radiotherapy or chemotherapy	64.3%	Based on an analysis of data from an Australian brain tumour registry (BRAIN), 110 of 171 patients (64.3%) did not receive radiotherapy or chemotherapy within the 6 months following surgery.	The commentary noted that some patients may undertake a trial of vorasidenib rather than initiate treatment with radiotherapy/ chemotherapy. The Sub-Committees noted that as vorasidenib does not provide a reduction in tumour size clinicians would likely still use radiotherapy/chemotherapy when needed rather than trial vorasidenib in symptomatic or imminently symptomatic patients.
The proportion of patients not in immediate need of radiotherapy/ chemotherapy	Y1: 100.00% Y2: 98.26% Y3: 84.96% Y4: 68.47% Y5: 48.37% Y6: 34.93% Y7: 25.14% Y8: 18.16%	Based on an analysis of time to next intervention among a matched cohort of 100 patients with Grade 2 IDH-mutant glioma in an Australian brain tumour registry (BRAIN). A lognormal function was fitted to the Kaplan-Meier data. Used to derive the eligible prevalent pool of patients.	Interventions in the analysis included surgery. Patients undergoing re-resection would still be eligible for treatment with vorasidenib. The Sub-Committees noted that this input is based on those patients from BRAIN who met the criteria for the INDIGO trial and excluded patients if they received radiotherapy/chemotherapy within 1 year of surgery. The Sub-Committees considered that this is not inconsistent with the previous input.
Grandfathered patients	[redacted] patients	Based on the expected number of patients in the sponsor's compassionate access program by the end of March 2025.	Grandfathered patients were appropriately removed from the prevalent patient pool.
Treatment utilisation			
Uptake rate (incident patients)	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]% Yr 6: [redacted]%	Assumption. The submission argued that uptake is expected to be high due to the lack of alternative treatments, the simplicity of oral dosing and the acceptability of the safety profile.	The Sub-Committees considered the estimates of uptake to be reasonable, however the uptake of vorasidenib is uncertain.
Uptake rate (prevalent patients)	Yr 1: [redacted]%		

Data	Value	Source	Commentary and sub-committee comments
Vorasidenib treatment persistence	Yr 1: 100% Yr 2: 77% Yr 3: 59% Yr 4: 49% Yr 5: 39% Yr 6: 32%	Based on the proportion of patients remaining progression-free at the start of each year in the vorasidenib arm of the economic model. Progression-free survival among patients in the vorasidenib arm of the economic model was derived from extrapolation of data for the vorasidenib arm of the INDIGO trial.	Progression events in the economic model were based on radiographic progression. It is unclear whether patients treated with vorasidenib in clinical practice will discontinue treatment with vorasidenib following an initial finding of radiographic disease progression. Additionally, patients may not receive MRI scanning as frequently as in the INIDIGO trial which may delay the identification of disease progression. The Sub-Committees considered there may be a potential underestimation of persistence. However, the PBAC also noted that modelled extrapolations of PFS were uncertain and more conservative extrapolations resulted in reduced treatment persistence.
Vorasidenib dose distribution	40 mg: 92.2% 20 mg: 5.8% 10 mg: 2.0%.	Based on the number of vorasidenib administrations by dose (10 mg: 2,169; 20 mg: 6,404; 40 mg: 101,902) among patients in the vorasidenib arm of the INDIGO trial (administrations recorded as a 0 mg dose excluded).	The Commentary and Sub-Committees considered this to be reasonable.
Vorasidenib treatment adherence	93.6%	Based on the number of vorasidenib administrations by dose (0 mg: 2,382; 10 mg: 2,169; 20 mg: 6,404; 40 mg: 101,902) as a proportion of the planned total dose of 40 mg daily among patients in the vorasidenib arm of the INDIGO trial.	The calculation was based on the planned daily dose of 40 mg in the trial and assumed that patients receiving a 10 mg or 20 mg dose were not fully adherent to treatment. Given the proposed availability of 10 mg and 20 mg tablets, this assumption was likely to underestimate treatment adherence (only 2.1% of administrations were recorded as 0 mg). However, treatment adherence in clinical practice may be lower than in the clinical trial environment.
Costs			
Vorasidenib	40 mg × 30 tablets: $[redacted] 10 mg × 60 tablets: $[redacted] 10 mg × 30 tablets: $[redacted]	Proposed effective price.	The cost per pack of 10 mg × 60 tablets and 10 mg × 30 tablets were incorrectly specified in the spreadsheet. The cost per pack of 60 tablets should be $[redacted] and the cost per pack of 30 tablets should be $[redacted].
Patient copayment	PBS: $22.99 RPBS: $4.83	Distribution across copayment groups based on CGRP antagonists dispensed in July 2023 to June 2024 (PBS Items 12469G, 12478R, 12603H, 12611R, 13115G, 13129B, 13342F, 13352R). Based on a 99.3%/0.7% PBS/RPBS split.	The Commentary and Sub-Committees considered this to be reasonable.
MBS costs	$300.20	MBS Item 63001 (MRI brain), assuming 80% of the Schedule fee.	The Commentary and Sub-Committees considered this to be reasonable.

Source: Section 4, pp109-115 of the submission' Section 4 financial implications Excel workbook.

Abbreviations: ABS, Australian Bureau of Statistics; AIHW, Australian Institute of Health and Welfare; CGRP, calcitonin gene-related peptide; IDH, isocitrate dehydrogenase; NOS, not otherwise specified.

6.63 Table 15 presents the estimated use and financial implications of listing vorasidenib on the PBS.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Vorasidenib 40 mg × 30 scripts	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Vorasidenib 10 mg × 60 scripts	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Vorasidenib 10 mg × 30 scripts	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Estimated financial implications of vorasidenib						
Cost to PBS/RPBS less copayments	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost to MBS	$[redacted][5]	$[redacted][5]	$[redacted]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Net cost to PBS/RPBS/MBS [a]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost to PBS/RPBS/MBS (corrected) [b]	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**
Corrected prevalent population calculations						
Prevalent population[c]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][3]	[redacted][3]	[redacted]	
Estimated financial implications of vorasidenib						
Cost to PBS/RPBS less copayments	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**

Source: Section 4 financial implications Excel workbook.

[a] MBS costs associated with an increase in the number of MRI scans (MBS Item 63001) due to improvements in progression-free survival associated with vorasidenib compared to active surveillance.

[b] Estimates updated using the correct cost per pack of 10 mg × 60 tablets ($[redacted]) and 10 mg × 30 tablets ($[redacted]). The cost per pack of 10 mg × 60 tablets and 10 mg × 30 tablets were incorrectly specified in the financial implications spreadsheet as $[redacted] and $6,885.67, respectively.

[c] Corrected so that persistence rates are applied to initial prevalent pool and not previous year.

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *5,000 to < 10,000*

[3] *< 500*

[4] *$40 million to < $50 million*

[5] *$0 to < $10 million*

6.64 The estimated net cost to the PBS/RPBS after correction of errors in the financial implications spreadsheet was $40 million to < $50 million in Year 1, increasing to $40 million to < $50 million in Year 6, a total cost of $200 million to < $300 million over the first 6 years of listing.

6.65 The Sub-Committees considered the estimated cost to the PBS/RPBS proposed by the submission to be reasonable overall, noting that:

- Costs associated with vorasidenib may be overestimated due to the inclusion of patients with non-Grade 2 disease.
- Costs associated with vorasidenib may be underestimated due to the potential for use outside the restriction in patients in immediate need of radiotherapy/chemotherapy, patients with previous anticancer therapy use, and those with an ECOG>1; the underestimation of treatment persistence which

assumed the same rate of detection of radiographic disease progression in the clinical trial as in clinical practice which would not be the case and may result in a longer duration of treatment in practice; exclusion of prevalent patients arising prior to 2020; an error in the costs per pack for 10 mg tablets.

- Treatment adherence was derived based on the planned daily dose of 40 mg daily in the trial and assumed that patients receiving a 10 mg or 20 mg dose were not fully adherent to treatment. Given the proposed availability of 10 mg and 20 mg tablets, this assumption was likely to underestimate treatment adherence, as only 2.1% of administrations were recorded as 0 mg. However, treatment adherence in clinical practice may be lower than in the clinical trial environment.
- The proposed restriction limits treatment to patients with an ECOG ≤1. However, no adjustment to the eligible population was applied to remove patients with an ECOG >1.
- Costs associated with liver function test monitoring were not included in the financial estimates. This was not appropriate and differed from the economic model, which included costs associated with monitoring of liver function tests (and costs of associated general practitioner and telehealth consultations) while on treatment with vorasidenib.

6.66 The Sub-Committees considered it possible that vorasidenib would have minimal utilisation outside of the proposed restriction as clinicians would likely prefer to use radiotherapy/chemotherapy where required rather than trial vorasidenib. The Sub-Committees considered it unlikely that vorasidenib would be used beyond expectations. The PBAC considered it was likely that many patients would stay on treatment beyond progression where there is a perceived continuing benefit, and that some patients may be treated for an extended period due to the indolent nature of the disease. However, the duration of treatment based on extrapolated PFS is uncertain.

Quality Use of Medicines

6.67 The pre-PBAC response indicated the sponsor is committed to supporting clinicians and patients to ensure that vorasidenib is used appropriately, and is currently developing a range of materials to support the appropriate and evidence-based use of vorasidenib in clinical practice. Materials are being prepared to assist prescribers in identifying suitable patients and managing safety, particularly in relation to liver function and seizure control. For patients, resources in development include educational content on IDH-mutant glioma, guidance on treatment expectations, and tools to support adherence to treatment, management of symptoms and monitoring for potential adverse effects.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of vorasidenib for the treatment of IDH-mutant astrocytoma or oligodendroglioma. The PBAC acknowledged the high unmet clinical need for treatments for astrocytoma or oligodendroglioma. The PBAC accepted the clinical claim of superior efficacy compared to active surveillance in terms of radiographic progression and acknowledged that delaying the need for chemotherapy and radiotherapy is a clinically meaningful outcome that is likely to impact on patient quality of life (QoL). The PBAC noted that due to the indolent nature of the disease it was not possible to demonstrate a difference in overall survival or QoL within the trial, and the associated limitations of the clinical evidence resulted in a high level of uncertainty in the incremental cost effectiveness ratio (ICER). Overall, the PBAC considered the ICER was likely to be underestimated and was high at the proposed price. The PBAC considered the duration of treatment in clinical practice may be substantially longer than was assumed in the economic model and financial estimates and a risk-sharing arrangement (RSA) would be required to address the potential for use beyond progression. The PBAC considered these issues could be resolved in a resubmission using the early re-entry pathway.

7.2 The PBAC acknowledged the high unmet clinical need for effective treatments for IDH-mutant astrocytoma or oligodendroglioma, noting that there are currently no other effective treatments available for patients not in immediate need of chemotherapy/radiotherapy. The PBAC noted that as the disease progresses patients experience headaches, nausea/vomiting, seizures, drowsiness, visual disturbance, speech/language problems, sensory loss, motor deficits and changes in cognitive and/or functional ability. These symptoms have a significant impact on QoL, including inability to work, drive, remain independent, and anxiety is associated with surveillance only, knowing that the condition will inevitably progress. The PBAC also acknowledged that chemotherapy/radiotherapy is associated with substantial toxicity and worsening of neurological deficits. Therefore, delaying progression and the need for chemotherapy/radiotherapy is valuable to patients and likely to result in improved quality of life.

7.3 The PBAC noted that the proposed restriction criteria were generally consistent with the TGA indication for vorasidenib. The PBAC considered the criterion limiting treatment to patients not in immediate need of radiotherapy or chemotherapy was appropriate and consistent with guidelines. Although it is possible that some patients with symptoms/impending symptoms or high-risk features who should receive chemotherapy/radiotherapy may be initially treated with vorasidenib (as the criterion is not tightly defined), the PBAC considered that clinicians are unlikely to delay radiotherapy/chemotherapy as vorasidenib does not appear to reduce tumour size. The PBAC considered that there is likely to be treatment beyond radiographic progression despite the criterion addressing this, as clinicians and patients may delay radiotherapy/chemotherapy until worsening of symptoms even if patients have radiographic progression. The PBAC noted that the cost-effectiveness of ongoing

treatment beyond radiographic progression was uncertain and could not be assessed as patients in INDIGO discontinued treatment at radiographic progression.

7.4 The proposed listing is broader than the TGA indication with respect to age, as the TGA indication limits treatment to patients aged 12 years and older. However the PBAC considered it was appropriate for the listing to be silent on age to ensure the very small number of younger patients, who are likely to benefit from treatment, are not excluded. The proposed listing is narrower than the TGA indication, which does not limit treatment on the basis of previous anticancer therapy, performance status, the presence of residual or recurrent disease. The PBAC considered these differences between the TGA indication and proposed listing were appropriate to align with the population in the pivotal trial (INDIGO).

7.5 The submission noted that the proposed restriction does not specify a duration of time since surgery, whereas the INDIGO trial enrolled patients whose most recent surgery was at least one year (and not more than 5 years) prior to randomisation. The sponsor argued that it would be reasonable for the restriction to not specify a fixed time window for initiation of vorasidenib as subgroup analyses indicate that treatment outcomes did not vary meaningfully with earlier or later initiation. The PBAC considered it was appropriate to allow flexibility with regard to the time since surgery, as proposed in the restrictions.

7.6 The PBAC considered that the proposed clinical place for vorasidenib in patients with WHO Grade 2 IDH-mutant astrocytoma or oligodendroglioma who have residual or recurrent disease after at least one prior surgery for glioma, and who are not in immediate need of radiotherapy or chemotherapy was appropriate and consistent with guidelines and the clinical evidence available. The PBAC considered that clinicians are unlikely to use vorasidenib in patients with high-risk disease (including Grade 3 or 4) or with progression on radiotherapy/chemotherapy as there is no evidence to suggest it would be effective. The PBAC noted that there may be trials in other treatment settings in the future (e.g. after prior chemotherapy), however the appropriate clinical place based on the INDIGO trial is clear and effectiveness has not been demonstrated for use outside the proposed population.

7.7 The PBAC considered the nominated comparator of active surveillance was appropriate as no other treatments are available for patients not in immediate need of radiotherapy/chemotherapy.

7.8 The PBAC noted the submission was based on one head-to-head randomised trial comparing vorasidenib to placebo in patients with Grade 2 IDH-mutant astrocytoma or oligodendroglioma (INDIGO). The trial was unblinded after the second interim analysis based due to early demonstration of efficacy and patients in the placebo arm, including patients who had not yet experienced disease progression, were able to cross over to receive vorasidenib treatment. The PBAC noted that no comparative data were available beyond the extended follow-up analysis, with a median follow-up of 17.3 months for PFS.

7.9 The PBAC noted that for the primary outcome of radiographic PFS, treatment with

vorasidenib was associated with a statistically significant improvement in PFS compared to placebo (hazard ratio: 0.35; 95% CI: 0.25, 0.49). For the secondary outcome of time to next intervention treatment, vorasidenib was associated with a statistically significant delay compared to placebo (hazard ratio: 0.25; 95% CI: 0.16, 0.40). There were no meaningful OS data from the INDIGO trial. With follow-up for OS of ~20 months one patient in the vorasidenib arm had died due to disease progression, and no patients in the placebo arm had died at the time of extended follow-up analysis. The PSCR and pre-PBAC response noted evidence from trials in similar tumour types (RTOG 9802 study in patients with high risk grade 2 glioma and a meta-analysis of trials in patients with glioblastoma (Han et al 2014)) demonstrated a delay in progression that translated to an improvement in OS. The PBAC considered it is unclear to what extent the improvements in radiographic PFS associated with vorasidenib treatment will translate into improvements in OS, and noted further analyses of the INDIGO trial will not be informative due to the large number of patients who crossed over from the placebo arm to receive vorasidenib. The PBAC noted that due to the indolent nature of the disease it was not possible to demonstrate a difference in OS within the trial.

7.10 The PBAC noted there was limited collection of QoL data following radiographic disease progression in the INDIGO trial, and no differences in QoL outcomes between vorasidenib and placebo were demonstrated. The PBAC noted that substantial differences in QoL would not be expected to occur within the trial as the most significant impacts are experienced later in the disease course due to symptomatic progression. The PBAC agreed with the Sub-Committees that despite the trial's inability to demonstrate an effect on OS, the PFS benefit shown was substantial, likely to be highly clinically relevant for patients and to result in QoL benefits. Overall the PBAC considered the claim of superior clinical efficacy was supported by the data based on radiographic PFS, however longer-term benefits are unknown.

7.11 The PBAC noted that a higher proportion of patients treated with vorasidenib experienced AEs, including Grade ≥3 AEs. The PBAC considered the claim in inferior safety compared with active surveillance was reasonable, and that there were no major safety concerns, though long term safety data are not available.

7.12 The PBAC noted that the submission presented a modelled cost-effectiveness analysis based on the results of the INDIGO trial, with additional data from an analysis of Australian brain tumour registry data to model OS. The PBAC considered that the limited duration of follow up in the trial and the lack of OS data resulted in a high level of uncertainty in the modelled outcomes. The PBAC considered the main area of uncertainty was the extrapolation of PFS for patients treated with vorasidenib, which also resulted in a large OS difference because post-progression survival was assumed to be the same in both arms. The PBAC noted the Weibull function was more conservative than lognormal, but was still a good fit for the KM data. Application of the Weibull function for extrapolation of PFS for the vorasidenib arm increased the ICER from $155,000 to < $255,000/QALY gained to $155,000 to < $255,000/QALY

gained. In addition, the PBAC noted that the health state utilities, though based on the available QoL data from INDIGO, appeared high given the symptom burden for patients with glioma. Application of alternative utility values from the submission for dabrafenib + trametinib for low grade glioma from Garside (2007) (Table 19, dabrafenib + trametinib Public Summary Document, March 2024 PBAC meeting) and correction of drug cost calculations resulted in a further increase in the ICER to $155,000 to < $255,000/QALY. The PBAC considered that these sensitivity analyses suggested that the ICER presented in the submission is likely underestimated. Further, the PBAC noted the modelled treatment duration was based on extrapolated radiographic PFS, however the PBAC considered that treatment beyond radiographic progression is likely to be common and some patients may be treated for many years. Although treatment discontinuation upon radiographic progression was consistent with the INDIGO trial, the PBAC considered that it is likely to underestimate the true cost of vorasidenib treatment, which would further underestimate the ICER. Given these areas of uncertainty, the PBAC considered that the ICER was likely to be underestimated and was unacceptably high at the proposed price for vorasidenib.

7.13 The PBAC noted that the submission used an epidemiological approach to estimate the utilisation and financial implications of listing vorasidenib. The PBAC considered that the approach was generally reasonable after corrections to the cost and persistence rate calculations. However, the PBAC considered that prevalent patients were likely to be underestimated and patients from before 2020 should be included in the estimates given the long natural history of the condition. In addition, the PBAC considered that the treatment duration for vorasidenib (64.5 months) was highly uncertain as it was based on extensive extrapolation of radiographic PFS for the vorasidenib arm in the INDIGO trial and was driven by the extrapolation function chosen (see paragraph 6.59). In addition, the PBAC considered that treatment duration in clinical practice is likely to extend beyond the radiographic progression (despite the restrictions) and therefore the extrapolated trial PFS may also underestimate the true treatment duration. The PBAC considered that the time to next treatment may be a better indicator of the likely actual treatment duration for vorasidenib, though it would still be impacted by the immaturity of the INDIGO trial data.

7.14 The PBAC considered that at the proposed price for vorasidenib the cost per patient per month for treatment was very high, particularly in the context of a treatment that may continue for many years, due to the variable and often extended time period between surgery and symptomatic progression. The PBAC considered that, given the high level of uncertainty regarding the duration of treatment, the uncertain benefit of treatment beyond radiographic progression, the high cost for vorasidenib, and uncertainty regarding the extent of overall gain in health outcomes, a risk-sharing arrangement would give the committee confidence that the cost for vorasidenib treatment would be contained and acceptably cost-effective. The PBAC considered it would be appropriate for financial caps for vorasidenib to be calculated based on a

duration of treatment reflecting radiographic PFS consistent with the evidence from INDIGO (and extrapolated consistent with the revised model) and costs for use beyond progression should be rebated as such use is unlikely to be cost-effective.

7.15 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for vorasidenib using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:

- Revision of the economic model to incorporate more conservative assumptions regarding PFS/OS (Weibull extrapolation function for PFS) and utility values (as per Dabrafenib + trametinib submission, March 2024 PBAC meeting).
- Including the revisions of the economic model as proposed, the resultant ICER should be of $75,000 to < $95,000/QALY or less, reflecting the high level of uncertainty regarding the magnitude of long-term benefits of treatment.
- Revised financial estimates with corrections to cost and persistence rate calculations, inclusion of prevalent patients from before 2020 (as per paragraph 7.13) and revised mean treatment duration (as per paragraph 7.14).
- Proposal of a risk-sharing arrangement that addresses the potential for use beyond radiographic progression (as per paragraph 7.14).

7.16 The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Servier is disappointed that the PBAC did not recommend the listing of vorasidenib for the treatment of isocitrate dehydrogenase (IDH)-mutant astrocytoma or oligodendroglioma. However, Servier is pleased that the PBAC has acknowledged the high unmet clinical need for effective treatments for IDH-mutant astrocytoma or oligodendroglioma and that treatment with vorasidenib is likely to have a meaningful impact on patient quality of life by delaying the need for chemotherapy and radiotherapy. Servier thanks the IDH-mutant astrocytoma and oligodendroglioma clinical and patient community for their valuable input to help inform the PBAC's decision making. Servier is committed to working with the Department to facilitate equitable patient access to vorasidenib as soon as possible