7.13 BEVACIZUMAB
solution for intravenous infusion, 100 mg in 4 mL and 400 mg in 16 mL,
Avastin®, Roche Products Pty Limited.

1 Purpose of Application

1.1 The minor submission requested the Section 100 (Efficient Funding of Chemotherapy), Authority Required (in writing) listing of bevacizumab for the treatment of relapsed or refractory glioblastoma.

1.2 A group of seven Australian neuro-oncologists wrote to the PBAC requesting that the Committee consider bevacizumab for this indication due to the high unmet clinical need. This letter was supported by the Cure Brain Cancer Foundation and The Brain Cancer Group. The sponsor was informed of the correspondence, and subsequently submitted a minor submission.

1.3 Bevacizumab for relapsed or progressing glioblastoma was rejected by the PBAC in November 2010 based on an uncertain clinical benefit and an unacceptably high and uncertain cost-effectiveness ratio. The current minor submission proposed a [redacted]% price reduction on the ex-manufacturer price ([redacted]), and provided updated clinical data and information regarding utilisation through the sponsor's Patient Access Program.

2 Requested listing

2.1 The restriction proposed in the pre-PBAC response is outlined below.

Name, Restriction, Manner of administration and form	Max. Qty	No.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BEVACIZUMAB Bevacizumab 400 mg/16 mL injection, 16 mL vial Bevacizumab 100 mg/4mL injection, 4 mL vial	1,800 mg	5	Published Public: $7,437.44 Private: $7,579.62 Effective Public: $[redacted] Private: $[redacted]	Avastin® Roche

Category / Program	Chemotherapy
Prescriber type:	☒Medical Practitioners
Condition:	Glioblastoma
PBS Indication:	Relapsed or recurrent glioblastoma
Treatment phase:	**Initial**
Restriction Level / Method:	Authority Required - In Writing

Clinical criteria:	Patient must have confirmed glioblastoma, AND Patient must have radiologic evidence of evaluable disease AND Patient must have evidence of symptomatic progression, AND Patient must have progressed on or be intolerant to temozolomide, AND Initial treatment must be limited to 12 weeks under this restriction, AND Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less, AND The condition must be previously untreated with this drug, AND The treatment must not exceed a dose of 10 mg per kg every 2 weeks; OR The treatment must not exceed a dose of 15 mg per kg every 3 weeks.
Administrative Advice	The authority application must be made in writing and must include: (1) a completed authority prescription form; (2) a completed Glioblastoma PBS Authority Application - Supporting Information Form; (3) evidence of confirmed glioblastoma; (4) evidence that the patient has either progressed on, or is intolerant to, temozolomide. NOTE: Special Pricing Arrangements apply.
Prescriber instructions	Symptomatic progression is defined as: Deterioration of neurologic function i.e. motor dysfunction, seizures, lack of co-ordination, changes to personality, reduced ability to communicate, neurocognitive decline A significant increase in corticosteroid dose for symptom control Deterioration of general symptoms i.e. headache, nausea, vomiting or poorly controlled vasogenic oedema.

Treatment phase:	**Continuing**
Restriction Level / Method:	Authority Required - Telephone
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition, AND Patient must not have evidence of symptomatic progression, AND Patient must not have evidence of radiographic progression AND The treatment must not exceed a dose of 10 mg per kg every 2 weeks; OR The treatment must not exceed a dose of 15 mg per kg every 3 weeks.
Administrative Advice	Applications for authorisation under this criterion may be made by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). NOTE: Special Pricing Arrangements apply

Prescriber instructions	Symptomatic progression is defined as: Deterioration of neurologic function i.e. motor dysfunction, seizures, lack of co-ordination, changes to personality, reduced ability to communicate, neurocognitive decline A significant increase in corticosteroid dose for symptom control Deterioration of general symptoms i.e. headache, nausea, vomiting or poorly controlled vasogenic oedema.

2.2 The restriction proposed in the resubmission stated that the patient must have confirmed glioblastoma, but did not specify how this should be diagnosed or confirmed. To address this, the pre-PBAC response proposed the addition of criteria in the initial PBS-restriction specifying that patients must have both radiologic evidence of evaluable disease and symptomatic progression, with a definition of symptomatic progression provided.

2.3 The submission stated that the initial restriction was intended to provide 12 weeks of therapy, corresponding with clinician advice that symptomatic benefits become apparent after approximately three months in those patients who respond to treatment. This was broadly consistent with advice provided in correspondence (from seven neuro-oncologists), that stated "patients who respond to treatment with bevacizumab generally respond rapidly, with symptomatic improvement evident within two to four doses of treatment (4-8 weeks). If a patient is not benefiting from treatment at this point, bevacizumab is typically discontinued". In addition, data from the Patient Access Program indicated that the median duration of therapy was [redacted].

2.4 The restriction proposed that for continuing access beyond the initial 12 weeks, patients must not have evidence of worsening symptomatic and radiographic progression, with symptomatic progression defined as deterioration of neurologic function, a significant increase in corticosteroid dose, or deterioration of general symptoms. The Secretariat noted that these continuation criteria are potentially subjective and that several definitions of progression exist in this setting including the Response Assessment in Neurology (RANO) criteria and the Neurologic Assessment in Neuro-Oncology (NANO) criteria. The pre-PBAC response stated that, given the limitations and subjectivity associated with these measures, their inclusion in the continuation criteria would not add substantively to an objective assessment of progression.

2.5 The proposed restriction requires patients to have progressed on or be intolerant to temozolomide, without providing specific definitions around temozolomide intolerance. The pre-PBAC response stated "in the first-line setting, temozolomide is the only therapeutic option for glioblastoma that has a proven overall survival advantage versus best supportive care and is well tolerated. Bevacizumab, while improving symptoms in those who respond, has yet to demonstrate a survival gain for this indication. Given this, it would be inappropriate for a prescriber to treat glioblastoma with bevacizumab earlier in the treatment algorithm than clinically appropriate." The PBAC agreed with the pre-PBAC response and considered that

clinicians would use temozolomide if clinically feasible and that leakage of bevacizumab into first-line glioblastoma in patients able to tolerate temozolomide was unlikely. Thus, the PBAC advised that this criterion did not require further definition.

2.6 The restriction requires patients to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 prior to commencing bevacizumab. This aligns with the inclusion criteria of various studies of bevacizumab in this setting, including the CABARET study, Taal 2014 and Wick 2017.

2.7 The PBAC considered that the restriction should specify that bevacizumab must be the sole PBS-subsidised therapy for this condition. This is consistent with the TGA approved indication for bevacizumab, which states it is indicated for use as a single agent in this condition.

2.8 The PBAC considered there was a potential risk of leakage outside the requested PBS listing, such as use in patients with lower grade tumours and spinal tumours.

2.9 The Product Information states that the recommended dose of bevacizumab for Grade IV glioma (glioblastoma) is either: 10 mg/kg every two weeks; or 15 mg/kg every three weeks. The proposed maximum amount and repeats would allow either regimen to be used: the proposed maximum amount of 1,800 mg corresponds with a dosage of 15 mg/kg in a 120 kg patient (three repeats would be required); while the maximum of five repeats corresponds with a fortnightly dosing regimen (a maximum amount of 1,200 mg would be required for this regimen). The PBAC considered that the restriction should include a note indicating that doses over 10 mg/kg every two weeks or 15 mg/kg every three weeks will not be approved, consistent with inclusion of the dosage regimen in the current PBS-listing for bevacizumab in metastatic colorectal cancer.

<u>Patient Access Program</u>

2.10 The submission and pre-PBAC response stated that patients could receive bevacizumab through a Patient Access Program, whereby patients make a payment per cycle, with the patient cost capped at approximately $[redacted] for an on-going supply. However, the substantial cost to access treatment though this program results in inequitable access, and was noted as a burden in some of the consumer comments.

2.11 The submission stated that an average of [redacted] patients have been treated with bevacizumab for relapsed glioblastoma annually over the last six years (2013-2018), as discussed further in *'Estimated PBS usage and financial implications'*.

2.12 The financial estimates assumed that [redacted] patients would be grandfathered onto the PBS, which was revised to [redacted] patients in the pre-PBAC response. The submission did not propose a Grandfather restriction, though the pre-PBAC response stated that the sponsor is willing to work with PBAC to develop an appropriate grandfathering restriction. The pre-PBAC response stated that "upon PBS-listing of bevacizumab, it is anticipated that if a patient is continuing to respond to bevacizumab and have yet to

reach the expenditure cap of approximately $[redacted], they would cease out-of-pocket payment and move onto PBS-subsidised stock via a grandfathering restriction." The PBAC considered that grandfathered access is not appropriate for patients who have already paid to access bevacizumab through the Patient Access Program, and that the sponsor should provide on-going supply (i.e. it would not be appropriate to subsidise these doses through the PBS). An alternative option may be for the sponsor to establish a compassionate access program following a positive PBAC recommendation until the date of PBS listing wherein patients are not charged for access.

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

3 Background

3.1 Bevacizumab is TGA registered for: "as a single agent, is indicated for the treatment of patients with Grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy".

3.2 In November 2010, the PBAC considered bevacizumab for the same indication as requested (i.e. as monotherapy, for the treatment of patients with relapsed or progressing glioblastoma). The submission was rejected based on uncertain clinical benefit and an unacceptably high and uncertain cost-effectiveness ratio (Section 12, Bevacizumab Public Summary Document, November 2010).

3.3 Specific issues of concern raised at the November 2010 meeting included that the PBAC considered:

- that there were no studies providing direct comparisons of bevacizumab with the chosen comparators, temozolomide, best supportive care and salvage chemotherapy. The PBAC considered there were significant comparability issues with the trials presented;
- there were limitations to the use of progression free survival (PFS) and response rates as outcomes in brain cancer, particularly in relation to the vascular endothelial growth factor (VEGF) inhibitors, which includes bevacizumab;
- that bevacizumab possibly has efficacy in overall survival (OS) but the extent of benefit had not been quantified; and
- there were further randomised controlled trials underway in the first-line treatment setting (Section 12, Bevacizumab Public Summary Document, November 2010).

3.4 Compared with the previous submission, the current minor submission:

- states that current treatment options upon relapse are older chemotherapy options such as lomustine or carboplatin and does not discuss the role of rechallenge with temozolomide, while the previous submission nominated a mixture of temozolomide, best supportive care and salvage chemotherapy as the comparator;

- states that it is now "standard practice for appropriate patients to be offered treatment with bevacizumab upon relapse", with bevacizumab being widely used through a Patient Access Program; and
- proposes a [redacted]% price reduction on the ex-manufacturer price of bevacizumab, [redacted].

4 Population and disease

4.1 Glioblastoma (also known as Grade IV glioma) is the most aggressive malignant primary brain tumour in adults and is nearly always fatal, with a median overall survival from initial diagnosis of about 12-15 months. Despite aggressive first-line treatment, tumours invariably recur. In the absence of cure, the aim of therapy is to slow progression of the cancer and reduce symptoms associated with the disease, which include headache, nausea, vomiting, seizures, behavioural changes and focal neurological deficits[1].

4.2 Standard of care treatment of newly diagnosed glioblastoma is maximal surgical resection, chemo-radiotherapy with temozolomide followed by adjuvant temozolomide. The submission stated that current treatment upon relapse typically involves chemotherapies such as lomustine or carboplatin. Median overall survival (OS) for patients with recurrent glioblastoma is approximately 6-8 months[2,3].

4.3 The submission stated that there are no therapies in late stage (Phase III) clinical development for the treatment for patients with relapsed or refractory glioblastoma.

4.4 Glioblastomas are rich in blood vessels (i.e. highly vascular) and also rich in vascular endothelial growth factor (VEGF) that promotes new blood vessel formation (the process of angiogenesis). Anti-angiogenic agents (such as bevacizumab) inhibit the process of new blood vessel formation and promote regression of existing vessels.

4.5 The PBAC considered that the proposed place in therapy - in relapsed or refractory glioblastoma, after a patient has progressed on (or is intolerant to) temozolomide – was appropriate.

[1] Sizoo E, Braam L, Postma T, et al. Symptoms and problems in the end-of-life phase of high-grade glioma patients. Neuro-Oncology. 2010;10(11)

[2] Wong E, Hess K, Gleason M, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. Journal of Clinical Oncology. 1999;17(8)

[3] Lamborn K, Yung W, Chang S. Progression-free survival: An important endpoint in evaluating therapy for recurrent high-grade gliomas. Neuro-oncology. 2008;10:162

5 Comparator

5.1 The minor resubmission did not nominate a comparator. The previous submission nominated temozolomide, salvage chemotherapy and best supportive care as the treatments that would be substituted by bevacizumab, with procarbazine being used to estimate the effectiveness of salvage chemotherapy and best supportive care (Section 12 Bevacizumab Public Summary Document, November 2010).

5.2 This minor resubmission requested listing in the same place in therapy as the previous submission (i.e. in patients who have progressed on, or who are intolerant to, prior temozolomide). However, the minor resubmission stated that current treatment options upon relapse are older chemotherapies such as lomustine or carboplatin, and did not discuss the role of rechallenge with temozolomide.

5.3 The PBAC considered that standard care (salvage chemotherapy, best supportive care) is the appropriate comparator.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (783), health care professionals (27) and organisations (5) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with bevacizumab including improved quality of life and symptomatic improvement. Benefits included improved function and well-being, improved mobility, improved cognition, improved swallowing and ability to communicate, decreased tumour size, management of radionecrosis, continued functioning at home and a reduction in steroid dose and steroid related side effects. The comments described bevacizumab as generally being well tolerated. The comments also described the social inequity and financial hardship experienced by patients accessing bevacizumab through the Patient Access Program.

6.3 The PBAC noted the correspondence received from the Cure Brain Cancer Foundation, the Brain Cancer Group, the Brain Tumour Alliance Australia, the Co-operative Trials Group for Neuro-Oncology, the Clinical Oncology Society of Australia Neuro-oncology group. The PBAC noted that these organisations were strongly supportive of PBS-listing bevacizumab in this population.

6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the bevacizumab submission categorising it as an “other supported application” based on the Friedman et al, BELOB, CABERET and AVEREG trials. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for bevacizumab, which was limited to 2 (out of a

maximum of 5, where 5 and 4 represent the grades with substantial improvement)[4].

Clinical evidence

6.5 Details of the trials presented in the submission are in the table below.

Table 1: Trials and associated reports presented in the resubmission

Trial ID / First author	Protocol title / Publication title	Publication citation
AVF3708g Friedman et al (2009)	A Phase II, multicentre, randomized, noncomparative clinical trial to evaluate the efficacy and safety of bevacizumab alone or in combination with irinotecan for the treatment of glioblastoma multiforme in first and second relapse. Research Report No. CSR AVF3708g. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma.	31 October 2008. *J Clin Oncol* 2009; 27(28): 4733-4740
BELOB Taal et al (2014)	Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial	*Lancet Oncol 2014; 15: 943–53*
CABARET Field et al 2017	Health-related quality of life outcomes from CABARET: a randomized phase 2 trial of carboplatin and bevacizumab in recurrent glioblastoma	*J Neurooncol (2017) 133:623–631*
AVAREG Brandes et al 2016	AVAREG: a phase 2, randomized, noncomparative study of fotemustine or bevacizumab for patients with recurrent glioblastoma	*Neuro-Oncology 18(9), 1304–1312, 2016*
EORTC Wick 2017	Lomustine and Bevacizumab in Progressive Glioblastoma	*N Engl J Med 2017;377:1954-63.*

6.6 The November 2010 PBAC submission included single-arm data (from study AVF3708g, published as Friedman et al 2009) which showed a median PFS of 4.2 months (95% CI: 2.9, 5.8 months) and median OS of 9.3 months (95% CI: 8.2, not reached) in patients treated with bevacizumab monotherapy (n=85). This was compared with data from Yung et al 2000, a randomised, multi-centre, open-label, phase II trial (n=225) of temozolomide versus procarbazine. Yung et al 2000 showed a median PFS of 2.9 months with temozolomide and 1.9 months with procarbazine. Data from AVF3708g and Yung et al 200 were used to inform the economic model.

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

Table 2: Studies included in the November 2010 submission for bevacizumab

Outcome	Proportion of patients (n/N) and (95% or 97.5% CI)		
	Bevacizumab studies	Temozolomide studies	Procarbazine study
Median PFS (months)			
AVF3708g	4.2 (95% CI: 2.9, 5.8)	–	–
Kreisl et al. 2009	3.7 (95% CI: 2.8, 6.0)[a]	–	–
Yung et al. 2000	–	2.9 (95% CI: NR)	1.9 (95% CI: NR)
Brada et al. 2001	–	2.1 (95% CI: NR)	–
Yang et al. 2006	–	1.8 (95% CI: NR)	–

Source: November 2010 PBAC Minutes for bevacizumab
NR = not reported

6.7 The resubmission stated that, since the previous consideration there have been further studies of bevacizumab in relapsed glioblastoma, as shown in the table below. The first row presents the results of both arms of AVF3708g.

Table 3: Studies of bevacizumab versus various comparators in patients with relapsed glioblastoma

Author	Comparator treatment	Beva	Comp	Beva	Comp	Beva	Comp	Beva	Comp
		N		ORR (CR+PR) (%)		Median PFS (months)		Median OS (months)	
Bevacizumab monotherapy versus comparator ("comp")									
AVF3708g (Friedman 2009)	Beva + irinotecan	85	82	28.2	37.8	4.2	5.6	9.2	8.7
Taal 2014 (BELOB)	lomustine	50	46	38	5	3	1	8	8
	Beva + lomustine		52		39		4		12
Field 2015 (CABARET)[a]	Beva + carboplatin	62	60	6	14	3.5	3.5	7.5	6.9
Brandes 2016 (AVAREG)	fotemustine	59	32	29	9	3.4	3.4	7.3	8.7
Bevacizumab + lomustine versus lomustine (no bevacizumab monotherapy arm)									
Wick 2017 (EORTC)	lomustine	288	149	41.5	13.9	4.2	1.5	9.1	8.6

Source: Table 1, p4 of the minor resubmission.
Bev = bevacizumab; Comp = comparator, ORR = objective response rate, CR= complete response, PR =partial response, PFS = progression free survival, OS = overall survival
[a] This is the Australian 'Caberet' study referred to in correspondence from the group of seven neuro-oncologists. The study concluded that adding carboplatin to bevacizumab resulted in more toxicity than bevacizumab alone without additional clinical benefit.

6.8 The submission further stated that a recent Cochrane review on the role of anti-angiogenic therapy for high-grade glioma (Ameratunga 2018), reported a pooled hazard ratio (HR) for PFS for bevacizumab versus no bevacizumab (6 studies with 2,362 participants) of 0.65 (95% confidence interval (CI): 0.60, 0.72). The HR for overall survival (OS) was not statistically significant (7 studies with 2,502 participants) with a HR of 0.94 (95% CI: 0.85, 1.02). These meta-analyses appeared to include studies in both the newly diagnosed and recurrent settings, however the Cochrane review

stated that the findings were consistent across both patient populations.[5] It was unclear whether the studies included in the Cochrane review used bevacizumab monotherapy or combination regimens.

6.9 The submission stated that these studies demonstrate that bevacizumab prolongs PFS in patients with recurrent glioblastoma. However, the submission acknowledged that these new data do not confirm an OS benefit for bevacizumab for this indication.

6.10 The PBAC noted that three of the new studies were randomised controlled trials that included a comparison of bevacizumab versus an older chemotherapy: BELOB (Taal 2014), AVAREG (Brandes 2016) and EORTC (Wick 2017). PBAC considered that these trials, along with the evidence presented in the previous submission, suggest that an improvement in PFS versus older chemotherapies may be a plausible outcome, however there remains significant uncertainty regarding clinical benefit, which is unchanged since the November 2010 PBAC outcome. Furthermore, the PBAC considered that these studies did not support an improvement in overall survival, which PBAC has previously considered to be the most robust indicator of benefit in brain cancer (Section 12, November 2010 PBAC Minutes).

Quality of life and other patient relevant benefits

6.11 The minor submission claimed bevacizumab provided improved quality of life due to symptomatic benefits and reductions in steroid doses.

6.12 Correspondence received from a group of seven Australian neuro-oncologists stated that, in their clinical opinion, up to 30-40% of patients appear to gain a meaningful clinical benefit from treatment with bevacizumab. The submission noted that this is generally consistent with the objective response rate (ORR) observed in the trials reported in the minor submission.

6.13 In terms of patient-relevant benefits, the correspondence stated that patients treated with bevacizumab "experience a reduction in swelling on the brain, and an improvement in general symptoms such as headaches as well as their specific neurologic deficits such as movement and motor function, coordination, changes to personality and ability to communicate. A reduction in dexamethasone use whilst on bevacizumab also reduces the risk of corticosteroid-related complications. This contributes in many cases to improving a patient's social, physical, functional and emotional well-being and that of their family carers."

6.14 The submission acknowledged that quality of life data have not been captured that would enable translation of the PFS benefit into a patient-relevant outcome. The PBAC noted that Wick 2017 did not find an improvement in neurocognitive function or health related quality of life, and therefore considered that the magnitude of benefit in terms of quality of life outcomes remains uncertain.

[5] Ameratunga M, Pavlakis N, Wheeler H, et al. Anti-angiogenic therapy for high-grade glioma (review). Cochrane Database of Systematic Reviews. 2018(11)

Durable response

6.15 The submission claimed that bevacizumab has been shown to result in a small but clinically relevant proportion of patients achieving a long-lasting response. The submission cited data from the Patient Access Program that showed that [redacted]% of patients continue bevacizumab for over six months, and [redacted]% continue for over 12 months. It was unclear whether treatment duration was an adequate proxy for duration of response, particularly in the context of patients having paid a significant upfront cost for bevacizumab, and given the lack of alternative treatment options and the lack of a control arm for this comparison. The submission stated that while several attempts have been made to predict which patients will respond, it is currently not possible to identify who will benefit from treatment with bevacizumab.

Adverse events

6.16 The minor submission did not provide information on comparative harms or adverse events, but stated that current treatments typically involve older chemotherapies, which it stated are associated with significant toxicities.

6.17 The PBAC noted that bevacizumab was associated with some toxicities such as hypertension, thrombosis, and for a small group of patients there could be a risk of intracranial haemorrhage.

Clinical claim

6.18 The minor submission did not make a clinical claim.

6.19 The PBAC considered that it remains uncertain whether bevacizumab is superior to best supportive care and older chemotherapies in terms of PFS as the clinical meaningfulness of PFS as an endpoint in this condition is unknown. Furthermore, the PBAC considered that the magnitude of benefit of bevacizumab on quality of life and control of symptoms were difficult to quantify, given the lack of data reliably measuring quality of life in this setting. The PBAC recalled its previous advice that overall survival remains the most robust indicator of benefit in brain cancer (Section 12, November 2010 PBAC Minutes), however considered that given the high clinical need for this indication, PFS and quality of life outcomes could be evaluated as part of a cost-effectiveness analysis, recognising though that the clinical benefit of these outcomes remains highly uncertain based on the evidence presented.

6.20 The PBAC considered that there was insufficient information in the minor submission to draw a conclusion around the comparative safety and the risk versus benefit of bevacizumab. The PBAC considered that bevacizumab is generally well tolerated when used in other disease settings, however in the context of the uncertain clinical benefit in glioblastoma, it would be useful and important to evaluate the risk versus benefit profile.

Economic analysis

6.21 The submission stated that the new data do not confirm an OS benefit for bevacizumab for this indication. The submission further stated that "while a PFS benefit is clear, quality-of-life data have not been captured that would enable translation of this benefit into a patient-relevant outcome". Given this, the submission considered that there are no new data to support a cost-effectiveness evaluation of this indication via a traditional ICER approach.

Drug cost/patient/course: $[redacted]

6.22 The cost of bevacizumab per patient per course was based on the proposed effective bevacizumab price per dose ($[redacted], weighted between private and public use), which assumed 2 x 400 mg vials (based on the average patient weight in the Patient Access Program of [redacted] kg, and a dose of 10 mg/kg every two weeks). An average of [redacted] doses per patient was assumed based on an average of [redacted] months of treatment in the Patient Access Program.

6.23 This is lower than the price currently being paid by patients for continuing access to bevacizumab through the Patient Access Program (which the submission stated had an approximate cost to the patient of up to $[redacted]).

Estimated PBS usage & financial implications

6.24 The minor submission used an epidemiological approach to estimate the use and financial implications of listing bevacizumab for the treatment of relapsed or refractory glioblastoma.

6.25 The incidence of brain cancer in Australia was based on the Australia Cancer Incidence and Mortality (ACIM) workbooks titled 'Brain Cancer in Australia (AIHW Statistics)' (2017). Data from 2009 to 2014 were extrapolated based on a linear trend. The ACIM workbook 'Brain Cancer in Australia' (2018) was published in December 2018 (so was not available to the sponsor when the minor submission was submitted), and indicated a higher rate of growth in the incidence of brain cancer than some of the previous ACIM workbooks.

6.26 The minor submission assumed that 70% of primary malignant brain tumours are gliomas and 52% of these are glioblastomas (i.e. overall, the minor submission assumed that 36% of brain cancers are glioblastoma). These percentages were applied to the prevalence estimates to derive the number of patients in Australia with glioblastoma. The submission cited The Cure Brain Cancer Foundation and the '2009 Clinical Practice Guidelines for the Management of Adult Gliomas: Astrocytomas and Oligodendrogliomas' as the sources for these proportions. However, these were not primary sources and the original derivation of these proportions was unclear. During preparation of the Minor Overview, the Secretariat noted that an alternative AIHW

publication 'Brain and other central nervous system cancers'[6] directly reported the number of incident cases of glioblastoma in Australia in 2013, and thus provided an alternative source for estimating the number of patients with glioblastoma.

6.27 The submission then estimated the prevalence of brain cancer in Australia by assuming that 20% of incident patients from the previous year would survive. During preparation of the Minor Overview, the Secretariat considered that basing the estimates on the prevalence, rather than the incidence, may have overestimated the number of eligible patients in Years 2 to 6 given the short duration of treatment (and the application of a mean treatment duration), the high mortality rate, and the application of assumptions around the proportion of patients who would be treated (i.e. patients not treated in Year 1 who survive into Year 2 would be unlikely to re-enter the eligible patient pool).

6.28 The minor submission assumed that [redacted]% of glioblastoma patients would be appropriate for treatment with bevacizumab. The minor submission stated "clinicians indicate that of those who receive temozolomide as part of their first-line treatment regimen, approximately [redacted]% will be eligible for bevacizumab in the relapsed setting". The minor submission further stated that "it is generally accepted that all patients will relapse after first-line treatment", but that many patients die prior to completing first line therapy and a proportion are too unwell for bevacizumab treatment (e.g. patients with poor performance status, who are neurologically too unwell or with low platelet counts).

6.29 As no uptake assumption was applied, the minor submission effectively assumed that there would be 100% uptake in eligible patients. The minor submission noted that there is high utilisation of bevacizumab through the Patient Access Program despite significant upfront costs, and there is lack of effective treatment options in this setting.

6.30 The minor submission assumed that [redacted] patients would be grandfathered, based on utilisation of the Patient Access Program from 17 November to 18 November 2018. These [redacted] patients were added to the number of patients treated in Year 1. The pre-PBAC response reduced this to [redacted] grandfathered patients based on the number of patients who received bevacizumab through the Patient Access Program during the previous [redacted] (which is the mean treatment duration). As discussed in the 'Requested listing' section, the PBAC considered that if patients have already paid to access bevacizumab through the Patient Access Program it would not be appropriate to subsidise these doses through the PBS (i.e. on-going supply should be provided by the sponsor). Further, specifically including grandfathered patients in the financial estimates may double-count patient numbers, as these patients are likely to already be included in the eligible population.

[6] https://www.aihw.gov.au/getmedia/d2914a17-052e-45bb-bbd3-17047c7d5da1/20566.pdf.aspx?inline=true

Table 4: Estimated use and financial implications (from the minor submission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients with brain cancer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with glioblastoma (70% x 52%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients eligible for bevacizumab ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed PBS/RPBS [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of bevacizumab						
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS/MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[a] Assuming 11 scripts per patient, based on the mean duration of treatment in the Patient Access Program of [redacted] months (and one dose every two weeks)

Source: Table 5, p11 of the minor submission and Section 4 workbook 'Background and Assumptions' 'Epidemiology and Patient Number' 'Net cost of drug to PBS/RPBS' 'Cost to Govt for MBS' 'Net cost of drug to Government'

6.31 The minor submission estimated a net cost to the PBS/RPBS of less than $10 million in Year 6 of listing, with a total net cost to the PBS/RPBS of $30 to $60 million over the first 6 years of listing.

6.32 The minor submission estimated that around less than 10,000 patients would be treated per year in Years 2 to 6. It is noted that around less than 10,000 new patients per year have accessed bevacizumab through the Patient Access Program (based on the average number of new patients each year between 2014 and 2017), which would represent over 50% of the estimated treated population.

6.33 The pre-PBAC response:

- updated the incidence of brain cancer based on the ACIM work book 'Brain Cancer in Australia' published in December 2018;
- updated the incidence of glioblastoma based on the AIHW publication 'Brain and other central nervous system cancers' which directly reported the number of patients with glioblastoma. The pre-PBAC response used this estimate to derive the proportion of brain cancer cases that are glioblastoma (updated from 36% to 61%). The PBAC noted that this substantially increased the number of eligible patients;
- revised the estimate of patient numbers to be based on incidence, rather than prevalence. This was reasonable;

- reduced the MBS fees for administration to reflect shorter infusion times for subsequent doses and amending the calculation of patient co-payments. These changes were reasonable; and
- reduced the number of grandfathered patients from [redacted] to [redacted], as outlined in Paragraph 6.30.

6.34 The revisions in the pre-PBAC response increased the estimated cost to the PBS/RPBS to less than $10 million in Year 6 of listing, with a total net cost to the PBS/RPBS of $30 to $60 million over the first 6 years of listing.

Financial Management – Risk Sharing Arrangements

6.35 There was no Risk Sharing Arrangement (RSA) proposed in the submission.

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation on the Section 100 Authority Required listing of bevacizumab for the treatment of relapsed or refractory glioblastoma. The PBAC considered that although PFS and quality of life improvements are plausible outcomes, there remains significant uncertainty regarding the clinical benefit and the magnitude of any benefit. As a result, the PBAC considered that it was unable to determine the cost-effectiveness of bevacizumab in relapsed or refractory glioblastoma based on the information provided in the minor submission, and requested further information to help determine the cost-effectiveness of this therapy.

7.2 In deciding to defer, the PBAC acknowledged the high unmet clinical need in the proposed population.

7.3 The PBAC acknowledged the large number of comments from consumers, clinicians and organisations, which were generally supportive of listing bevacizumab for the treatment of relapsed or refractory glioblastoma. The PBAC noted that the comments described a range of benefits of treatment with bevacizumab including improved quality of life, symptomatic improvement, improved neurological function, improved mobility, and a reduction in steroid dose and steroid related side effects.

7.4 The PBAC noted that correspondence received from a group of seven Australian neuro-oncologists stated that, in their clinical opinion, up to 30-40% of patients appear to gain a meaningful clinical benefit from treatment with bevacizumab.

7.5 The PBAC noted that the minor resubmission had provided three new open-label randomised controlled trials, conducted since the original submission in 2010, that compared bevacizumab with older chemotherapies: BELOB (Taal 2014), AVAREG (Brandes 2016) and EORTC (Wick 2017). The PBAC considered that these trials, along with the evidence presented in the previous submission, suggested a possible improvement in PFS versus older chemotherapies, however there remains uncertainty

regarding the clinical benefit and magnitude of any benefit. Furthermore, the PBAC considered that no evidence had been presented that demonstrated that bevacizumab is associated with an improvement in overall survival, which the PBAC has previously considered to be the most robust measure of outcome in brain cancer.

7.6 The PBAC noted that improvement in PFS, quality of life and control of symptoms may all be plausible outcomes. However, the PBAC considered that the magnitude and extent of these potential benefits were difficult to quantify given the lack of data measuring quality of life in this setting, the lack of consistent clinical benefit demonstrated across the evidence presented, and because the clinical meaningfulness of PFS in this condition is unknown. Overall, the PBAC considered that there was insufficient information in the minor submission to accurately quantify the comparative benefit of bevacizumab.

7.7 The PBAC considered that bevacizumab is generally well tolerated when used in other disease settings, however the PBAC considered there was insufficient information in the minor submission to draw a conclusion around the comparative safety in this context. The PBAC considered that there remains uncertainty regarding the risk versus benefit profile of bevacizumab in glioblastoma, and requested further information in order to assess the cost-effectiveness.

7.8 The PBAC acknowledged the high financial burden on patients of accessing bevacizumab through the sponsor's patient access program, reported by patients to be at a cost of up to around $[redacted] per patient. The PBAC noted that a high proportion of patients with relapsed glioblastoma (approximately [redacted] patients annually) are prescribed and access bevacizumab despite the high out-of-pocket costs, and considered that this demonstrates a high perceived benefit of bevacizumab and a strong willingness to pay among patients.

7.9 The PBAC noted that a [redacted]% reduction to the effective price had been offered, which represented a substantial reduction to the price offered in the previous submission and considered that this, along with the sponsors willingness to enter into an RSA, were positive steps to mitigate its previous concerns regarding the cost-effectiveness of bevacizumab. The PBAC noted that the minor submission had not provided information regarding the cost-effectiveness of bevacizumab and acknowledged that there was unlikely to be sufficient data available to construct a reliable economic model in this particular setting. However, the PBAC considered additional information was required to establish a basis for determining the cost-effectiveness of bevacizumab in this indication.

7.10 The PBAC noted that the sponsor provided updated financial estimates in its pre-PBAC response that substantially increased the estimated cost to the PBS/RPBS from $30 to 60 million over 6 years to $30 to $60 million over 6 years. The PBAC considered that the estimated cost to the PBS/RPBS was high, particularly in the context of a therapy with primarily symptomatic benefits, with limited robust data on efficacy, and in the context of information not being presented in the submission regarding cost-

effectiveness.

7.11 The PBAC considered that the eligible population is uncertain and there is a risk of leakage outside the requested PBS listing (e.g. in patients with lower grade tumours and spinal tumours). The PBAC considered that an RSA in the form of an expenditure cap would be required to manage these risks, and noted that the pre-PBAC response stated that the sponsor is willing to work with the PBAC to negotiate a RSA. The PBAC considered than an RSA may also help to contain the total cost to Government in the context of the uncertain cost-effectiveness.

7.12 The PBAC considered that grandfathered access via the PBS would not be appropriate for patients who have already paid to access bevacizumab through the Patient Access Program, and considered the sponsor should provide on-going supply for these patients.

7.13 As part of the deferral process, the PBAC requested that the sponsor provide further information regarding the cost-effectiveness of bevacizumab in this indication and details of an RSA proposal.

7.14 The PBAC noted that this submission is not eligible for an Independent Review as it has been deferred.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Roche is committed to addressing the outstanding matters raised by the PBAC to bring bevacizumab to patients with relapsed or refractory gliobastoma at the earliest opportunity.