

5.09 RAMUCIRUMAB

100 mg in 10 mL vial, 500 mg in 50 mL vial,

Cyramza[®],

Eli Lilly Pty Ltd.

1 Purpose of application

- 1.1 The submission requested a Section 100 (Efficient Funding of Chemotherapy) listing for ramucirumab in combination with paclitaxel (RAM+PAC) for treatment of advanced or metastatic gastric or gastro-oesophageal junction (G/GEJ) adenocarcinoma after disease progression with prior platinum and fluoropyrimidine chemotherapy. The PBAC has not considered RAM+PAC previously.
- 1.2 The submission was based on a cost-utility analysis of RAM+PAC compared with paclitaxel monotherapy. The key components of the clinical issues addressed by the submission are summarised below.

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

Component	Description
Population	Patients with advanced or metastatic gastric (cancer) ^a or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy.
Intervention	Ramucirumab in combination with paclitaxel
Comparator	Paclitaxel monotherapy
Outcomes	Primary: Overall survival; Secondary: Progression free survival, patient reported outcomes and safety
Clinical claim	Ramucirumab in combination with paclitaxel is superior to paclitaxel alone, with a comparable safety profile, for the treatment of advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma after prior platinum <u>or</u> ^b fluoropyrimidine chemotherapy.

^a Described as a broader gastric cancer or gastroesophageal adenocarcinoma in Section 1.4 of the submission and as a narrower gastric or gastro-oesophageal adenocarcinoma in other sections.

^b As described in the submission (Table 1.1.1, p14 and Section 2.7.2, p71); however, the requested listing and the TGA approved indication requires the combination of a platinum and a fluoropyrimidine regimen represent the prior first-line therapy.

Source: Table 1.1.1, p14 of the main submission

2 Requested listing

- 2.1 Suggested additions by the Secretariat are in *italics* and deletions are in ~~strikethrough~~.

Public Summary Document – March 2018 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
RAMUCIRUMAB				Cyramza® Eli Lilly Australia Pty Ltd
500 mg/50 mL injection, 1 vial	551 mg	40	\$ [REDACTED] (Public)	
100 mg/10 mL injection, 1 vial	1920 mg		\$ [REDACTED] (Private)	

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Advanced and/or metastatic
Condition:	gastric cancer or gastro-oesophageal junction adenocarcinoma
PBS Indication:	Advanced and/or metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	The patient must have progressive disease after prior platinum and fluoropyrimidine chemotherapy; AND Patient must have an ECOG <i>performance</i> status 0 or 1, AND Treatment must be in combination with paclitaxel
Administrative Advice	Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
RAMUCIRUMAB				Cyramza® Eli Lilly Australia Pty Ltd
500 mg/50 mL injection, 1 vial	551 mg	32	\$ [REDACTED] (Public)	
100 mg/10 mL injection, 1 vial	1920 mg		\$ [REDACTED] (Private)	

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Advanced and/or metastatic
Condition:	gastric cancer or gastro-oesophageal junction adenocarcinoma
PBS Indication:	Advanced and/or metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma
Treatment phase:	Continuing treatment

Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition, AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug, AND Treatment must be in combination with paclitaxel
Prescriber Instructions	A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment of this drug.
Administrative Advice	Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

- 2.2 Gastric cancer and gastric adenocarcinoma were used interchangeably in the submission to represent the requested PBS population. The slightly narrower gastric adenocarcinoma sub-population (approximately 90% of all gastric cancers¹) is consistent with the key evidence and the TGA indication (advanced or metastatic gastric or gastro-oesophageal junction (G/GEJ) adenocarcinoma). The Pre-Sub-Committee-Response (PSCR) clarified that the intent of the submission is for treatment of metastatic gastro-oesophageal junction (G/GEJ) adenocarcinoma, a slightly narrower subset of the gastric cancer population. The ESC and PBAC advised that the indication should be defined as ‘gastric adenocarcinoma or gastro-oesophageal junction adenocarcinoma’ in the proposed restriction, to maintain consistency with the key trial evidence and the TGA-approved indication.
- 2.3 Prior therapy was inconsistently defined in the submission as either platinum or fluoropyrimidine or platinum and fluoropyrimidine chemotherapy. Failure on platinum and fluoropyrimidine chemotherapy is consistent with the TGA-approved indication for treatment with RAM+PAC and the eligibility criteria of the key RAINBOW trial. Platinum and fluoropyrimidine therapy is also the standard first-line treatment for gastric adenocarcinoma in Australian clinical practice. The PSCR acknowledged that prior therapy should be defined as ‘platinum and fluoropyrimidine chemotherapy’. The ESC advised that prior therapy with platinum and fluoropyrimidine chemotherapy was consistent with the TGA indication, key evidence and standard practice [emphasis added].
- 2.4 The PBAC considered that an Authority Required (STREAMLINED) listing for both initial and continuing treatment would be appropriate.
- 2.5 The submission did not propose a special pricing arrangement or risk sharing arrangement.

¹ The diagnosis and management of gastric cancer. BMJ 2013;347:f6367. doi: 10.1136/bmj.f6367

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

3 Background

Registration status

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 submission was for the former indication alone, i.e., in combination with paclitaxel.

4 Population and disease

4.1 Advanced or metastatic G/GEJ cancers are aggressive and difficult to treat and impact patients' quality of life (QoL). Everyday activities such as eating and swallowing are painful and challenging due to the high symptom burden. Most patients with advanced or metastatic G/GEJ cancers fail to respond to, or they progress after, first-line treatment with platinum and fluoropyrimidine chemotherapy.

4.2 The submission proposed RAM+PAC for the treatment of G/GEJ adenocarcinoma patients who have progressed after prior treatment with platinum and fluoropyrimidine chemotherapy.

4.3 The ESC advised that there are no standard Australian guidelines for treating G/GEJ adenocarcinoma patients, however, those patients who test positive for human epidermal growth factor receptor 2 (HER2) were likely be treated with trastuzumab which is available on the PBS as first-line therapy. The ESC noted that in Australia, the prevalence of HER2 positivity in advanced G/GEJ adenocarcinoma ranges from 10% to 20% according to the definitions used for positivity in the literature².

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

² Boku N. HER2-positive gastric cancer. *Gastric Cancer*. 2014;17(1):1-12, Kumarasinghe MP, et al. *Pathology*. 2017;49(6):575-81., Lee S, et al. *Histopathology*. 2011;59(5):832-40.

5 Comparator

- 5.1 The submission nominated paclitaxel monotherapy as the comparator. This is an appropriate comparator. Other agents such as irinotecan, docetaxel, FOLFIRI or FOLFOX (folinic acid, fluorouracil and irinotecan or oxaliplatin) may also be replaced by RAM+PAC. The ESC considered that paclitaxel monotherapy was the appropriate comparator.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. At the hearing, representatives of the sponsor discussed the clinical benefits of ramucirumab in relation to disease state and toxicity. It was noted that ramucirumab provided benefit to patients in a relatively rare, aggressive and difficult to treat disease, and the observed toxicity was manageable with standard medication. Representatives of the sponsor noted that key uncertainties in the economic model were addressed in the pre-PBAC response and acknowledged that price remained the main driver of the cost effectiveness.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from and organisations (1) via the Consumer Comments facility on the PBS website.
- 6.3 The Medical Oncology Group of Australia (MOGA) expressed its support for the ramucirumab submission, on the basis of unmet need after failure of standard prior therapies, and demonstrated improvement in survival in a phase III trial. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for ramucirumab, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)³, based on a comparison with paclitaxel.

Clinical trials

- 6.4 The submission was based on one head-to-head randomised trial (RAINBOW) comparing RAM+PAC with placebo plus paclitaxel (PBO+PAC) in 665 patients with advanced junction G/GEJ adenocarcinoma who had progressed on first-line platinum and fluoropyrimidine chemotherapy (with or without an anthracycline).
- 6.5 The RAINBOW trial was stratified for geographic region, time to disease progression on first-line chemotherapy (<6 months vs. ≥6 months), and disease measurability (measurable vs. non-measurable). The submission claimed that a pre-specified subgroup of the intention-to-treat (ITT) population (Region 1) was likely to be more

³ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

closely representative of Australian patients. Region 1 included patients from Australia, Europe, Israel and the USA (60% of the trial population).

6.6 The ESC noted that only 6% of patients in the RAINBOW trial had prior targeted anti-HER2 therapy with trastuzumab for HER2 positive G/GEJ adenocarcinoma which is less than the estimates for the Australian population.

6.7 Details of the trial presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
RAINBOW	Clinical study report IMCL CP12-0922: A Randomized, Multicenter, Double-Blind, Placebo controlled Phase 3 Study of Weekly Paclitaxel With or Without Ramucirumab (IMC-1121B) Drug Product in Patients with Metastatic Gastric Adenocarcinoma, Refractory to or Progressive After First Line Therapy With Platinum or Fluoropyrimidine.	February 2014
	<u>Publications</u>	
	Wilke H, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial.	The Lancet Oncology 2014; 15 (11):1224-1235
	Al-Batran SE, et al. Rainbow: Global, phase 3, randomized, double-blind study of ramucirumab plus paclitaxel vs placebo plus paclitaxel patients with previously treated gastric or gastroesophageal junction adenocarcinoma-patient-reported outcomes and performance status.	Annals of Oncology 2014; 25 ii111
	Al-Batran SE, et al. RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel patients with previously treated gastric or gastroesophageal junction (GEJ) adenocarcinoma: Quality-of-life (QoL) results.	Annals of Oncology 2016; 27 (4): 673-679
	Bodoky G, et al. Characterizing tumour responses from RAINBOW, a randomized phase III trial of ramucirumab (RAM) plus paclitaxel (PAC) vs placebo (PBO) plus PAC in patients (pts) with previously treated advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma.	Journal of Clinical Oncology 2016; 34 (4)
	Cascinu S, et al. Age subgroup analysis of efficacy and safety data from two phase 3 studies of second-line ramucirumab (RAM) versus placebo (PL) in patients (pts) with previously treated gastric or gastroesophageal junction (GEJ) adenocarcinoma (RAINBOW and REGARD).	Annals of Oncology 2015; 26 (6), p.vi.
	Hironaka S, et al. RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab (RAM) plus paclitaxel (PTX) versus placebo (PL) plus PTX in the treatment of metastatic gastroesophageal junction and gastric adenocarcinoma (mGC) following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy-Efficacy analysis in Japanese and Western patients.	Journal of Clinical Oncology 2014; 32 (15):
Kim TY, et al. Exposure–response relationship of ramucirumab in	Gastric Cancer 2017; 1-9	

Trial ID	Protocol title/ Publication title	Publication citation
	East Asian patients from RAINBOW: a randomized clinical trial in second-line treatment of gastric cancer.	
	Kim TY, et al. Exposure-response relationship of second-line ramucirumab in east Asian patients with advanced gastric cancer from RAINBOW, a global, randomized, double-blind, phase 3 study.	Annals of Oncology 2016; 27 ii116-ii117
	Kusumoto T, et al. Efficacy and safety of paclitaxel/ramucirumab as the second-line chemotherapy in Japanese patients with advanced gastric cancer.	Journal of Clinical Oncology 2017; 35 (15)
	Lorenzen S, et al. Summary of biomarker data from 2 randomized, double-blind placebo-controlled phase 3 trials (RAINBOW and REGARD) of second-line Ramucirumab for advanced gastric or gastroesophageal junction carcinoma.	Oncology Research and Treatment 2016; 39 263-264.
	Muro, K et al. RAINBOW: A global, phase 3, double-blind study of ramucirumab (RAM) plus paclitaxel (PTX) versus placebo (PL) plus PTX in the treatment of advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy-An age-group analysis.	Journal of Clinical Oncology 2015; 33 (3).
	Muro, K et al. Subgroup analysis of East Asians in RAINBOW: A phase 3 trial of ramucirumab plus paclitaxel for advanced gastric cancer.	Journal of Gastroenterology and Hepatology (Australia) 2016; 31 (3): 581-589
	Opincar, L et al. Hypertension and proteinuria risks during ramucirumab therapy for metastatic gastric cancer.	Supportive Care in Cancer 2016; 24 (1):S191
	Shitara, K et al. Subgroup analyses of the safety and efficacy of ramucirumab in Japanese and Western patients in RAINBOW: a randomized clinical trial in second-line treatment of gastric cancer.	Gastric Cancer 2016; 19 (3):927-938
	Tebernero J, et al. Exposure-Response Analyses of Ramucirumab from Two Randomized, Phase III Trials of Second-Line Treatment for Advanced Gastric or Gastroesophageal Junction Cancer.	Molecular Cancer Therapeutics 2017; 16(10): 2215-2222
	Tebernero J, et al. Exposure-response (E-R) relationship of ramucirumab (RAM) from two global, randomized, double-blind, phase 3 studies of patients (Pts) with advanced second-line gastric cancer.	Journal of Clinical Oncology 2015; 33 (3):
	Van Cutsem E, et al. Biomarker analyses of second-line ramucirumab in patients with advanced gastric cancer from RAINBOW, a global, randomized, double-blind, phase 3 study.	Annals of Oncology 2016; 27 ii120
	Wilke H, et al. A randomized, multicenter, double-blind, placebo (PBO)-controlled phase III study of paclitaxel (PTX) with or without ramucirumab (IMC-1121B; RAM) in patients (pts) with metastatic gastric adenocarcinoma, refractory to or progressive after first-line therapy with platinum (PLT) and fluoropyrimidine (FP) Protocol	Journal of Clinical Oncology 2012; 30 (15).
	Wilke H, et al. RAINBOW: A global, phase 3, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastric adenocarcinoma	Journal of Clinical Oncology 2014; 32 (15)

Trial ID	Protocol title/ Publication title	Publication citation
	<p>following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy: Results of a multiple Cox regression analysis adjusting for prognostic factors</p> <p>Wilke H, et al. RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy rainbow IMCL CP12-0922 (I4T-IE-JVBE).</p>	Journal of Clinical Oncology 2014; 32 (3)

Source: Table 2.2.1, pp32-34 of the main submission

6.8 The key features of the direct randomised trial are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Ramucirumab plus paclitaxel vs. paclitaxel						
RAINBOW	665	R, DB, MC 6 mths	Low	Advanced or metastatic G/GEJ adenocarcinoma who have failed first-line platinum- and fluoropyrimidine-containing combination therapy	OS, PFS	used

DB=double blind; G/GEJ=gastric or gastroesophageal junction; MC=multi-centre; OS=overall survival; PFS=progression-free survival; R=randomised.

Source: Sections 2.3 and 2.4, pp36-50 of the submission.

6.9 Overall, the risk of bias for the primary outcome of overall survival (OS) and the secondary outcome of progression free survival (PFS) was low.

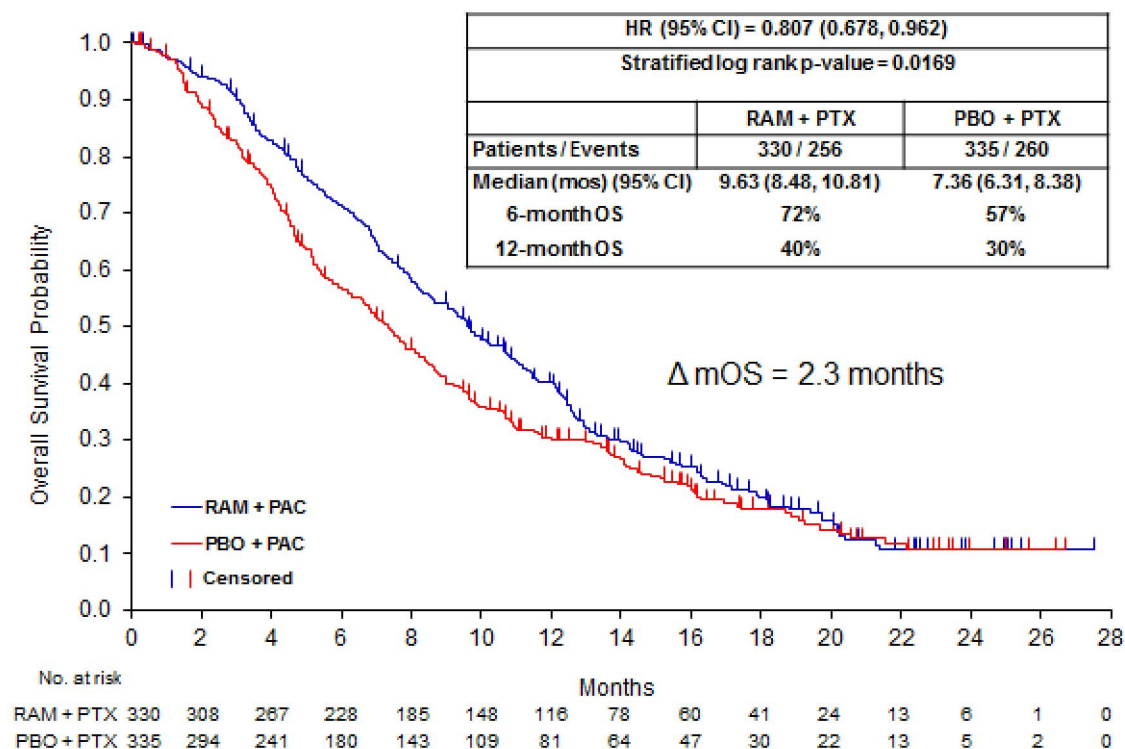
6.10 Despite the double blind design of the RAINBOW trial, there was a high likelihood that vascular endothelial growth factor (VEGF) inhibitor class adverse effects (such as hypertension, proteinuria, bleeding and thromboembolic events) would have occurred more often in the RAM+PAC arm thus leading to unmasking. The risk of bias from unmasking is considered high and could have impacted on subjective outcomes such as quality of life (QoL).

6.11 A higher proportion of patients in the PBO+PAC arm had missing QoL data than in the RAM+PAC arm and the risk of bias for the QoL outcome was therefore considered to be high. The impact of non-response on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 Global Health scores) could not be assessed. This was also highlighted in the TGA delegate evaluation report.

Comparative effectiveness

6.12 The OS results for the ITT population from the RAINBOW trial and the corresponding Kaplan-Meier curves are presented below.

Figure 1: Kaplan-Meier plot of overall survival in RAINBOW (ITT population)



CI = confidence interval; HR hazard ratio; OS = overall survival; PAC or PTX = paclitaxel; PBO = placebo; RAM = ramucirumab.

Source: Figure 2.5.1, p52 of the main submission

- 6.13 The OS data were fairly mature as survival in both arms was about 10% by the end of the follow-up time. Loss to follow-up was low in the RAINBOW trial (3 (0.9%) patients in the RAM+PAC arm and 9 (2.7%) patients in the PBO+PAC arm).
- 6.14 In the primary OS analysis, treatment with RAM+PAC reduced the risk of death by approximately 20% (HR = 0.807; 95% CI: 0.678, 0.962; p=0.0169), representing a gain in median OS of 2.3 months. The 6- and 12-month survival rates for RAM+PAC vs. PBO+PAC were 71.5% vs. 56.9% and 40.1% vs. 30.2%, respectively.
- 6.15 Treatment switching was not allowed. Post-discontinuation therapy was predominantly chemotherapy such as irinotecan or docetaxel, and was balanced between treatment arms. This was unlikely to have had a substantial impact OS given their limited efficacy.
- 6.16 The OS results in pre-specified subgroups (stratified at randomisation) are as follows:
- The point estimates of the OS HRs associated with RAM+PAC over PBO+PAC differed between the ≥ 6 months and < 6 months' time to progression on prior first-line therapy although the interaction p-value was not significant [Time to progression ≥ 6 months subgroup (HR = 0.62; 95% CI (0.42, 0.90) vs. Time to progression < 6 months complement (HR = 0.87; 95% CI (0.71, 1.06)];
 - The OS HRs differed for the disease measurability strata, with a statistically significant reduction in risk of death associated with RAM+PAC over PBO+PAC in

the measurable disease at baseline subgroup (HR = 0.75; 95% CI (0.62, 0.91)) compared with a non-statistically significant benefit in OS in patients with non-measurable disease at baseline (HR = 1.10; 95% CI (0.74, 1.64)). The PSCR (p2) argued that the difference in OS outcome in patients in whom disease is measurable versus the non-measurable population was unlikely to be clinically significant. The ESC agreed with the PSCR, and further advised that it would be difficult to restrict PBS-subsidised access to patients with measurable disease alone in practice; and

- The OS HRs differed among Region subgroups with a reduction in risk of death in Region 1 (HR = 0.73; 95% CI (0.58, 0.91)) compared with no benefit in Regions 2 (HR = 0.80; 95% CI (0.38, 1.7)) and 3 (HR = 0.99; 95% CI (0.73, 1.34)). The sample size of Region 2 (~6% of the ITT) was relatively small compared to the other Region subgroups. Thus the observed HR in the overall ITT population (HR = 0.87) may have been driven by the larger Region 1 subgroup. The ESC noted that Australian patients accounted for 6% of the ITT (41/665) and 10% of Region 1.

The ESC considered that overall, it was difficult to determine whether RAM+PAC was equally effective in all subgroups tested.

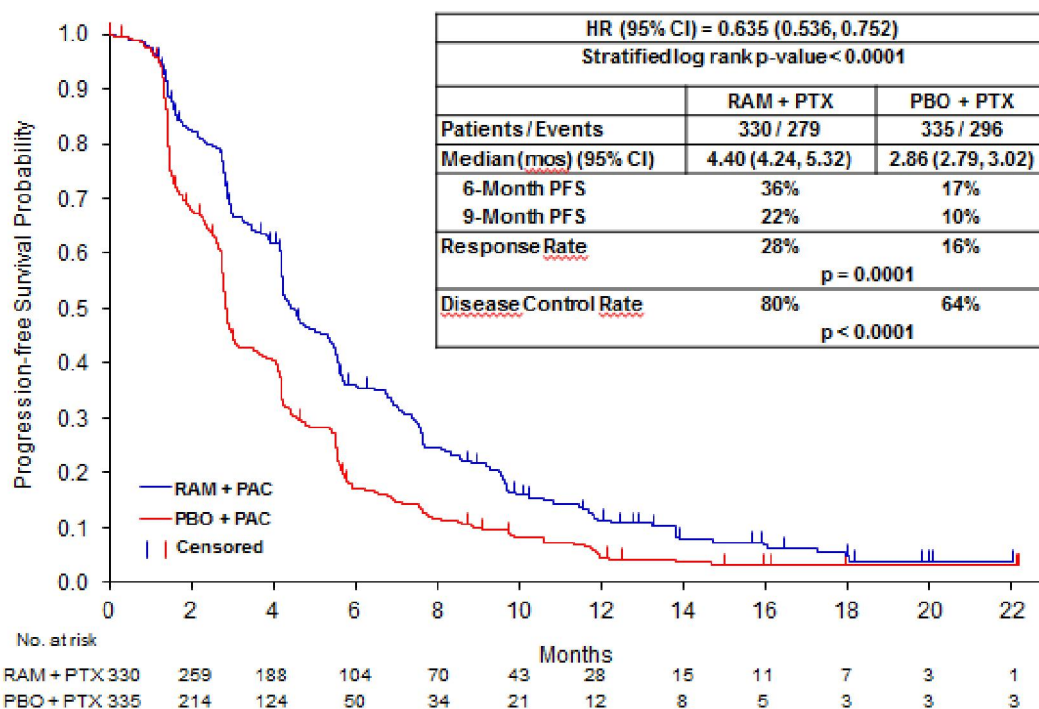
6.17 The ESC further noted the results of two additional subgroup analyses based on primary tumour site and histology:

- In a subgroup analysis of those with gastric versus GEJ disease, OS outcomes in patients with gastric cancer were poorer than in patients with GEJ adenocarcinoma. There was no OS benefit in gastric cancer patients taking ramucirumab compared to placebo (n=264) (HR 0.899 (95% CI 0.736-1.096)) versus a significant survival benefit in GEJ patients taking ramucirumab compared to placebo (n=66) (HR 0.521 (95% CI 0.348-0.781)). The ESC noted that approximately 80% of patients enrolled in the RAINBOW trial had primary gastric tumour.
- In a subgroup analysis for histological subtype, patients with intestinal disease subtype (n=145) (OS HR 0.705 (95% CI 0.534-0.932)) benefited more from RAM+PAC treatment than those with diffused subtype (n=115) (HR 0.856 (95% CI 0.641-1.145)). The ESC advised that in practice, it would be more difficult to detect progression in patients with diffused subtype of disease.

The ESC further noted that patients were not stratified at randomisation for disease site and histological subtype, and therefore considered that it was difficult to determine whether these were clinically meaningful findings, or if the effects observed were due to the exploratory nature of the subgroup analyses.

6.18 The results of the secondary outcome of PFS for the ITT population from the RAINBOW trial and the corresponding Kaplan-Meier curves are presented in the figure below.

Figure 2: Kaplan-Meier plot of progression free survival in RAINBOW (ITT population)



CI = confidence interval; HR = hazard ratio; PBO = placebo; PAC or PTX = paclitaxel; RAM = ramucirumab.
 Source: Figure 2.5.3, p54 of the main submission.)

- 6.19 Treatment with RAM+PAC reduced the risk of progression or death by 36% (HR = 0.64; 95% CI: 0.54, 0.75; p<0.0001), representing a gain in median PFS of 1.5 months. The 9 month PFS rate difference between RAM+PAC and PBO+PAC was approximately 12 % (22% vs. 10%)
- 6.20 QoL was assessed in the RAINBOW trial. The submission claimed that a greater percentage of patients in the RAM+PAC arm experienced stable or improved QoL parameters for a longer period of time, compared with patients in the PBO+PAC arm. However, there were missing data for a substantial number of patients in the trial (e.g. 34.3% and 62.4% in the PBO+PAC control arm at the midpoint of the 2nd cycle and start of the 4th cycle, respectively) which made a meaningful interpretation of the QoL results difficult. The PSCR indicated that for the QoL response analysis, patients for whom QoL data were not available were grouped with those who reported worse QoL, noting that the majority of patients who discontinued therapy did so because of disease progression, which is usually associated with worsened QoL.

Comparative harms

- 6.21 Treatment emergent adverse events (TEAEs) in the RAINBOW trial are summarised in the table below.

Table 4: Summary of adverse events

Characteristic	RAM+PAC N=327 n (%)	PBO+PAC N=329 n (%)	RAM+PAC vs PBO+PAC	
			RR (95% CI)	RD (95% CI)
TEAE	324 (99.1)	322 (97.9)	1.01 (0.99, 1.03)	0.01 (-0.01, 0.03)
Treatment-emergent SAE	153 (46.8)	139 (42.2)	1.11 (0.93, 1.31)	0.05 (-0.03, 0.12)
TEAE Grade \geq 3	267 (81.7)	206 (62.6)	1.3 (1.18, 1.44)	0.19 (0.12, 0.26)
TEAE leading to discontinuation of any study drug	102 (31.2)	80 (24.3)	1.28 (1, 1.65)	0.07 (0, 0.14)
TEAE leading to discontinuation of ramucirumab or placebo	68 (20.8)	68 (20.7)	1.01 (0.75, 1.36)	0 (-0.06, 0.06)
TEAE leading to discontinuation of paclitaxel	91 (27.8)	76 (23.1)	1.2 (0.93, 1.57)	0.05 (-0.02, 0.11)
TEAE leading to death	39 (11.9)	51 (15.5)	0.77 (0.52, 1.13)	-0.04 (-0.09, 0.02)

SAE = serious adverse event; TEAE = Treatment-emergent adverse event; RAM=ramucirumab; PAC=paclitaxel; PBO=placebo; CI = confidence interval; RR = relative risk; RD = risk difference

Source: Table 2.5.9, p57 of the main submission

6.22 The Grade \geq 3 TEAEs for which there were key differences between treatment arms are summarised in the table below.

Table 5: Grade \geq 3 TEAEs in the RAINBOW trial (safety population)

Event ^a	RAM+PAC N=327 n (%)	PBO+PAC N=329 n (%)	RAM+PAC vs PBO+PAC	
			RR (95% CI) ^b	RD (95% CI) ^b
Patients with any Grade \geq 3 TEAE ^c	267 (81.7)	206 (62.6)	1.30 (1.18, 1.44)	0.19 (0.12, 0.26)
Fatigue	39 (11.9)	18 (5.5)	2.18 (1.27, 3.73)	0.06 (0.02, 0.11)
Abdominal pain	20 (6.1)	11 (3.3)	1.83 (0.89, 3.76)	0.03 (-0.00, 0.06)
Neutropenia	133 (40.7)	62 (18.8)	2.16 (1.66, 2.80)	0.22 (0.15, 0.29)
Leukopenia	57 (17.4)	22 (6.7)	2.61 (1.63, 4.16)	0.11 (0.06, 0.16)

Notes: According to Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 = mild, Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = death related to AE

^aAs per Medical Dictionary for Regulatory Activities (MedDRA®) Version 16.0.

^bCalculated for the purposes of the evaluation.

^cTEAEs leading to death (Grade 5: RAM+PAC: 39/327 (11.9%); PBO+PAC: 51/329 (15.5%).

TEAE = Treatment-emergent adverse event; RAM=ramucirumab; PAC=paclitaxel; PBO=placebo; CI = confidence interval; RR = relative risk; RD = risk difference.

Source: RAINBOW CSR Table JVBE.12.3.2 p126, Table JVBE 12.3.3 p128 and Tables 2.5.9-10, pp57-8 of the main submission.

6.23 There was a significantly higher proportion of Grade \geq 3 TEAEs (82% vs.63%) in the RAM+PAC arm compared with the PBO+PAC arm.

6.24 There was a statistically significant increase in the frequencies of occurrence of bleeding/haemorrhage (except for gastrointestinal haemorrhage), epistaxis, hypertension and proteinuria events (any grade) in the RAM+PAC treatment arm compared with the PBO+PAC treatment arm.

- 6.25 There was an approximate 110% increase in the risk of Grade ≥ 3 neutropenia in patients who were treated with RAM+PAC. The higher frequency of haematological toxicities such as neutropenia could have been the result of a higher cumulative dose of paclitaxel in the RAM+PAC treatment arm.
- 6.26 The PSCR argued that treatment related AEs were likely to be associated with the higher cumulative dose of paclitaxel and consequences of the disease, rather than ramucirumab specifically, and therefore they should be considered in the context of the disease which is uniformly fatal, and inflicts significantly declining QoL particularly in the later stages.
- 6.27 The ESC disagreed with the PSCR's arguments, noting that:
- discontinuations in the RAINBOW study were mostly due to progressive disease and not toxicity. As such, no significant difference in discontinuations due to toxicity was observed between both arms;
 - the treatment specific toxicities observed (see Figure 3) were known anti-angiogenic effects common with VEGF inhibitors like ramucirumab; and
 - that the higher incidence of hypertension may result in greater use of simple anti-hypertensive drugs.
- 6.28 The pre-PBAC response acknowledged the increased AE profile arising from the addition of ramucirumab to paclitaxel.

Figure 3. Adverse events associated with anti-angiogenic effects

	Ramucirumab plus paclitaxel (n=327)				Placebo plus paclitaxel (n=329)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Bleeding or haemorrhage	123 (38%)	12 (4%)	1 (<1%)	1 (<1%)	51 (16%)	4 (1%)	2 (<1%)	2 (<1%)
Proteinuria	51 (16%)	4 (1%)	0	0	20 (6%)	0	0	0
Liver injury or failure	39 (12%)	12 (4%)	3 (<1%)	0	28 (9%)	11 (3%)	2 (<1%)	0
Hypertension	34 (10%)	48 (15%)	0	0	10 (3%)	9 (3%)	0	0
Gastrointestinal haemorrhage†	21 (6%)	10 (3%)	1 (<1%)	1 (<1%)	15 (5%)	3 (<1%)	1 (<1%)	1 (<1%)
Infusion-related reaction	17 (5%)	2 (<1%)	0	0	12 (4%)	0	0	0
Renal failure	16 (5%)	4 (1%)	2 (<1%)	0	11 (3%)	0	1 (<1%)	2 (<1%)
Congestive heart failure	6 (2%)	2 (<1%)	0	0	2 (<1%)	1 (<1%)	0	1 (<1%)
Venous thromboembolic events	5 (2%)	7 (2%)	0	1 (<1%)	7 (2%)	8 (2%)	1 (<1%)	2 (<1%)
Arterial thromboembolic events	3 (<1%)	1 (<1%)	2 (<1%)	0	2 (<1%)	2 (<1%)	0	1 (<1%)
Gastrointestinal perforation	0	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0

* Pooled adverse-event terms. † Events pooled as gastrointestinal haemorrhage are also pooled as bleeding or haemorrhage.

Source: *Lancet Oncol.* 2014 Oct;15(11):1224-35. doi: 10.1016/S1470-2045(14)70420-6

Benefits/harms

6.29 A summary of the comparative benefits and harms for RAM+PAC versus PBO+PAC is presented in the table below.

Table 6: RAINBOW trial: Summary of comparative benefits and harms for RAM+PAC and PBO+PAC

Benefits: ITT population						
	RAM+PAC N=330	PBO+PAC N=335	Absolute difference	HR (95% CI)		
OS median (mths) ^a	9.63 (8.48, 10.81)	7.36 (6.31, 8.38)	2.3	0.81 (0.68, 0.96) ^b		
PFS median (mths)	4.4 (4.2, 5.3)	2.9 (2.8, 3.0)	1.5	0.64 (0.54, 0.75) ^b		
Harms : Safety population						
	RAM+PAC n/N	PBO+PAC n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				RAM+PAC	PBO+PAC	
Patients with any Grade ≥3 TEAE ^c	267/327	206/329	1.30 (1.18, 1.44)	81.7	62.6	0.19 (0.12, 0.26)
• Hypertension	46/327	8/329	5.79 (2.77, 12.07)	14.1	2.4	0.12 (0.08, 0.16)
• Neutropenia	133/327	62/329	2.16 (1.66, 2.80)	40.7	18.8	0.22 (0.15, 0.29)

^a Median duration of follow-up: RAM+PAC 9.28 months; PBO+PAC 6.83 months

^b Primary analysis stratified by randomization strata (geographical region, time to progression from start of first-line therapy, and disease measurability).

^c TEAEs leading to death (Grade 5: RAM+PAC: 39/327 (11.9%); PBO+PAC: 51/329 (15.5%).

ITT = intention-to-treat; HR = hazard ratio; RAM = ramucirumab; PBO = placebo; RD = risk difference; RR = risk ratio; TEAE = treatment emergent adverse event.

Source: Tables 2.5.4, p54, Table 2.5.2, p51, Table 2.5.9, p57 of the main submission and Tables JBVE.12.3.2-12.3.3 and 2.5.9-10 of the RAINBOW CSR.

- 6.30 There was some observed benefit in PFS and OS at the expense of an increased risk of toxicity. On the basis of direct evidence presented in the submission, for patients with advanced or metastatic G/GEJ adenocarcinoma who had progressed after prior platinum and fluoropyrimidine chemotherapy and were treated with the addition of ramucirumab to their standard paclitaxel therapy for a median duration of 9.3 months:
- experienced a gain of 2.3 months survival which corresponded to a 19% reduction in risk of death (regardless of cause) over paclitaxel alone.
 - experienced a gain of one and a half months in which they did not experience disease progression or death, representing a 35% reduction in risk of progression or death, compared to paclitaxel alone.
- 6.31 For every 100 patients who had ramucirumab in addition to their paclitaxel therapy:
- 19 additional patients experienced a Grade ≥ 3 AE compared with paclitaxel alone.
 - 12 additional patients experienced Grade ≥ 3 hypertension. There was an approximate 420% increase in the risk of Grade ≥ 3 hypertension in patients who were treated with RAM+PAC compared with paclitaxel alone.
 - 22 additional patients experienced Grade ≥ 3 neutropenia compared with paclitaxel alone.

Clinical claim

- 6.32 The submission claimed that RAM+PAC was superior in terms of effectiveness and non-inferior (stated as “comparable”) in terms of safety, compared with PBO+PAC.
- 6.33 The clinical claim presented in the submission for the effectiveness of RAM+PAC was a 2.3 month gain in median OS, which corresponded to a 19% reduced risk of death over a median duration of follow-up of approximately 9 months.
- 6.34 The clinical claim presented in the submission for safety was not adequately supported by the evidence presented as there was a demonstrated increased risk of AEs (of any grade and of Grade ≥ 3) resulting from the RAM+PAC combination. This may also have negatively impacted on QoL. The QoL data were difficult to interpret; as also suggested by the TGA delegate’s evaluation report, which noted that no meaningful comparisons could be made from the QoL results given the extensive missing data.
- 6.35 The ESC advised that the use of RAM+PAC is likely to prolong the duration of exposure with paclitaxel (compared with paclitaxel alone) and therefore result in higher cumulative toxicity. Further, the ESC noted that RAM+PAC had significant toxicities that are specifically associated with antiangiogenic therapies such as

ramucirumab, and therefore advised the submission's claim of non-inferior comparative safety compared with paclitaxel alone was not appropriate.

- 6.36 Consequently, the key clinical concern is whether the observed benefit would be acceptable in the context of the added toxicity and a potentially poorer QoL resulting from the addition of ramucirumab to paclitaxel.
- 6.37 The ESC advised that while there was a modest clinical benefit with RAM+PAC treatment, the outstanding clinical uncertainty was whether the observed OS gain outweighed the increased toxicity (potentially as a result of both antiangiogenic effects of ramucirumab and prolonged exposure to paclitaxel) of the combination.
- 6.38 The pre-PBAC response claimed that as G/GEJ cancer is a rare condition with very poor prognosis, even small absolute gains in OS outcomes can represent important relative increases in survival.
- 6.39 The PBAC acknowledged the paucity of options available to patients following progression on first-line systemic treatment for advanced G/GEJ adenocarcinoma, however, it considered that the magnitude of benefit in terms of short term survival gain with ramucirumab was modest. Further, the PBAC noted that the addition of ramucirumab to paclitaxel increased the toxicity without evidence of a definitive improvement in QoL.
- 6.40 The PBAC therefore considered that while the submission's claim of superior comparative effectiveness over paclitaxel monotherapy was acceptable in light of the modest OS improvement in the ITT population of the RAINBOW trial, the claim of non-inferior comparative safety was not reasonable, noting the significantly higher incidence of Grade 3 AEs in the RAM+PAC arm, and the cumulative effect of longer paclitaxel exposure (due to the longer treatment duration in the RAM+PAC arm) and known anti-angiogenic effects common with VEGF inhibitors like ramucirumab.

Economic analysis

- 6.41 The submission presented a cost-utility analysis based on the RAINBOW trial and a modelled economic evaluation. The model structure and rationale are summarised in the table below.

Table 7: Summary of model structure and rationale

Component	Description	Justification/comments
Type of analysis	Cost utility analysis	This is reasonable.
Outcomes	Quality-adjusted life years and life years	This is reasonable.
Time horizon	Lifetime (7.23 years)	The time horizon was selected based on the model output rather than external data. The ICER is not sensitive to changes in this estimate.
Methods used to generate results	Partitioned state survival	This is reasonable.
Health states	Pre-progression, Post-Progression, Death	These are reasonable.
Cycle length	1 week	This is reasonable, however a 28 day cycle may have been more consistent with the cycles of treatment.
Transition probabilities	Overall survival from the RAINBOW trial and extrapolated from the end of trial observation assuming the same hazard within the treatment arms following an exponential distribution. Progression-free survival from the RAINBOW trial modelled using a parametric extrapolation from the start of model	This is reasonable.
Software package	Microsoft Excel 2016	-

ICER = incremental cost-effectiveness ratio.

Source: Table 3.1.1, p71 of the submission.

- 6.42 The base case economic evaluation used the empirical Kaplan-Meier OS data from the RAINBOW trial until the time of the last event (22 months, 11% of patients still alive), and extrapolated to the model time horizon using an exponential function. Given the trial data were relatively mature, the extrapolated portion of OS data did not have a substantial impact on the results of the economic model. The ESC considered that this was reasonable.
- 6.43 Progression-free survival data from RAINBOW were mature (3.9% and 3.3% of patients had not experienced an event, respectively, in the RAM+PAC and PAC arms). However, the submission stated that direct use of the Kaplan-Meier data in the model was not appropriate, due to the high level of interval censoring observed. Although this may be more reasonable in the base case, a sensitivity analysis should have been presented using the observed Kaplan-Meier data. It was uncertain whether the approach taken in the submission introduced bias, and if so, in what direction. The modelled curve did appear to underestimate PFS in the comparator arm, relative to that observed.
- 6.44 Similarly, although the majority of patients had discontinued treatment at the maximum follow-up in RAINBOW, parametric models were fitted to the observed time on treatment data and extrapolated to the model time horizon. The observed Kaplan-Meier data were not used in the model (i.e. a log-normal distribution was selected to model the entire time horizon). The ESC considered that while the curves looked reasonable by visual inspection, it was difficult to determine the impact of the chosen method of extrapolation without exploring the curves generated using the observed data.

- 6.45 In the RAINBOW trial, hospitalisations were measured prior to disease progression and up to 30 days post-progression. The majority of hospitalisations were due to AEs which were costed separately (as part of AE costs) in the model. Thus the residual hospitalisation costs represented hospitalisation due to reasons other than AEs. These costs were observed to be a major driver of the cost-offsets in the model. The submission did not provide any justification to support an assumed difference between the treatment arms in hospitalisations due to reasons other than AEs. The non AE-related hospitalisations may be unrelated to treatment and reflect random variation between patients. The ESC considered that the number of additional hospitalisations assumed in both the pre-progression and post-progression health states were not likely to be realised in practice.
- 6.46 In addition, the approach used to estimate the hospitalisation costs was also not appropriate. The submission converted the probability of all hospitalisations observed in the trial into a weekly rate. Applying a one-off cost for hospitalisations may be more appropriate. This rate was then adjusted for the proportion of hospitalisations due to AEs (83% in RAM+PAC and 57% in PAC). The resulting rate of hospitalisations for reasons other than AEs modelled was four times with PAC than with RAM+PAC (approximately 2% vs 0.5%). However, the source used to adjust for hospitalisations due to AEs could not be verified during the evaluation. While the proportion of hospitalisations due to AEs with RAM+PAC used in the model was similar to that in the CSR (83.3% modelled, 82.6% in the CSR), the proportion of hospitalisations due to AEs with PAC differed (56.9% modelled, 75.3% in the CSR). Using the estimates from the CSR substantially increases the ICER.
- 6.47 While the weekly rate of hospitalisation was estimated using data collected prior to disease progression, this same rate was also applied throughout the post-progression health state. No evidence was presented in the submission to support a difference in hospitalisation rates between treatment arms after disease progression and cessation of ramucirumab treatment. The inclusion of these costs in the post-progression health state was not appropriate. This is a major driver of the cost-effectiveness claim of ramucirumab and is not supported.
- 6.48 As noted above, the QoL data from the RAINBOW trial did not provide a meaningful comparison between arms. In the model, the submission assumed that utility weights varied by health state, but not specifically by treatment arms. Baseline utility data from all patients was assumed to be the utility for the progression-free health state and the utility collected at the end of treatment due to disease progression was assumed to be the utility for post-progression health state. A disutility due to AEs related to treatment was applied in the pre-progression health state. Using the utility collected at a single time point immediately after disease progression may not be reflective of utility in this health state, as utility is likely to continue to decrease over time. Furthermore, patients who responded to the QoL questionnaires may not be representative of all patients in the trial and may represent a healthier cohort of the patients. Therefore the utility values may have been overestimated.

Furthermore, utilities used in the literature⁴ were considerably lower than those used in the submission for both health states. The ESC noted that the ICER was not sensitive to change in utilities when tested in a sensitivity analysis conducted during the evaluation.

6.49 The submission used a lifetime time horizon in the base case economic evaluation. This was estimated to be 7.23 years. The time horizon was based on output from the model, and was chosen as the time point at which the per-cycle percentage change in the average cost-effectiveness ratio for all treatments reached 0.01%. A time horizon of 2 years was reported in the literature previously³. However, the ICER was not sensitive to changes in the time horizon. The ESC considered that the time horizon was highly optimistic in light of the clinical evidence, but acknowledged that the time horizon was not a significant driver of the economic model. The PBAC also considered that the time horizon was highly optimistic, and advised that a time horizon of 2 years would be more reasonable for this disease state, noting that in this case, the time horizon had minimal impact on the ICER.

6.50 The key drivers of the model are summarised in the table below.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Cost of hospitalisation	A higher hospitalisation cost was assumed for the comparator arm than for the RAM+PAC arm	High, favours RAM+PAC
	A lower rate of hospitalisation due to AEs for the comparator arm used in the model compared with that reported in the CSR	High, favours RAM+PAC
Drug acquisition cost	The submission did not include dispensing fee and estimated the cost of ramucirumab based on the average dose per treatment cycle, rather than per administration.	Moderate, favours RAM+PAC. <i>This was accounted for in the respecified base case presented in the PSCR (p4)</i>

AE = adverse event; CSR = clinical study report; RAM = ramucirumab; PAC = paclitaxel.
Source: Section 3.9 of the submission.

6.51 The ESC noted that although the submission presented a base case ICER of \$45,000/QALY - \$75,000/QALY gained, this model incorporated an erroneous value for the AEMP of ramucirumab. On correcting for this error, the commentary estimated that the base case ICER was \$15,000/QALY - \$45,000/QALY gained. The ESC noted that this error was acknowledged in the PSCR.

6.52 Further, the PSCR acknowledged the issues raised in the commentary and presented a respecified base case ICER of \$75,000/QALY – \$105,000/QALY gained, reflecting (i) the corrected AEMP; (ii) the inclusion of dispensing fees; (iii) costing of vials on a per administration basis, rather than a per treatment cycle basis; and (iv) an update to the cost of irinotecan to reflect the efficient combination of vials to deliver the average dose.

6.53 The cost-offsets in the post-progression health state were based on data collected prior to disease progression, and had uncertain applicability. The ESC noted that the

⁴ Lam SW, Wai M, Lau JE, McNamara M, Earl M, Udeh B. Cost-Effectiveness Analysis of Second-Line Chemotherapy Agents for Advanced Gastric Cancer. *Pharmacotherapy*. 2017 Jan;37(1):94-103.

submission did not justify why hospitalisation rates between the two treatment arms would differ after disease progression and cessation of ramucirumab treatment. The cost-offsets due to hospitalisations in the pre-progression health state were likely to be overestimated as the submission applied a rate of hospitalisation in the comparator arm of the model which was four times the rate in the intervention arm. This difference was not supported by the evidence presented in the submission. The method used to include hospitalisation costs was highly uncertain and led to substantial bias in favour of ramucirumab. The ESC considered that the differential rate of hospitalisation for reasons other than AEs was not appropriate, and was a major driver of the model. The ESC therefore advised that an assumption of equal risk of hospitalisation in both the pre- and post-progression states would be more appropriate, noting that this would increase the hospitalisation costs in the RAM+PAC arm, as post-progression survival was longer in this arm.

6.54 The pre-PBAC response noted ESC’s advice regarding the assumptions of rates of hospitalisation in the economic model, and presented a respecified base case of \$75,000/QALY – \$105,000/QALY, assuming an equal rate of hospitalisation in the post-progression health in both arms of the model. The disaggregated costs, by resource type, assumed in the pre-PBAC response are presented in the table below.

Table 9: Disaggregated summary of costs used in the economic evaluation (discounted) – pre-PBAC base case

	RAM+PAC	PAC	Incremental cost
Ramucirumab acquisition	\$	\$	\$
Paclitaxel acquisition	\$	\$	\$
Premedication (pre-progression)	\$	\$	\$
Administration (pre-progression)	\$	\$	\$
Follow-up	\$	\$	\$
Best supportive care	\$	\$	\$
Adverse events	\$	\$	\$
Hospitalisation costs (pre-progression)	\$	\$	-\$
Hospitalisation costs (post-progression)	\$	\$	-\$
Third-line treatment (inc. administration)	\$	\$	-\$
Total	\$	\$	\$

PAC = paclitaxel; RAM+PAC = ramucirumab and paclitaxel.
Source: economic model spreadsheet, pre-PBAC response

6.55 The PBAC noted that despite the rates being the same in both model arms, 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 therefore considered that it would be more reasonable to assume no hospitalisations in the post-progression health state.

6.56 As the pre-PBAC’s response did not address all of ESC’s concerns, further sensitivity analyses were undertaken by the Department and are presented below.

Table 10: The results of key sensitivity analyses – pre-PBAC base case

	Incremental cost	Incremental QALY	ICER	% change
Pre-PBAC base case	\$ [REDACTED]	0.086	\$ [REDACTED]	-
Univariate analyses				
(i) No hospitalisations in post-progression	\$ [REDACTED]	0.086	\$ [REDACTED]	[REDACTED] %
(ii) Hospitalisation due to AEs comparator arm, 75%	\$ [REDACTED]	0.086	\$ [REDACTED]	[REDACTED] %
(v) Assuming equal rate of hospitalisation in pre-progression	\$ [REDACTED]	0.086	\$ [REDACTED]	[REDACTED] %
Multivariate analyses				
(i) + (ii)	\$ [REDACTED]	0.086	\$ [REDACTED]	[REDACTED] %
(i) + (ii) + (v)	\$ [REDACTED]	0.086	\$ [REDACTED]	[REDACTED] %

AE = adverse event; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

Source: economic model spreadsheet, pre-PBAC response

6.57 The PBAC noted that assuming no hospitalisation in both arms in the post-progression state raised the pre-PBAC ICER to more than \$200,000/QALY. The PBAC considered that cost-effectiveness of ramucirumab was unacceptably high at this ICER, particularly because of its modest clinical benefit and significant toxicity. The PBAC therefore advised that ramucirumab would be acceptably cost-effective at an ICER range of \$15,000 - \$45,000 per QALY to \$15,000 - \$45,000 per QALY, noting that the ICER presented in the submission (corrected for the erroneous AEMP value) was \$15,000/QALY – \$45,000/QALY. The PBAC noted that a price reduction of approximately [REDACTED] % would be required to reduce the ICER to the acceptable range of \$15,000 - \$45,000 per QALY to \$15,000 - \$45,000 per QALY.

Drug cost/patient/course

6.58 The submission estimated that the average cost of ramucirumab was \$ [REDACTED]. This was based on one 100 mg and one 500 mg vial per administration, assuming 10 administrations (based on the median treatment cycles of 5, observed in the RAINBOW trial). Approximately [REDACTED] administrations of ramucirumab were modelled in the economic evaluation.

Estimated PBS usage & financial implications

6.59 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the use and financial impact of ramucirumab. Due to a paucity of data available to reliably inform the estimates, the submission claimed conservative estimates were used in the base case, resulting in an overestimate of the financial impact.

6.60 The estimated use and financial implications of listing ramucirumab for use in combination with paclitaxel is presented in the table below.

Table 11: 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						
Number of scripts dispensed ^a						
Estimated financial implications of Ramucirumab						
Cost of ramucirumab Revised ^b	\$	\$	\$	\$	\$	\$
Copayments ^c Revised	\$ -	\$ -	\$ -	\$ -	\$ -	\$ -
Cost to the PBS/RPBS Revised	\$	\$	\$	\$	\$	\$
Estimated financial implications for other medicines						
Paclitaxel						
Additional cost of paclitaxel Revised ^d	\$	\$	\$	\$	\$	\$
Copayments ^c Revised	\$ -	\$ -	\$ -	\$ -	\$ -	\$ -
Cost to the PBS/RPBS Revised	\$	\$	\$	\$	\$	\$
Premedications						
Additional cost of premedications Revised ^e	\$	\$	\$	\$	\$	\$
Net financial implications						
Net cost to the PBS/RPBS Revised	\$	\$	\$	\$	\$	\$
Increased cost to MBS Revised ^f	\$	\$	\$	\$	\$	\$

^a Assuming 10 per year as estimated by the submission.

^b Estimate has been revised during the evaluation to incorporate the pharmacy mark-up, dispensing fees and use the efficient combination of vials.

^c Copayments were not included in the submission's estimates as it was assumed that the setting of administration was as a day admitted patient in either a public or private hospital. An average patient co-payment was estimated during the evaluation.

^d Revised during the evaluation to include the additional compound fee at a TGA-licensed compounding site (PBAC bevacizumab PSD, November 2015) (see Table 4.3.3, Attachment 4).

^e Estimates were revised during the evaluation due to an error in the calculation of the number of RPBS patients who qualify for the PBS safety net, where the proportion of patients who qualify for the safety net was multiplied by the number of private/general patient scripts.

^f The basis for the increased number of MBS services due to the listing of ramucirumab was not clear, as cell references in the workbook were not linked. The estimates have been revised to assume a complete blood count (MBS 65070), liver function test (MBS 66512) and serum electrolyte test (MBS 66509) for each additional private in-patient administration (see Section 4.5 of the Commentary).

Source: Table 4.2.3, pp138-139; Table 4.3.1, p142; Table 4.3.2, p143; Table 4.4.1 and Table 4.5.1, p144 of the submission and 'Other PBS Items' sheet, 'Section 4 Workbook (Cytarabine) FINAL.xlsx' workbook.

6.61 The submission presented univariate and multivariate sensitivity analyses around the assumptions used to estimate the number of patients eligible for RAM+PAC. Given the level of uncertainty in the estimates used in the base case analysis, it was unclear whether the presented analyses represent plausible alternatives. The budget impact was sensitive to changes in these parameters.

6.62 An additional sensitivity analysis was conducted during the evaluation applying the same number of administrations of ramucirumab as was used in the economic model (i.e. [redacted] instead of [redacted]). The financial impact of listing ramucirumab was sensitive to this change ([redacted] % increase).

- 6.63 The ESC advised that RAM+PAC would also be used for patients who are HER2 positive and had progressed on trastuzumab in the first-line together with platinum chemotherapy. The ESC considered that although only 6% of patients in the RAINBOW trial had prior targeted anti HER2 therapy with trastuzumab, prior trastuzumab use should be accounted for in the financial estimates, in accordance with the prevalence of HER2 positivity in advanced G/GEJ adenocarcinoma, which is reported to range from 10% to 20% in the literature (see paragraph 4.3).
- 6.64 The PBAC noted that the financial estimates would need to be revised prior to listing to account for the price reduction required to achieve cost-effectiveness and prior trastuzumab use.

Financial Management – Risk Sharing Arrangements

- 6.65 No risk sharing arrangements have been presented in the submission.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Section 100 Efficient Funding of Chemotherapy Authority Required (STREAMLINED) listing of ramucirumab for the treatment of G/GEJ adenocarcinoma. The PBAC considered that a substantial price reduction would be required for ramucirumab to be cost-effective against paclitaxel in the proposed PBS population.
- 7.2 In making this recommendation, the PBAC noted that G/GEJ adenocarcinoma was a highly aggressive cancer with a poor response to second line chemotherapy.
- 7.3 The PBAC agreed with the indication proposed by ESC, 'gastric adenocarcinoma or gastro-oesophageal junction adenocarcinoma' and noted that this was consistent with the key trial evidence and the TGA-approved indication.
- 7.4 The PBAC considered that an Authority Required (STREAMLINED) listing for both initial and continuing treatment would be appropriate.
- 7.5 The PBAC considered that the proposed place in therapy of ramucirumab with paclitaxel after progression on first-line treatment with platinum and fluoropyrimidine chemotherapy was appropriate. The PBAC advised that taxanes or irinotecan were the most common second-line treatment used in the Australian clinical practice. The PBAC welcomed MOGA's input on this submission, noting it only had an ESMO score of 2 (out of a maximum of 5).
- 7.6 The PBAC considered that paclitaxel monotherapy was the appropriate comparator.
- 7.7 The PBAC noted that the submission was based on a head-to-head randomised trial (RAINBOW) comparing RAM+PAC with PBO+PAC. The PBAC noted that OS data in the RAINBOW trial was mature as survival in both arms was about 10% by the end of the follow-up time.

- 7.8 The PBAC noted that in the primary OS analysis, treatment with RAM+PAC reduced the risk of death by approximately 20% (HR = 0.807), representing a gain in median OS of 2.3 months. The PBAC noted that the OS gain in Region 1 (HR = 0.73), a pre-specified geographical subgroup that was demographically aligned to the proposed PBS population, was slightly higher than the ITT population.
- 7.9 The PBAC noted that there was a statistically significant increase in the frequencies of occurrence of bleeding/haemorrhage (except for gastrointestinal haemorrhage), epistaxis, hypertension and proteinuria events (any grade) in the RAM+PAC treatment arm compared with the PBO+PAC treatment arm. The PBAC also noted that there was a significantly higher proportion of Grade ≥ 3 TEAEs (82% vs.63%) in the RAM+PAC arm compared with the PBO+PAC arm. The PBAC noted that the addition of ramucirumab to paclitaxel increased the toxicity without evidence of a definitive improvement in QoL.
- 7.10 The PBAC therefore considered that while the submission's claim of superior comparative effectiveness over paclitaxel monotherapy was acceptable in light of the modest OS improvement in the ITT population of the RAINBOW trial, the claim of non-inferior comparative safety was not reasonable, noting the significantly higher incidence of Grade 3 AEs in the RAM+PAC arm, and the cumulative effect of longer paclitaxel exposure (due to the longer treatment duration in the RAM+PAC arm) and known anti-angiogenic effects common with VEGF inhibitors like ramucirumab.
- 7.11 The PBAC noted that the submission presented a cost-utility analysis based on the RAINBOW trial, with a time horizon of 7.23 years. The PBAC considered that the time horizon was highly optimistic, and advised that a time horizon of 2 years would be more reasonable for this disease, noting that in the current submission this had minimal impact on the ICER.
- 7.12 The PBAC noted that the submission presented a base case (corrected for the erroneous AEMP value) of \$15,000/QALY - \$45,000/QALY. Correcting for several inappropriate assumptions in the base case identified in the commentary, the PSCR presented a respecified base case ICER of \$75,000/QALY – \$105,000/QALY gained, reflecting (i) the corrected AEMP; (ii) the inclusion of dispensing fees; (iii) costing of vials on a per administration basis, rather than a per treatment cycle basis; and (iv) an update to the cost of irinotecan to reflect the efficient combination of vials to deliver the average dose.
- 7.13 The PBAC noted that in response to ESC's concerns regarding the inappropriate assumption of differential rates of hospitalisations, particularly in the post-progression health state, the pre-PBAC response presented a respecified base case of \$75,000/QALY – \$105,000/QALY, assuming an equal rate of hospitalisation in the post-progression health state in both arms of the model.
- 7.14 The PBAC noted that despite the rates being the same in both arms of the model, 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

therefore considered that it would be more reasonable to assume no hospitalisations in the post-progression health state.

- 7.15 The PBAC noted that assuming no hospitalisation in both arms in the post-progression state raised the pre-PBAC ICER from \$75,000 – \$105,000 per QALY to more than \$200,000 per QALY. Further, the PBAC note that the price per vial of ramucirumab remained the only key driver of the model at this ICER. The PBAC considered that cost-effectiveness of ramucirumab was unacceptably high at this ICER, particularly in light of its modest clinical benefit and significant toxicity. The PBAC therefore advised that ramucirumab would be acceptably cost-effective at an ICER range of \$15,000 - \$45,000 per QALY to \$15,000 - \$45,000 per QALY, incorporating the above change to hospitalisations, noting that the original ICER presented in the submission by the sponsor (corrected for the erroneous AEMP value) was \$15,000/QALY - \$45,000 /QALY. The PBAC noted that a price reduction of approximately █% would be required to reduce the ICER to the acceptable range of \$15,000 - \$45,000 per QALY to \$15,000 - \$45,000 per QALY.
- 7.16 The PBAC noted the estimated use of ramucirumab is highly uncertain. The PBAC considered that the majority of patients who are fit enough for second line treatment will receive treatment with the combination of ramucirumab and paclitaxel, whereas the submission assumed that 60% of second line patients would receive paclitaxel-based therapy and 75% of these would be eligible for combination therapy with ramucirumab. Therefore the number of patients treated with ramucirumab and the financial impact of listing may be underestimated.
- 7.17 The PBAC noted the modest financial impact and low risk of leakage of listing ramucirumab, and advised that the financial estimates would need to be revised prior to listing to account for the price reduction required to achieve the desired cost-effectiveness and prior trastuzumab use as per ESC's advice (see paragraph 6.63).
- 7.18 The PBAC advised that the Early Supply Rule should not apply to the listing of ramucirumab.
- 7.19 The PBAC advised that under subsection 101(3BA) of the *National Health Act, 1953* that ramucirumab should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.20 The PBAC advised that ramucirumab is not suitable for prescribing by nurse practitioners.
- 7.21 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Proprietary Name and Manufacturer	
RAMUCIRUMAB			Cyramza®	Eli Lilly Australia Pty Ltd
500 mg/50 mL injection, 1 vial	551 mg	10		
100 mg/10 mL injection, 1 vial	1920 mg			

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> 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
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
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

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Proprietary Name and Manufacturer	
RAMUCIRUMAB			Cyramza®	Eli Lilly Australia Pty Ltd
500 mg/50 mL injection, 1 vial	551 mg	32		
100 mg/10 mL injection, 1 vial	1920 mg			

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> 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
Treatment phase:	Continuing treatment

Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
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

9 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.

10 Sponsor's Comment

The sponsor had no comment.