7.18 RAMUCIRUMAB
100 mg in 10 mL vial, 500 mg in 50 mL vial, Cyramza®, Eli Lilly Australia Pty Ltd.

1 Purpose of Application

1.1 The PBAC recommended an Authority Required (STREAMLINED) listing for ramucirumab in combination with paclitaxel (RAM+PAC) for the treatment of patients with gastric or gastro-oesophageal junction (G/GEJ) adenocarcinoma in March 2018. The PBAC considered that a substantial price reduction (of approximately [redacted]%) would be required for RAM+PAC to be cost-effective against PAC in the proposed PBS population.

1.2 The minor resubmission requested that the PBAC revise the basis of its March 2018 recommendation on the basis of a price reduction of around [redacted]% and revisions to the economic model and the range of ICERs considered to be acceptably cost effective.

2 Requested listing

2.1 The submission did not request any changes to the restriction wording that was recommended in March 2018 (PSD, p26-7). The requested dispensed prices for the maximum amount (DPMAs) in the minor resubmission appeared to have been calculated based on a maximum amount of 551 mg, as per the requested listing in the March 2018 major submission. The Secretariat updated the requested DPMAs for the maximum amount of 1,920 mg using the published and effective approved ex-manufacturer prices (AEMPs) that were requested in the minor resubmission (see Table 1). Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer	
RAMUCIRUMAB 500 mg/50 mL injection, 1 vial 100 mg/10 mL injection, 1 vial	1,920 mg	10	Published price: ~~$[redacted]~~ *$[redacted]* (Public Hospital) ~~$[redacted]~~ *$[redacted]* (Private hospital) Effective price: ~~$[redacted]~~ *$[redacted]* (Public Hospital) ~~$[redacted]~~ *$[redacted]* (Private hospital)	Cyramza®	Eli Lilly Australia Pty Ltd

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Advanced or metastatic
Condition:	gastric adenocarcinoma or gastro-oesophageal junction adenocarcinoma
PBS Indication:	Advanced or metastatic gastric adenocarcinoma or gastro-oesophageal junction adenocarcinoma

Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment phase:	Initial treatment
Clinical criteria:	Patient must have progressive disease after prior platinum and fluoropyrimidine chemotherapy; AND Patient must have an ECOG performance status 0 or 1, AND Treatment must be in combination with paclitaxel
Administrative advice	*Special pricing arrangements apply*

Treatment phase:	Continuing treatment
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug for this condition, AND Treatment must be in combination with paclitaxel
Administrative advice	*Special pricing arrangements apply*

2.2 The requested published and effective AEMPs in the minor resubmission, compared with the previous submission, are presented in Table 1.

Table 1: Requested AEMPs in the previous and current submissions

Form	March 2018 submission AEMP*	July 2019 minor resubmission		Price reduction
		Published AEMP	Effective AEMP	
100 mg/10 mL injection, 1 vial	$[redacted]	$[redacted]	$[redacted]	[redacted]%
500 mg/50 mL injection, 1 vial	$[redacted]	$[redacted]	$[redacted]	[redacted]%

Source: Table 1, p6 and Table 2, p7 of the minor resubmission.
AEMP = approved ex-manufacturer price
*The March 2018 submission did not request a Special Pricing Arrangement.

3 Background

3.1 Ramucirumab was approved for registration by the TGA on 9th July 2015 for the following indications:

- Ramucirumab (CYRAMZA®), in combination with paclitaxel, is indicated for the treatment of adult patients with advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy.
- Ramucirumab (CYRAMZA®), as monotherapy, is indicated for the treatment of adult patients with advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy when treatment in combination with paclitaxel is not appropriate.

The PBS listing sought in the previous and current submissions was for the former indication alone, i.e. in combination with paclitaxel.

3.2 In March 2018, the PBAC recommended RAM+PAC for the treatment of G/GEJ adenocarcinoma. The PBAC considered that a substantial price reduction would be required for RAM+PAC to be cost-effective against PAC in the proposed PBS population.

- The ESC considered that the use of differing hospitalisation rates between the two treatment arms in the economic model in the post-progression health state, based on data collected prior to disease progression, was inadequately justified (March 2018 PBAC minutes, paragraph 6.53).
- The pre-PBAC response presented a revised base case ICER of $105,000/QALY - $200,000/QALY gained which assumed equal rates of hospitalisation (4.7%) in the treatment arms in the post-progression health state (March 2018 PBAC minutes, paragraph 7.13).
- The PBAC noted that, despite the hospitalisation rates being the same, because these rates were applied on a per cycle basis and as the time spent in the post-progression state was longer with PAC than RAM+PAC, post-progression hospitalisation costs remained the main driver of cost offsets in the model (PSD, paragraph 7.14). The PBAC therefore considered it would be more reasonable to assume no hospitalisations in the post-progression health state; this change increased the ICER to more than $200,000/QALY gained (March 2018 PBAC minutes, paragraph 7.15).
- The PBAC considered that the estimate of cost-effectiveness of ramucirumab was unacceptably high at more than $200,000/QALY gained, particularly in light of its modest clinical benefit and significant toxicity. Accordingly, the PBAC considered that a substantial price reduction, of around [redacted]%, to reduce the ICER to an acceptable range of $15,000/QALY - $45,000/QALY gained, would be required for RAM+PAC to be cost-effective against PAC in the proposed PBS population (March 2018 PBAC minutes, paragraph 7.15).

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

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

Consumer comments

4.2 The Medical Oncology Group of Australia (MOGA) expressed its support for the RAM+PAC resubmission. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for

ramucirumab in combination with paclitaxel, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[1], based on a comparison with PAC.

Economic analysis

4.3 The minor resubmission presented a revised base case ICER of $45,000/QALY - $75,000/QALY gained. To achieve this ICER, the following changes were made to the model:

- a revised price that was around [redacted]% lower than the price requested in the previous submission (see Table 1);
- updates to the public and private Efficient Funding of Chemotherapy dispensing fees; and
- equal rates of post-progression hospitalisation in the two treatment arms, of 3.1% (p8 of the minor resubmission).

4.4 The minor resubmission requested that the PBAC reconsider the post-progression hospitalisation rate in cancer patients to be greater than zero on the basis of the follow-up period hospitalisation rates from the key clinical trial, RAINBOW, as well as other publications citing hospitalisation rates and costs in cancer patients.

4.5 Similar to the PBAC's consideration in March 2018, the PBAC noted that these hospitalisation rates, despite being the same, were applied on a per cycle basis, and because the time spent in the post-progression state was longer with PAC than RAM+PAC, the post-progression hospitalisation costs in the economic model in the minor resubmission remained a key driver of cost offsets. If hospitalisation costs in the post-progression health state were equal in the two treatment arms, the ICER would increase to $105,000/QALY - $200,000/QALY gained (compared with the submission base case of $45,000/QALY - $75,000/QALY gained). Table 2 presents the hospitalisation rates applied to the two treatment arms in the post-progression health state in the economic model, and the resulting post-progression hospitalisation costs and ICER per QALY gained.

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

Table 2: Hospitalisation rates and costs in the post-progression health state and the results of the economic model by requested AEMP

Scenario	Probability of hospitalisation post-progression		Incremental post-progression hospitalisation costs	Requested AEMP		ICER ($/QALY)
	RAM+ PAC	PAC		100 mg/ 10 mL	500 mg/ 50 mL	
March 2018 major submission base case	3.1%	4.7%	-$[redacted]	$[redacted]	$[redacted]	$[redacted]
Pre-PBAC response revised base case	4.7%	4.7%	-$[redacted]			$[redacted]
PBAC revised base case^	0.0%	0.0%	$[redacted]			$[redacted]
July 2019 minor resubmission base case	3.1%	3.1%	-$[redacted]	$[redacted]	$[redacted]	$[redacted]
PBAC revised base case^	0.0%	0.0%	$[redacted]			$[redacted]

Source: Compiled during the preparation of the minor overview using the March 2018 PBAC minutes and "Item 5.09_Updated_CE_Model_ ramucirumab (Cyramza Eli Lilly)_April 2019" excel workbook.

AEMP = approved ex-manufacturer price; ICER = incremental cost effectiveness ratio; PAC = paclitaxel; RAM+PAC = ramucirumab in combination with paclitaxel; QALY = quality adjusted life year.

*The March 2018 major submission presented a base case ICER of $45,000-$75,000 per QALY gained. The Commentary corrected for an error during the evaluation (and was acknowledged in the Pre-Sub-Committee Response), which resulted in a revised base case ICER of $$15,000-$45,000 per QALY gained.

^Calculated such that incremental post-progression hospitalisation costs were $0 (which was achieved by changing the probability of hospitalisation in the post-progression period for both treatment arms to 0%).

4.6 The minor resubmission requested that the PBAC reconsider the range of ICERs considered to be acceptably cost effective in a high unmet need disease state to be $45,000-$105,000 per QALY gained (instead of $40,000-$45,000 per QALY gained), based on the precedent of trastuzumab for HER2 positive, metastatic (equivalent to stage IV) adenocarcinoma of the stomach or gastro-oesophageal junction in July 2015.

Estimated PBS usage & financial implications

4.7 The minor resubmission presented revised financial estimates with an estimated net cost to the PBS of less than $10 million in Year 6 of listing, with a total net cost to the PBS of $20-$30 million over the first six years of listing. This is summarised in the table below as well as the expected patient/prescription numbers.

Table 3: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of ramucirumab						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$0	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[a] Assuming 10 scripts (of 1 x 100 mg vial and 1 x 500 mg vial) per year, as estimated by the submission.
Source: 'Section 4 Workbook (Cyramza) update 27052019.xlsx' excel workbook.

4.8 As a minor submission, the financial estimates were not independently evaluated. The estimates provided by the sponsor did not include revisions made by the evaluators to the March 2018 major submission relating to copayments and the costs for administration and monitoring (PBAC minutes, Table 11). In March 2018, the PBAC considered that the estimated use of ramucirumab is highly uncertain and may have been underestimated (PBAC minutes, paragraph 7.16).

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC did not recommend a change to the basis of its March 2018 recommendation for ramucirumab in combination with paclitaxel (RAM+PAC) for the treatment of patients with gastric or gastro-oesophageal junction adenocarcinoma.

5.2 The PBAC recalled that in March 2018 it recommended RAM+PAC for the treatment of G/GEJ adenocarcinoma on the basis that a substantial price reduction of around [redacted]% would be required for RAM+PAC to be cost-effective against PAC in the proposed PBS population (see paragraph 3.2).

5.3 The PBAC noted the argument in the minor resubmission that the rate of hospitalisation in the post-progression health state should be more than zero. The PBAC noted that despite applying the same rate of hospitalisation in both arms of the model (of 3.1% in the minor resubmission), because these were applied on a per cycle basis, and as time spent in post-progression state was longer with PAC than RAM+PAC, post-progression hospitalisation costs remained the main driver of cost offsets in the model. The PBAC noted that the minor resubmission did not provide a justification for why post-progression hospitalisation costs would be significantly higher for patients treated with PAC when compared to RAM+PAC in clinical practice. Accordingly, the

PBAC considered that it was appropriate to set the hospitalisation rates in the post-progression health state such that the resulting incremental post-progression hospitalisations cost was $0. The PBAC noted that the model was sensitive to this assumption, resulting in an ICER of $105,000-$200,000 per QALY gained; the PBAC considered this to be the appropriate base case for decision making.

5.4 The PBAC considered that the cost-effectiveness of ramucirumab was unacceptably high at this ICER, particularly in light of its modest clinical benefit and significant toxicity (paragraph 7.10, March 2018 PSD). The PBAC reiterated its advice from March 2018 that ramucirumab would be acceptably cost-effective at an ICER range of $40,000-$45,000 per QALY gained, incorporating the above change to hospitalisations in the post-progression health state.

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

Outcome:
Rejected

6 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.

7 Sponsor's Comment

The sponsor had no comment.