

7.01 BEVACIZUMAB

**solution for intravenous infusion, 100 mg in 4 mL and
400 mg in 16 mL,
Avastin[®], Roche Products Pty Limited**

1 Purpose of Item

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

2 Background

- 2.1 The resubmission aimed to address concerns raised by the PBAC in its March 2019 deferral of bevacizumab for this indication.
- 2.2 In its March 2019 deferral “the PBAC considered that although progression free survival (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.” (Paragraph 7.1, March 2019 Public Summary Document (PSD)).
- 2.3 In March 2019, the PBAC also considered that there was uncertainty regarding the risk versus benefit profile of bevacizumab in glioblastoma and that the eligible population is uncertain and there is a risk of leakage outside the requested PBS listing (Paragraphs 7.1 and 7.7, March 2019 PSD).
- 2.4 To address these concerns, the resubmission:
- provided information regarding the safety of bevacizumab in glioblastoma;
 - provided cost-effectiveness analyses (cost per additional year without progression and cost per responder);
 - provided updated data from the Patient Access Program;
 - updated the financial estimates to reduce the cost to the PBS/RPBS; and
 - proposed a risk-sharing arrangement (RSA).

3 Requested listing

3.1 The restriction proposed in the March 2019 pre-PBAC response is outlined below. Suggested additions by the Secretariat are in italics and deletions are in strikethrough.

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

Category / Program	Chemotherapy
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Condition:	Glioblastoma
PBS Indication:	Relapsed or recurrent glioblastoma
Treatment phase:	Initial
Restriction Level / Method:	Authority Required - In Writing
Clinical criteria:	<p>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 <i>The treatment must be the sole PBS-subsidised therapy for this condition</i> 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.</p>
Administrative Advice	<p>The authority application must be made in writing and must include:</p> <p>(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.</p> <p>NOTE: Special Pricing Arrangements apply.</p>

Public Summary Document – May 2019 PBAC Meeting

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

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 <i>The treatment must be the sole PBS-subsidised therapy for this condition</i> 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. which may include motor dysfunction, seizures, lack of co-ordination, changes to personality, reduced ability to communicate, neurocognitive decline OR A significant increase in corticosteroid dose for symptom control Deterioration of general symptoms <i>Increasing symptoms of raised intracranial pressure which may include i.e. headache, nausea, vomiting or poorly controlled vasogenic oedema</i>

- 3.2 The proposed price was █% lower than the price proposed in the November 2010 submission (based on the effective Approved Ex-Manufacturer Price for an 800 mg dose) and the same as the price proposed in the March 2019 submission. The proposed price is consistent with the price for advanced cervical cancer, which is the lowest price indication listed on the PBS. The resubmission stated that the sponsor is anticipating that a biosimilar of bevacizumab will enter the market during the second year of listing, and that while the exact timing of PBS-listing is not known, the listing of a biosimilar will trigger a 25% statutory price reduction.
- 3.3 In its previous consideration, the PBAC considered that the restriction should specify that bevacizumab must be the sole PBS-subsidised therapy for this condition (Paragraph 2.7, March 2019 PSD). This was consistent with the TGA approved

indication for bevacizumab, which states it is indicated for use as a single agent in this condition. However, the resubmission proposed that bevacizumab be listed for use in combination with chemotherapy and provided new information from a survey of neuro-oncologists, which indicated that 55% of patients use bevacizumab as monotherapy and 45% of patients use bevacizumab in combination with chemotherapy (based on responses from three neuro-oncologists experienced in the use of bevacizumab to treat relapsed glioblastoma). As such, the PBAC advised that the restriction should not specify whether bevacizumab should be used as monotherapy (or in combination with chemotherapy) to allow clinician judgement.

- 3.4 The restriction proposed in the previous submission stated that the patient must have confirmed glioblastoma, but did not specify how this should be diagnosed or confirmed. To address this, the previous 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 after treatment in the first-line setting (unless the patient is intolerant to temozolomide). The PBAC considered that symptomatic progression should be defined as: deterioration of neurologic function (which may include motor dysfunction, seizures, lack of co-ordination, changes to personality, reduced ability to communicate or neurocognitive decline) or increasing symptoms of raised intracranial pressure (which may include headache, nausea, vomiting or poorly controlled vasogenic oedema). The PBAC considered that ‘a significant increase in corticosteroid dose for symptom control’ was not required because corticosteroids would be increased due to deterioration of neurological function or raised intracranial pressure, rather than a marker on its own.
- 3.5 The submission proposed an ‘initial treatment’ restriction that would provide 12 weeks of therapy. The PBAC noted that advice provided in correspondence (from seven neuro-oncologists) 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”. As such, the PBAC considered that an initial treatment period of eight weeks (rather than 12 weeks) would be sufficient to determine patient response and to minimise unnecessary use in those patients who do not respond.
- 3.6 For continuing access beyond the initial treatment phase, patients must not have evidence of worsening symptomatic progression. The resubmission stated this would permit continuing treatment only in patients benefiting from therapy. The PBAC considered that the definition of symptomatic progression should align with the initial restriction. The PBAC considered that it was not necessary to specify that the ‘patient must not have evidence of radiographic progression’ in the continuation criteria as this may encourage unnecessary imaging procedures and symptomatic progression alone may be sufficient.

- 3.7 While the resubmission did not propose a grandfathered restriction it stated that it “expects some patients receiving bevacizumab under the Patient Access Program to be grandfathered onto the PBS” (page 15). However, in March 2019, 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).” (Paragraph 6.30, March 2019 PSD). The March 2019 PSD also outlined that “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” (Paragraph 2.12, March 2019 PSD). The pre-PBAC response stated that the sponsor is willing to establish a compassionate access program, following the point at which pricing and the Risk Share Arrangement (RSA) is agreed upon.
- 3.8 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, with a note indicating that doses over 10 mg/kg every two weeks or 15 mg/kg every three weeks will not be approved. The PBAC noted this would correspond with a maximum of 3 repeats in the initial setting (with a note stating that ‘initial treatment must be limited to 8 weeks under this restriction’). The PBAC noted that the submission had requested a maximum of 5 repeats in the continuation setting, which would allow for 12 weeks of therapy per original prescription. The PBAC considered this was appropriate in the context of a rapidly progressing condition.

4 Comparator

- 4.1 At the March 2019 meeting, the PBAC considered that standard care (salvage chemotherapy, best supportive care) was the appropriate comparator (Paragraph 5.3, March 2019 PSD).
- 4.2 The resubmission used lomustine as a proxy for standard care (salvage chemotherapy) stating that, according to a survey of neuro-oncologists, 73% of patients with relapsed/refractory glioblastoma currently receive lomustine rather than temozolomide or another chemotherapy, and that “no current second-line therapies for these patients are considered effective”.
- 4.3 The resubmission stated that no other therapies are currently in late stage (Phase III) clinical development for the treatment of relapsed or refractory glioblastoma.

5 Consideration of the evidence

Comparative efficacy

- 5.1 Details of the key studies presented in the resubmission are in the table below. No new studies were included compared with the previous submission.

Table 1: Trials and associated reports presented in the resubmission

Trial ID / First author	Protocol title / Publication title	Publication citation
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	<i>Lancet Oncol</i> 2014; 15: 943–53
AVAREG Brandes et al 2016	AVAREG: a phase 2, randomized, noncomparative study of fotemustine or bevacizumab for patients with recurrent glioblastoma	<i>Neuro-Oncology</i> 18(9), 1304–1312, 2016
EORTC Wick et al 2017	Lomustine and Bevacizumab in Progressive Glioblastoma	<i>N Engl J Med</i> 2017;377:1954–63.

5.2 The key features of the studies presented are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Treatments	Patient population	Outcomes
Taal 2014 (BELOB)	153	Phase 2, R, OL, MC	1) beva 2) beva+lomustine 3) lomustine	1st recurrence of glioblastoma after chemoradiotherapy	OS at 9 months, Median PFS
Wick 2017 (EORTC)	437	Phase 3, R,	1) beva+lomustine 2) lomustine	1st recurrence of glioblastoma after chemoradiotherapy	OS, PFS
Brandes 2016 (AVAREG)	91	Phase 2, R, OL, “non-comparative”	1) beva 2) fotemustine	1st recurrence of glioblastoma after chemoradiotherapy	OS at 6 months

Source: Ameratunga et al,

Abbreviations: DB, double blind; MC, multi-centre; OL, open-label; R, randomised.

5.3 The resubmission stated that Wick 2017 and Taal 2014 were the only randomised controlled trials (RCT) of bevacizumab versus no anti-angiogenic therapy in recurrent glioblastoma that were identified and included in a recent Cochrane review of anti-angiogenic therapy for high-grade glioma (Ameratunga et al 2018). Both studies compared bevacizumab in combination with chemotherapy (lomustine) versus chemotherapy (lomustine) alone, with Taal 2014 also comparing bevacizumab monotherapy versus chemotherapy (lomustine). The resubmission conducted a pooled analysis of both studies.

5.4 While Brandes 2016 also compared bevacizumab to chemotherapy (fotemustine) in recurrent glioblastoma, it was excluded from the Cochrane review because it was a “non-comparative” RCT (the publication states that no formal efficacy comparison was made between the treatment arms) and that there were inadequate data to assess the endpoints of the Cochrane review’s meta-analysis (hazard ratios for OS and PFS). The resubmission also excluded Brandes 2016 from its cost-effectiveness analysis as the publication did not report the median number of treatment cycles or fotemustine doses.

5.5 The resubmission stated that Wick 2017 and Taal 2014 used the Response Assessment in Neuro-Oncology (RANO) criteria to define disease progression and response (Wen

et al 2010),¹ with the objective response rate (ORR) being the sum of the complete and partial response rates.

- 5.6 The results of the studies are presented below for bevacizumab monotherapy for the outcomes of objective response rate and median progression free survival (PFS).

Table 3: Bevacizumab monotherapy versus salvage chemotherapy (relapsed glioblastoma)

Comparator treatment	Beva	Chemo	Beva	Chemo	Beva	Chemo	Beva	Chemo
	N		Median number of 6-week cycles (IQR)		ORR (CR+PR) (%)		Median PFS (months)	
Taal 2014 (BELOB) Phase 2 (up to 46 months)								
Lomustine	50	46	2 (1-3)	1 (1-3)	38% (24, 53)	5% (1, 7)	3 (3, 4)	1 (1, 3)
Brandes 2016 (AVAREG) Phase 2 (up to 22 months). Excluded from Cochrane review.								
Fotemustine	59	32	NR	NR	29%	9%	3.4	3.4

Source: Table 1, p4 of the minor resubmission.

Beva = bevacizumab; ORR = objective response rate, CR= complete response, IQR = inter-quartile range; NR = not reported, PR =partial response, PFS = progression free survival, OS = overall survival

Bevacizumab dose: 10 mg/kg q2w

^a Lomustine dose: 110 mg/m² q6w for 6 cycles

^b Fotemustine dose: Induction: 75 mg/m² on days 1, 8, 15. Maintenance: 100 mg/m² (max.) q3w

- 5.7 The results of the studies are presented below for bevacizumab in combination with lomustine.

¹ The RANO criteria define progression as: "Progression is defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids; a significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events; the appearance of any new lesions; clear progression of nonmeasurable lesions; or definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose". Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group. Wen P, et al; Journal of Clinical Oncology 2010 28:11, 1963-1972.

Table 4: Bevacizumab plus lomustine versus lomustine (relapsed glioblastoma)

Comparator treatment	Bev+Lom	Lom	Bev+Lom	Lom	Bev+Lom	Lom	Bev+Lom	Lom
	N		Median number of 6-week cycles (IQR)		ORR (CR+PR), %		Median PFS, months (95% CI)	
Taal 2014 (BELOB) Phase 2 (up to 46 months)								
Lomustine ^a	52	46	3 (2-7)	1 (1-3)	39%	5% (1, 7)	4	1 (1, 3)
Wick 2017 (EORTC) Phase 3 (37 months)								
Lomustine ^b	288	149	3 ^c	1	41.5% (35.5, 47.8)	13.9% (8.6, 20.8)	4.2 (3.7, 4.3)	1.5 (1.5, 2.5)
Pooled analysis	332 ^d	195	3	1	40.5%	11.8%	4.17	1.38

Source: Table 1, p4 of the minor resubmission.

Bev = bevacizumab; CR= complete response; Lom = lomustine; ORR = objective response rate; OS = overall survival; PR =partial response; PFS = progression free survival

Bevacizumab dose: 10 mg/kg q2w

^a Lomustine dose in monotherapy arm: 110 mg/m² q6w (max. 6 cycles). In the combination arm, most patients (44/52) received lomustine 90 mg/m² q6w, the remaining patients (8/52) received 110 mg/m² q6w. While the resubmission also presented the results separately for the different lomustine doses, only the combined results are presented here for simplicity and given the small number of patients who received the higher dose.

^b Lomustine dose in monotherapy arm: 110 mg/m² q6w (max. 6 cycles). Lomustine dose in the combination arm: 90 mg/m² q6w

^c Not reported in the publication. Estimated by the resubmission based on patient numbers and median cycles in the other treatment groups.

^d The resubmission's pooled analysis did not include the 8 patients who received lomustine 110 mg/m² q6w in the combination arm.

- 5.8 The PBAC noted that the median duration of treatment in the Patient Access Program was 15 weeks (3.4 months), which was broadly consistent with the median PFS observed across the studies (3 to 4.2 months).
- 5.9 The resubmission stated that the ORRs with bevacizumab are consistent with the observations of seven senior Australian neuro-oncologists involved in the care of patients with glioblastoma, that “up to 30-40% of patients appear to gain a meaningful clinical benefit from treatment with bevacizumab”. The resubmission stated that these improvements include: a reduction in swelling on the brain; an improvement in overall symptoms (e.g., headaches) and specific neurological deficits (e.g., movement and motor function, coordination, changes to personality, ability to communicate); a reduction in dexamethasone dose and corticosteroid-related complications (pneumocystis pneumonia, candidiasis, diabetes, psychosis, myopathy); improvements in the social, physical, functional and emotional well-being of patients and carers.
- 5.10 The previous submission claimed that bevacizumab has been shown to result in a small but clinically relevant proportion of patients achieving a long-lasting response. The resubmission provided updated data from the Patient Access Program (based on data from █████ patients who were treated with bevacizumab for relapsed or refractory glioblastoma between 10 October 2010 and 29 March 2019) that showed that 33% of patients continue bevacizumab for six months or more, 12% continue for 12 months or more, and 5% continue for 18 months or more. As stated in the March 2019 PSD, 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 (Paragraph 6.15, March 2019 PSD).

Comparative harms

- 5.11 In March 2017 “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” (Paragraph 6.20, March 2019 PSD).
- 5.12 To address this, the resubmission referred to the Cochrane review of anti-angiogenic therapy for high-grade glioma, which stated “similar to trials of anti-angiogenic therapies in other solid tumours, adverse events related to this class of therapy (in glioblastoma) included hypertension and proteinuria, poor wound healing, and the potential for thromboembolic events, although generally, the rate of grade 3 and 4 adverse events was low (< 14.1%) and in keeping with the literature”. The report further stated “the studies of bevacizumab reported similar rates of common and serious toxicities including wound complications (0.8%to 3.3%), hypertension (4.2% to 27%), thromboembolic complications (2.5% to 7.7%), and gastrointestinal perforation (0.8% to 5.3%). These findings mainly differed due to different combination regimens and different populations of people” (Ameratunga 2018, p.2, 19).

Adverse events reported in Taal 2014 (which included a bevacizumab monotherapy arm) are reported below.

Table 5: Grade 3 or higher adverse events reported in Taal 2014

Grade 3 or higher adverse event	Beva N = 50	Beva+ lom N = 52	Lomustine N= 46
Hypertension	13 (26%)	14 (27%)	3 (7%)
Infection	3 (6%)	5 (10%)	2 (4%)
Thrombosis	0	3 (6%)	0
Platelet count	1 (2%)	9 (17%)	9 (20%)
White cell count	0	6 (12%)	8 (17%)
Nausea and vomiting	1 (2%)	1 (2%)	2 (4%)

Source: Table 2, Taal 2014

- 5.13 The resubmission stated that intracranial haemorrhage (ICH) is the adverse event of most concern when considering using bevacizumab to treat glioblastoma. Wick 2017 reported that one patient died due to ICH in the bevacizumab + lomustine arm (out of 283 patients). The resubmission also stated that a retrospective study of 1,024 patients with ICH and 4,191 patients who received bevacizumab for treatment of cancer at a US medical centre demonstrated ICH in cancer patients treated with bevacizumab was rare (12 patients) and the rate did not appear to be increased over the baseline ICH rate in a similar population not treated with bevacizumab (Khasraw et al 2012).

Benefits/harms

- 5.14 A summary of the comparative benefits and harms for bevacizumab (as monotherapy, or in combination with lomustine) versus lomustine is presented in the table below.

Table 6: Summary of comparative benefits and harms

Benefits								
Overall response rate								
Study	Beva	Beva+ lom	Lomustine	Events/100 patients			RD versus lom	
				Beva	Beva+ lom	Lomustine	Beva	Beva+ lom
Taal 2014	18/48	19/49	2/41	38	39	5	33%	34%
Wick 2017	-	108/260	19/137	-	42	14	-	28%
Harms								
Study	Beva	Beva+ lom	Lomustine	Events/100 patients			RD versus lom	
				Beva	Beva+ lom	Lomustine	Beva	Beva+ lom
Hypertension (Grade 3 or higher) (reported as arterial hypertension in Wick 2017)								
Taal 2014	13/50	14/52	3/46	26	27	7	20%	20%
Wick 2017	-	67/283	1/147	-	24	1	-	23%
Thrombosis (Grade 3 or higher) (reported as pulmonary embolism in Wick 2017)								
Taal 2014	0/50	3/52	0/46	0	6	0	0%	6%
Wick 2017	-	14/283	0/147	-	5	0	-	5%

Source: Compiled during preparation of the overview based on Table 2, text p1958, Wick 2017; Tables 2-3, Taal 2014.

5.15 On the basis of direct evidence presented in the submission, for every 100 patients treated with bevacizumab monotherapy in comparison to lomustine (for standard care):

- Approximately 33 additional patients would achieve an objective response;
- Approximately 20 additional patients would experience Grade 3 or higher hypertension.

Clinical claim

5.16 The resubmission did not make a clinical claim. The PBAC considered that bevacizumab has superior efficacy compared with standard care (including older chemotherapies) in terms of response rates and PFS, and hence quality of life through control over deterioration and symptom management. The PBAC also considered that bevacizumab has non-inferior safety compared with standard care (including older chemotherapies).

Economic analysis

- 5.17 The November 2010 submission estimated an incremental cost-effectiveness ratio of \$75,000 – \$105,000 per quality-adjusted life year. However, the economic evaluation relied on a gain in overall survival (OS), which was implicitly incorporated within the model structure with bevacizumab being assumed to add an additional line of therapy in the treatment algorithm. Thus, the results of the previous model (if updated for resource costs such as the ■% lower bevacizumab price) are not relevant as the March 2019 submission acknowledged that the data do not confirm an OS benefit for bevacizumab in this condition.

Trial-based cost-effectiveness analyses

- 5.18 The resubmission conducted cost-effectiveness analyses based on the cost per additional year without progression and cost per additional responder. These are reported below (bevacizumab monotherapy and combination therapy have been reported in separate tables).
- 5.19 No costs were included in the comparator arm (standard care, represented by lomustine in the clinical trials) as lomustine is not PBS-listed. This was conservative. The cost of bevacizumab was based on the 10mg/kg every two week regimen (which was used in Wick 2017 and Taal 2014) and an average patient weight of 77kg (based on the average weight of patients in the Patient Access Program).

Bevacizumab monotherapy

Table 7: Cost-effectiveness analysis based on Taal 2014: bevacizumab monotherapy

	Bevacizumab	Lomustine	Difference
Drug cost per dose	\$ [REDACTED]	\$0	
Administration cost per dose	\$ [REDACTED] to \$ [REDACTED]	\$0	
Drug and admin cost per dose	\$ [REDACTED] to \$ [REDACTED]		
Median doses (cycles * 3)	2 * 3	1 * 3	3
Total cost per patient	\$ [REDACTED]	\$0	\$ [REDACTED]
Median PFS, months (years)	3 (0.25)	1 (0.125)	2 (0.167)
Cost per additional year without progression			\$ [REDACTED]
ORR, %	38%	5%	33%
Cost per additional responder (ORR)			\$ [REDACTED]

Abbreviations: ORR, objective response rate (complete or partial response); PFS, progression-free survival

Bevacizumab in combination with chemotherapy

Table 8: Cost-effectiveness analysis for combination therapy - cost per additional year without progression

	Beva + Lomustine	Lomustine	Difference
Taal 2014 (all doses)			
Median doses (cycles * 3)	9	3	6
Total cost per patient	\$ [REDACTED]	\$0	\$ [REDACTED]
Median PFS, months (years)	4	1	3 (0.25 years)
Cost per additional year without progression			\$ [REDACTED]
Wick 2017			
Median doses (cycles * 3)	9	3	6
Total cost per patient	\$ [REDACTED]	\$0	\$ [REDACTED]
Median PFS, months (years)	4.2	1.5	2.7 (0.23 years)
Cost per additional year without progression			\$ [REDACTED]
Pooled analysis (Taal 2014 and Wick 2017)			
Median PFS, months (years)	4.2	1.4	2.8 (0.23 years)
Cost per additional year without progression			\$ [REDACTED]

Abbreviations: Beva, bevacizumab; N, number of patients; PFS, progression-free survival

Public Summary Document – May 2019 PBAC Meeting

Table 9: Cost-effectiveness analysis for combination therapy - cost per additional responder

	Beva + Lomustine	Lomustine	Difference
Taal 2014 (all doses)			
ORR, %	39%	5%	34%
Cost per additional responder			\$ [REDACTED]
Wick 2017			
ORR, %	41.5%	13.9%	27.6%
Cost per additional responder			\$ [REDACTED]
Pooled analysis (Taal 2014 and Wick 2017)			
ORR, %	40.5%	11.8%	28.7%
Cost per additional responder			\$ [REDACTED]

Abbreviations: Beva, bevacizumab; N, number of patients; ORR, objective response rate (complete or partial response);

5.20 The cost per responder (ORR) ranged from approximately \$ [REDACTED] (bevacizumab monotherapy) to \$ [REDACTED] (combination therapy), based on ORRs ranging from 38% to 42%. The resubmission reiterated that this was consistent with clinician advice provided that 30-40% of patients experience a meaningful clinical benefit with bevacizumab. The resubmission stated that these improvements can include:

- a reduction in swelling on the brain
- an improvement in overall symptoms, such as headaches, as well as specific neurological deficits, such as movement and motor function, coordination, changes to personality and ability to communicate
- a reduction in dexamethasone dose which also reduces the risk of corticosteroid-related complications, including infections (pneumocystis pneumonia, candidiasis), diabetes, psychosis, and myopathy;
- an improvement in a patient’s social, physical, functional and emotional well-being and that of their carers.

5.21 The resubmission stated that the PBAC previously considered a cost per responder (ORR) of between \$ [REDACTED] and \$ [REDACTED] to be acceptable “in the context of difficult to treat and relatively rare diseases” in its consideration of brentuximab vedotin for relapsed/refractory CD30-positive cutaneous T-cell lymphomas (CTCL) (Paragraph 4.25, brentuximab, November 2018 Public Summary Document (PSD)). To provide context to the clinical meaningfulness of response in the CTCL setting, in July and November 2018, the PBAC had noted: the impact of pruritus, chronic inflammation and ulceration and frequent infections on quality of life for patients with CTCL; and the consumer comments described a range of benefits of treatment with brentuximab vedotin including the ability to return to normal daily activities, relief from rash, constant itch, peeling skin, frequent skin and ear infections, total body hair loss, hand nail deterioration and loss (Paragraphs 4.1 and 6.2, brentuximab July 2018 PSD).

- 5.22 The PBAC also recalled that it had accepted a cost per responder analysis for vorinostat for cutaneous T-cell lymphomas. In this context, in November 2016, the PBAC had considered that this responder analysis was informative in the context of CTCL, as “response” in this condition may include a variety of benefits such as substantial improvements in quality of life, enabling local treatment for lesions (e.g. radiotherapy), the potential of being eligible for a stem cell transplant and cost offsets for reduced use of alternative treatments (Paragraph 6.38, vorinostat November 2016 PSD).
- 5.23 The PBAC noted that the cost-effectiveness analyses presented in the resubmission had a number of limitations including that the duration of bevacizumab use was assumed to correspond with the duration of PFS reported in the studies, and the analyses used medians rather than means (as mean data were not available from the studies). The PBAC also noted that the only resource costs included were bevacizumab drug and administration costs. The PBAC considered that this was likely conservative as no drug costs (or additional medical care costs) were assumed in the comparator arm.

Cost-effectiveness analyses based on Patient Access Program

- 5.24 The resubmission conducted a supplementary cost-effectiveness analysis using data from the Patient Access Program. Based on this data, the resubmission estimated that the cost per additional year without progression would be \$ [REDACTED]. However, the PBAC considered there were a number of limitations with this analysis (in addition to some of the limitations outlined in Paragraph 5.23) that made the analysis difficult to interpret, including that treatment duration was used as a proxy for PFS (as the Patient Access Program does not collect data on patient responses to treatment), and drug costs were based on the number of doses ordered which would likely underestimate drug costs as some patients would have received the three-weekly dosing regimen which requires a higher dose. Given these limitations, the PBAC considered that the cost-effectiveness analyses based on data from the Patient Access Program were not a reliable basis for determining the cost-effectiveness of bevacizumab. The PBAC considered that the trial-based cost-effectiveness analyses were more informative.

Drug cost/patient/course: \$ [REDACTED] (in the financial estimates)

- 5.25 The cost of bevacizumab per patient per course was unchanged from the March 2019 submission and based on the proposed effective 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 77 kg, and a dose of 10 mg/kg every two weeks). An average of 11 doses per patient was assumed based on an average of 5.1 months of treatment in the Patient Access Program.

- 5.26 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

- 5.27 In its previous consideration, “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 – \$60 million over 6 years to \$30 – \$60 million per year 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” (Paragraph 7.10, March 2019 PSD).
- 5.28 To reduce risks to the Commonwealth, the resubmission reduced the proportion of eligible patients from 50% in the previous submission to 40%. The resubmission stated this was based on advice from clinical experts who indicated that approximately 40-50% of glioblastoma patients would be eligible for bevacizumab in the relapsed/refractory setting.
- 5.29 Further, the resubmission removed grandfathered patients from the financial estimates, stating “while Roche expects some patients receiving bevacizumab under the patient access program to be grandfathered onto the PBS, the financial estimates do not take this into account, ensuring any risk associated with cost impacts from grandfathered PBS patients remains with Roche” (page 15). This also aligns with the previous minutes which stated that “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” (Paragraph 6.30, March 2019 PSD).
- 5.30 The resubmission continued to use updated AIHW data, per the previous pre-PBAC response including the updated incidence of brain cancer based on the ACIM work book ‘Brain Cancer in Australia’ published in December 2018 and the incidence of glioblastoma based on the AIHW publication ‘Brain and other central nervous system cancers’. The resubmission corrected other issues noted in the March 2019 PSD including revising the estimate of patient numbers to be based on incidence rather than prevalence, reducing the MBS fees for administration to reflect shorter infusion times for subsequent doses and amending the calculation of patient co-payments (per Paragraph 6.33, March 2019 PSD).

Public Summary Document – May 2019 PBAC Meeting

Table 10: 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 ^a	████	████	████	████	████	████
Number of patients with glioblastoma (61%) ^b	████	████	████	████	████	████
Number of patients eligible for bevacizumab (40%)	██	██	██	██	██	██
Number of patients treated	██	██	██	██	██	██
Number of scripts dispensed PBS/RPBS ^c	████	████	████	████	████	████
Estimated financial implications of bevacizumab						
Cost to PBS/RPBS less copayments	\$████	\$████	\$████	\$████	\$████	\$████
Net cost to MBS	\$████	\$████	\$████	\$████	\$████	\$████
Net cost to PBS/RPBS/MBS	\$████	\$████	\$████	\$████	\$████	\$████
Previous submissions						
Cost to PBS/RPBS less copayments – March 2019	\$████	\$████	\$████	\$████	\$████	\$████
Pre-PBAC response	\$████	\$████	\$████	\$████	\$████	\$████

^a AIHW. Brain cancer ACIM workbook, 2018

^b AIHW. Brain and other central nervous system cancers, 2017

^c Assuming 11 scripts per patient, based on the mean duration of treatment in the Patient Access Program of 5.1 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'

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year and the net cost to the PBS/RPBS would be less than \$10 million per year.

- 5.31 The resubmission 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 – \$60 million over the first 6 years of listing. This was reduced from the March 2019 pre-PBAC response, which estimated a cost of \$30 – \$60 million over six years.
- 5.32 The resubmission estimated that around less than 10,000 patients would be treated per year. 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 around 50% of the estimated treated population.
- 5.33 The resubmission stated that the sponsor is anticipating that a biosimilar of bevacizumab will enter the market during the second year of listing, and that while the exact timing of PBS-listing is not known, the listing of a biosimilar will trigger a 25%

statutory price reduction further reducing the cost of listing bevacizumab for this indication. The resubmission did not include the impact of this in the financial estimates or cost-effectiveness analyses.

- 5.34 During preparation of the minor overview it was noted that the number of doses per patient may be overestimated as it was assumed that patients would use 11 doses, based on the Patient Access Program. This was based on a mean duration of 5.14 months of treatment, calculated as the difference between the last and first dates that a dose was ordered. This may overestimate the number of doses per patient on the PBS as it does not take into account any missed doses (due to treatment breaks or compliance) and patients who have paid significant upfront costs through the Patient Access Program may prolong treatment.

Financial Management – Risk Sharing Arrangements

- 5.35 The March 2019 PSD stated that “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 that an RSA may also help to contain the total cost to Government in the context of the uncertain cost-effectiveness” (Paragraph 7.11, March 2019 PSD).
- 5.36 The resubmission proposed a Risk Sharing Arrangement (RSA), and indicated this should be based on the financial estimates outlined in Table 12. The pre-PBAC response stated that the proposed RSA was “designed to address concerns held by the PBAC and provide financial certainty to the PBS with a [REDACTED] % rebate on any expenditure which exceeds the subsidisation caps”.

6 PBAC Outcome

- 6.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy), Authority Required listing of bevacizumab for the treatment of relapsed or refractory glioblastoma. The PBAC considered there is a clinical need for effective treatments in this patient group. The PBAC was satisfied that bevacizumab provides, for some patients, an improvement in efficacy over standard care (salvage chemotherapy).
- 6.2 The PBAC reaffirmed that it considered there is a high unmet clinical need for treatments for patients with relapsed or refractory glioblastoma, and again acknowledged the large number of comments from consumers, clinicians and organisations received for the March 2019 meeting. The PBAC also considered that the high rates of prescribing of bevacizumab among clinicians (with around 50% of eligible patients accessing bevacizumab through the Patient Access Program) indicated a high perceived benefit of bevacizumab.

Public Summary Document – May 2019 PBAC Meeting

- 6.3 The PBAC considered that bevacizumab was associated with improvements in response rates and progression free survival, and hence quality of life through control over deterioration and symptom management. While there remained uncertainty in the magnitude of some of these benefits, the PBAC noted that the benefits, as described by consumers and clinicians included: significantly improved quality of life, symptomatic improvement, improved neurological function, improved mobility, and a reduction in steroid dose and steroid related side effects. The PBAC noted that the comments described a restoration of dignity, which the PBAC considered to be meaningful, especially in the palliative stages of disease.
- 6.4 The PBAC noted that across studies, the objective response rate (ORR) with bevacizumab (either in monotherapy or in combination with lomustine) was between 30% to 40%, and that this was consistent with advice from a group of seven Australian neuro-oncologists that, in their clinical opinion, up to 30-40% of patients appear to gain a meaningful clinical benefit from treatment with bevacizumab. The PBAC noted this represented an incremental improvement in ORR of 20% to 34% versus standard care (salvage chemotherapy).
- 6.5 Further, the PBAC noted that the median PFS with bevacizumab observed across the studies (3 to 4.2 months) was broadly consistent with the median duration of treatment in the Patient Access Program of 15 weeks (3.4 months).
- 6.6 The PBAC considered that the benefits of bevacizumab would predominantly be in the palliative setting, and re-iterated its previous consideration that no evidence had been presented that demonstrated that bevacizumab is associated with an improvement in overall survival.
- 6.7 The PBAC considered that while bevacizumab was associated with hypertension and thrombosis, it is generally well tolerated when used in other disease settings. The PBAC considered that the safety of bevacizumab in patients with relapsed/refractory glioblastoma was likely to be similar to its safety in patients with other conditions. The PBAC noted that lomustine (the most commonly used salvage chemotherapy) is associated with thrombocytopenia and low white blood cell counts, nausea and vomiting, and possible pulmonary or kidney toxicities over time. The PBAC considered that treatment with bevacizumab may result in reductions in steroid doses, which may reduce steroid-related toxicities such as infections, diabetes, psychosis and myopathy. Overall, the PBAC considered that bevacizumab has non-inferior safety compared with standard care (including older chemotherapies, such as lomustine).
- 6.8 The PBAC recalled that insufficient information was provided in the March 2019 submission to determine the cost-effectiveness of bevacizumab in relapsed or refractory glioblastoma. The PBAC noted that further information was provided in the current resubmission, which showed that the cost per responder (ORR) was between \$ [REDACTED] and \$ [REDACTED]. The PBAC considered that this was acceptable based on previous PBAC recommendations in the context of difficult to treat and relatively uncommon diseases, and given the range of significant improvements in quality of life and

symptom control that ‘response’ appeared to represent in this context.

- 6.9 The PBAC noted that the estimated cost to the PBS/RPBS had reduced since its previous consideration due to a reduction in the estimated proportion of eligible patients, and removal of grandfathered patients given these patients would already be included in the incident population. Although acknowledging the number of doses per patient may have been overestimated, the PBAC considered that these changes were reasonable. The PBAC noted that the resubmission proposed an RSA with a [REDACTED] % rebate above the caps and considered it was appropriate to limit the total cost to the financial estimates presented through the proposed RSA, given the uncertain proportion of patients who would be eligible for bevacizumab and the potential for use outside the proposed restriction.
- 6.10 The PBAC noted that the resubmission proposed that bevacizumab be listed for use in combination with chemotherapy and provided new information from a survey of neuro-oncologists, which indicated that 55% of patients use bevacizumab as monotherapy and 45% of patients use bevacizumab in combination with chemotherapy. As such, the PBAC advised that the restriction should not specify whether bevacizumab should be used as monotherapy (or in combination with chemotherapy) to allow clinician judgement.
- 6.11 The submission stated that the initial restriction was intended to provide 12 weeks of therapy. The PBAC noted that the advice provided in correspondence (from seven neuro-oncologists), 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”. As such, the PBAC considered that an initial treatment period of eight weeks (rather than 12 weeks) would be sufficient to determine patient response and to minimise unnecessary use in those patients who do not respond. The PBAC considered that patients should only continue PBS-subsidised bevacizumab beyond eight weeks if they are benefiting from treatment.
- 6.12 The PBAC noted that the pre-PBAC response (p. 1) stated that the sponsor is willing to establish a ‘compassionate access program’, following the agreement on price and the Risk Share Arrangement (RSA). The PBAC considered that grandfathering of these patients may be appropriate if patients are not charged for access in the ‘compassionate use program’. The PBAC however noted that grandfathered patients should not be separately accounted for in the financial estimates as they were implicitly accounted for in the epidemiological approach used in the submission. The PBAC re-iterated its previous consideration that if patients have already paid to access bevacizumab through the Patient Access Program it would not be appropriate to subsidise further doses through the PBS (i.e. on-going supply in those patients who have paid should be provided by the sponsor) (Paragraph 6.30, March 2019 PSD).
- 6.13 The PBAC advised that bevacizumab is not suitable for prescribing by nurse practitioners.

Public Summary Document – May 2019 PBAC Meeting

- 6.14 The PBAC noted that the Early Supply Rule does not currently apply to Section 100 (Efficient Funding of Chemotherapy) listings.
- 6.15 The PBAC recommended that bevacizumab should not be treated as interchangeable with any other drugs.
- 6.16 The PBAC noted that this submission is not eligible for an Independent Review as it made a positive recommendation.

Outcome:

Recommended

7 Recommended listing

Add new listing:

Grandfathering restriction to be developed (pursuant to Paragraph 6.12).

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
BEVACIZUMAB			
Bevacizumab 400 mg/16 mL injection, 16 mL vial	1,800 mg	3	Avastin® Roche

Bevacizumab 100 mg/4mL injection, 4 mL vial

Category / Program	Chemotherapy
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Condition:	Glioblastoma
PBS Indication:	Relapsed or recurrent glioblastoma
Treatment phase:	Initial
Restriction Level / Method:	Authority Required - In Writing

Public Summary Document – May 2019 PBAC Meeting

<p>Clinical criteria:</p>	<p>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 8 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.</p>
<p>Administrative Advice</p>	<p>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.</p> <p>NOTE: Special Pricing Arrangements apply.</p>
<p>Prescriber instructions</p>	<p>Symptomatic progression is defined as: Deterioration of neurologic function which may include motor dysfunction, seizures, lack of co-ordination, changes to personality, reduced ability to communicate, neurocognitive decline OR Increasing symptoms of raised intracranial pressure which may include i.e. headache, nausea, vomiting or poorly controlled vasogenic oedema</p>

Public Summary Document – May 2019 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
BEVACIZUMAB Bevacizumab 400 mg/16 mL injection, 16 mL vial	1,800 mg	5	Avastin® Roche
Bevacizumab 100 mg/4mL injection, 4 mL vial			

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 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 which may include motor dysfunction, seizures, lack of co-ordination, changes to personality, reduced ability to communicate, neurocognitive decline OR Increasing symptoms of raised intracranial pressure which may include headache, nausea, vomiting or poorly controlled vasogenic oedema

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 grateful for the pragmatic approach taken by the PBAC in recommending bevacizumab for patients with relapsed or recurrent glioblastoma with high unmet need. The company also acknowledges the leadership of the clinical and patient community in driving strong support for this submission to the PBAC.