

6.04 BEVACIZUMAB

Solution for I.V. use, 100mg in 4ml and 400mg in 16ml Avastin®, Roche Products Pty Ltd

1 Purpose of Application

- 1.1 The submission requested a Section 100, Authority Required (STREAMLINED) listing for bevacizumab in combination with platinum-based chemotherapy or topotecan plus paclitaxel for the treatment of persistent, recurrent or metastatic cervical cancer not amenable to curative treatment with surgery and/or radiation.

2 Requested listing

- 2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
BEVACIZUMAB				
bevacizumab, 100 mg/4 mL injection, 1 x 4 mL vial	1,800mg	7	\$ [REDACTED] ^{a,b,c} \$ [REDACTED] ^{a,b,c,e}	Avastin Roche Products Pty Limited
bevacizumab 400 mg/16 mL injection, 1 x 16 mL vial				
bevacizumab, 100 mg/4 mL injection, 1 x 4 mL vial	1,800mg	7	\$ [REDACTED] ^{b,c,d} \$ [REDACTED] ^{b,c,d,e}	
bevacizumab 400 mg/16 mL injection, 1 x 16 mL vial				

^a Section 100 Public hospital

^b Calculated using the updated remuneration arrangements (from 1st July 2015)

^c Includes a one-off statutory 5% price reduction assumed to be applied from 1 April 2016

^d Section 100 Private hospital

^e The submission proposes a risk sharing arrangement in the form of a special pricing arrangement.

Category / Program	Section 100 – Efficient Funding of Chemotherapy Private Hospital/Private Clinic Authority Required (STREAMLINED) Public Hospital Authority Required (STREAMLINED)
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
Episodicity:	-
Severity:	Persistent, recurrent or metastatic disease Advanced
Condition:	Cancer of the cervix carcinoma of cervix
PBS Indication:	Advanced carcinoma of cervix
Treatment phase:	Initial treatment with chemotherapy (except when used concurrently with radiation therapy)

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Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	<p>Patient must have a GOG performance status of 0 or 1;</p> <p>AND</p> <p>The condition must not be amenable to curative treatment with surgery and/or radiation therapy</p> <p>The condition must not be amenable to curative treatment with surgery, OR</p> <p>The condition must not be amenable to radiation therapy;</p> <p>AND</p> <p>The condition must be previously untreated with this drug bevacizumab;</p> <p>AND</p> <p>The patient must not have been previously treated with chemotherapy except when used concurrently with radiation therapy</p> <p>Patient must not have prior chemotherapy treatment; OR</p> <p>Patient must have received prior chemotherapy with radiation therapy;</p> <p>AND</p> <p>The treatment must be in combination with platinum-based chemotherapy plus paclitaxel; OR</p> <p>The treatment must be in combination with topotecan plus paclitaxel if patient is unable to tolerate carboplatin or cisplatin platinum-based chemotherapy;</p>
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	<p><i>Advanced carcinoma of the cervix is defined as persistent carcinoma, recurrent carcinoma or metastatic carcinoma of the cervix.</i></p> <p>The patient's Gynaecologic Oncology Group (GOG) performance status and body weight must be documented in the patient's medical records at the time the treatment cycle is initiated.</p>
Administrative Advice	Special Pricing Arrangements apply.
Cautions	-

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Category / Program	Section 100 – Efficient Funding of Chemotherapy Private Hospital/Private Clinic Authority Required (STREAMLINED) Public Hospital Authority Required (STREAMLINED)
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
Episodicity:	-
Severity:	Advanced
Condition:	Carcinoma of cervix
PBS Indication:	Advanced carcinoma of cervix
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition; AND Patient must not have progressive disease; AND <i>The treatment must be in combination with platinum-based chemotherapy plus paclitaxel; OR</i> <i>The treatment must be in combination with topotecan plus paclitaxel if patient is unable to tolerate carboplatin or cisplatin platinum-based chemotherapy;</i>
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	<i>Advanced carcinoma of the cervix is defined as persistent carcinoma, recurrent carcinoma or metastatic carcinoma of the cervix.</i>
Administrative Advice	Special Pricing Arrangements apply.
Cautions	-

Category / Program	Section 100 – Efficient Funding of Chemotherapy Private Hospital/Private Clinic Authority Required (STREAMLINED) Public Hospital Authority Required (STREAMLINED)
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

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Episodicity:	-
Severity:	Advanced
Condition:	Carcinoma of cervix
PBS Indication:	Advanced carcinoma of cervix
Treatment phase:	Grandfathering treatment Initial PBS-subsidised treatment (Grandfather patient)
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	<p>The condition must not be amenable to curative treatment with surgery and/or radiation therapy AND The patient must have a GOG performance status of 0 or 1 AND The patient must be previously treated with non-PBS listed bevacizumab for persistent, recurrent or metastatic cervical cancer prior to (insert listing date). Patient must have previously received non-PBS-subsidised therapy with this drug for this condition prior to xx/Month/Year;</p> <p>AND</p> <p><i>Patient must not have progressive disease;</i></p> <p>AND</p> <p><i>The treatment must be in combination with platinum-based chemotherapy plus paclitaxel; OR</i></p> <p><i>The treatment must be in combination with topotecan plus paclitaxel if patient is unable to tolerate carboplatin or cisplatin platinum-based chemotherapy;</i></p>
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	<p><i>Advanced carcinoma of the cervix is defined as persistent carcinoma, recurrent carcinoma or metastatic carcinoma of the cervix.</i></p> <p>The patient's Gynaecologic Oncology Group (GOG) performance status and body weight must be documented in the patient's medical records at the time the treatment cycle is initiated.</p>
Administrative Advice	Special Pricing Arrangements apply.

- 2.2 The Pre-Sub-Committee Response (PSCR) requested addition of the word ‘curative’ to radiation therapy in the restriction, to read as ‘The condition must not be amenable to curative radiation therapy’. The ESC considered this was reasonable.
- 2.3 The proposed use of bevacizumab did not specify cisplatin as the platinum component of chemotherapy, whereas the recommended TGA indication specified that bevacizumab should be in combination with cisplatin or topotecan plus paclitaxel. Therefore the proposed PBS listing is broader than the recommended TGA indication. The combination of carboplatin + paclitaxel is the current standard of care in Australia. The submission claimed that the two platinum agents are non-inferior in terms of overall survival (OS) in the treatment of advanced cervical cancer. However, establishing the relative treatment effect of carboplatin + paclitaxel versus cisplatin + paclitaxel does not necessarily inform on the comparative efficacy and safety associated with the use of bevacizumab in addition to carboplatin + paclitaxel are the same as bevacizumab in addition to cisplatin + paclitaxel. This issue therefore remains an area of uncertainty. However, if bevacizumab receives a positive PBAC recommendation specifying its use with cisplatin, patients in clinical practice for whom carboplatin is more suitable may switch to cisplatin to gain access to bevacizumab. The PSCR described precedent in a comparable situation in the treatment of ovarian cancer where the PBAC considered that docetaxel or cisplatin may replace paclitaxel or carboplatin respectively in some regimens. The ESC agreed with the commentary that the equivalence between carboplatin + paclitaxel versus cisplatin + paclitaxel has not been clearly shown in the submission. The selection of 90% CI, rather than the most commonly used 95% CI, was not justified in Trial JCOG 0505. Carboplatin + paclitaxel could be inferior to cisplatin + paclitaxel if a stricter 95% CI was used, as the upper bound of the wider 95% CI for the hazard ratio might exceed 1.29.
- 2.4 The submission proposed that advanced (persistent, recurrent or metastatic) cervical cancer patients would be eligible for bevacizumab plus chemotherapy should it be listed on the PBS. The proposed treatment algorithm included the use of bevacizumab in patients with persistent or recurrent stage 1 disease (non-metastatic). Data presented from the key GOG 0240 trial showed that 100% of patients had at least one metastatic site. To reflect the trial evidence, it was suggested that the listing specify proven metastases as a requirement for all patients. The Pre-Sub-Committee Response (PSCR) argued that those with persistent or recurrent disease were not excluded from trial but were not recruited and there was no reason to believe that they would respond differently. The ESC noted that amongst those with persistent or recurrent stage 1 disease, there is significant clinical need, a very low likelihood of obtaining direct clinical data, and pathophysiologic evidence to support the use of VEGF inhibitors
- 2.5 A grandfathering restriction for initial treatment was also proposed in the submission for patients receiving bevacizumab in combination with chemotherapy for advanced cervical cancer via the Roche Medicines Assistance Program prior to the PBS listing of bevacizumab for this indication.
- 2.6 Listing was sought on the basis that bevacizumab in combination with the stated chemotherapies is cost-effective in comparison to chemotherapy alone.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

3 Background

- 3.1 **TGA status:** Bevacizumab received orphan drug designation from the TGA for the treatment of persistent, recurrent or stage IV carcinoma of the cervix in April 2014. The indication recommended at the Advisory Committee on Prescription Medicines (ACPM) meeting on 5 June 2015 is:

Bevacizumab in combination with paclitaxel and cisplatin is indicated for the treatment of persistent, recurrent or metastatic carcinoma of the cervix.

Bevacizumab in combination with paclitaxel and topotecan is an acceptable alternative where cisplatin is not tolerated or not indicated.

- 3.2 Bevacizumab was registered on the Australian Register of Therapeutic Goods (ARTG) for advanced cervical cancer in September 2015.
- 3.3 Other TGA-approved indications for bevacizumab include metastatic colorectal cancer, locally recurrent or metastatic breast cancer, advanced, metastatic or recurrent non-squamous non-small cell lung cancer, advanced or metastatic renal cell cancer, grade IV glioma, epithelial or recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer. Bevacizumab is currently listed on the PBS for advanced International Federation of Gynaecology and Obstetrics (FIGO) Stage IIIB, IIIC or Stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer, and metastatic colorectal cancer.
- 3.4 This is the first submission to the PBAC for bevacizumab in combination with chemotherapy for the treatment of advanced cervical cancer.

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

4 Clinical place for the proposed therapy

- 4.1 Cervical cancer is a malignant tumour found in the tissues of the cervix. Early lesions are treated surgically and locally advanced lesions are managed with concurrent chemotherapy and pelvic radiation. Metastatic disease, persistent or recurrent lesions not amenable to radical local excision or regional radiation, are treated with chemotherapy.
- 4.2 The submission proposed that bevacizumab in combination with platinum-based chemotherapy plus paclitaxel or with topotecan plus paclitaxel for the treatment of persistent, recurrent or metastatic cervical cancer patients who are not amenable to curative treatment with surgery and/or radiation therapy.

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

5 Comparator

- 5.1 The submission nominated chemotherapy alone (platinum-based chemotherapy plus paclitaxel or topotecan plus paclitaxel for those who are unable to tolerate carboplatin or cisplatin) as the comparator for bevacizumab in combination with chemotherapy. The evaluation stated that this is the appropriate comparator.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (16), health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with bevacizumab including increased mobility and energy, reduced pain, reduced weight loss, improved digestive functions, and improved mental status and better quality of life.

Clinical trials

6.3 The submission was based on one head-to-head trial (GOG 0240) comparing bevacizumab in combination with chemotherapy (cisplatin plus paclitaxel or topotecan plus paclitaxel) to chemotherapy alone (n=452).

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

Table 1: Key trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
GOG 0240	Primary clinical study report No. 1058089 - A randomized phase III trial of cisplatin plus paclitaxel with and without NCI supplied bevacizumab (NSC #704865, IND #113912) versus the non-platinum doublet, topotecan plus paclitaxel, with and without NCI supplied bevacizumab, in Stage IVB, recurrent or persistent carcinoma of the cervix.	March 2014
	Update clinical study report No. 1059786 - A randomized phase III trial of cisplatin plus paclitaxel with and without NCI supplied bevacizumab (NSC #704865, IND #113912) versus the non-platinum doublet, topotecan plus paclitaxel, with and without NCI supplied bevacizumab, in Stage IVB, recurrent or persistent carcinoma of the cervix.	July 2014.
	Tewari KS, Sill MW, Long HJ, et al. Improved survival with bevacizumab in advanced cervical cancer.	New England Journal of Medicine 2014; Year; 370:734-43
	Penson RT, Huang HQ, Wenzel LB, et al. Bevacizumab for advanced cervical cancer: patient-reported outcomes of a randomised, phase 3 trial (NRG Oncology-Gynaecologic Oncology Group protocol 240).	Lancet Oncology 2015; 16:301-11
	Abstract – Tewari KS, Penson RT, Ramondetta LM, et al. Final	ESMO Congress; Madrid,

Trial ID	Protocol title/ Publication title	Publication citation
	overall survival analysis of the phase III randomized trial of chemotherapy with and without bevacizumab for advanced cervical cancer: Gynaecologic Oncology Group Study.	Spain, 2014
	Abstract - Tewari KS, Sill MW, Long HJ, et al. Incorporation of bevacizumab in the treatment of recurrent and metastatic cervical cancer: A phase III randomised trial of the Gynaecologic Oncology Group.	Journal of Clinical Oncology 2013; 31(suppl; abstract 3)

NCI = National Cancer Institute.

Source: Table b.2.3, p6 of Section B of the submission.

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

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Use in modelled evaluation
Bevacizumab + chemotherapy vs. chemotherapy						
GOG 0240	452	R, OL 61 weeks*	Low	Advanced cervical cancer patients who are not amenable to curative treatment with surgery and/or radiation therapy.	OS	Used

R=randomised; OL=open label; OS=overall survival.

* ITT population data cut-off: 12 December 2012: The median duration of follow-up was 47.3 weeks in the chemotherapy alone arm compared with 57.1 weeks in the bevacizumab + chemotherapy arm. The pooled duration of follow up was 52.2 weeks.

ITT population data cut-off: 7 March 2014: The median duration of follow-up was 52.6 weeks in the chemotherapy alone arm compared with 70.0 weeks in the bevacizumab + chemotherapy arm. The pooled duration of follow up was 61.3 weeks.

Source: compiled during the evaluation

6.6 The primary outcome of the trial was OS and there was a low risk of confounding given that only a small proportion (approximately 6%) of patients on chemotherapy alone received bevacizumab post-progression. For the secondary outcomes of progression free survival (PFS - investigator based), quality of life (QoL) and adverse events, there was a high risk of bias given the open-label design of the trial.

Comparative effectiveness

6.7 The results of OS and PFS are summarised below in Table 3. The Kaplan-Meier curve of OS based on the most recent data cut-off (7 March 2014) are presented in Figure 1. The results demonstrated a statistically significant reduction in risk of death (approximately 25%) resulting from the addition of bevacizumab to either cisplatin plus paclitaxel or topotecan plus paclitaxel. This benefit was observed regardless of the chemotherapy companion (topotecan + paclitaxel or cisplatin + paclitaxel) for bevacizumab. The results of OS were consistent across the two cut-off dates.

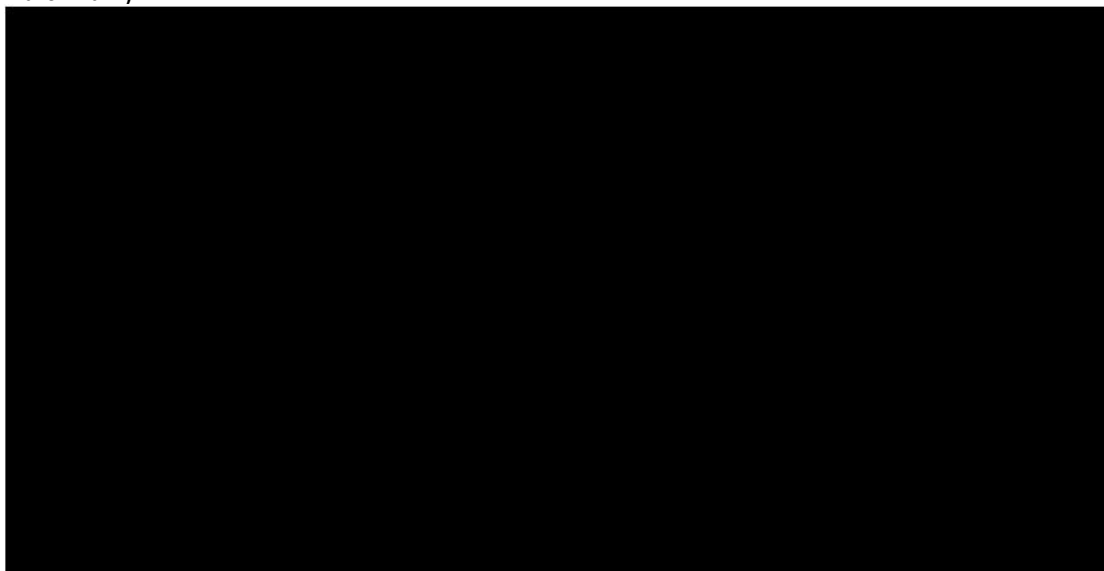
Table 3: Overall survival and PFS stratified analysis by bevacizumab treatment (GOG 0240 ITT)

Parameter	GOG-0240			
	Bev+Chemo N=227 n (%)	Chemo alone N=225 n (%)	Relative risk difference (95 % CI) (Bev+Chemo vs. Chemo alone)	Absolute risk difference (95 % CI) (Bev+Chemo vs. Chemo alone)
Clinical cut-off 12 December 2012				
Overall survival				
Patients with event	████████	████████	████████	████████
Time to event (months)				
Median	16.8	12.9		
95% CI for median	████████	████████		
p-value (log-rank test)	0.0132			
Hazard ratio (95% CI)	0.74 (0.58, 0.94)			
Progression free survival				
Patients with event	████████	████████	████████	████████
Time to event (months)				
Median	8.3	6.0		
95% CI for median	████████	████████		
p-value (log-rank test)	<0.0001			
Hazard ratio (95% CI)	0.66 (0.54, 0.81)			
Clinical cut-off 7 March 2014				
Overall survival				
Patients with event	████████	████████	████████	████████
Time to event (months)				
Median	████	████		
95% CI for median	████████	████████		
p-value (log-rank test)	████████			
Hazard ratio (95% CI)	████████████████			

ITT = intention to treat; HR = hazard ratio based on a stratified cox model; Bev = bevacizumab; Chemo = chemotherapy; CI = confidence interval.

Source: Table ES.4, p7, Executive Summary of the submission.

Figure 1: GOG 0240: Kaplan-Meier curve of overall survival based on updated analysis (clinical cut-off 7 March 2014)



Chemo = chemotherapy; Bv = bevacizumab.

Source: GOG-0240 Updated clinical study report (CSR), Figure 2, Page 37; Clinical Appendix

Comparative harms

- 6.8 The overall safety data from GOG 0240, between the bevacizumab and non-bevacizumab treatment arms, are summarised in Table 4 below. The proportions of patients experiencing Grade ≥ 3 adverse events (AEs), serious AEs (SAEs) and adverse events of special interest (AESI) in the bevacizumab plus chemotherapy arm were substantially higher than the chemotherapy alone arm. Key differences in Grade ≥ 3 AEs, between the bevacizumab and non-bevacizumab treatment arms, mainly related to gastrointestinal and vascular disorders (gastrointestinal perforations, hypertension and thromboembolic events).
- 6.9 Interpretation of these safety data should consider that the trial population enrolled patients who had a minimal risk to the randomised trial treatments.

Table 4: Overview of adverse events and deaths in GOG 0240 – Primary safety analysis (safety population)

Adverse event	Number of patients (%)		Relative risk (95% CI) (Bev + Chemo vs. Chemo alone)
	Bev + Chemo N=218	Chemo alone N=222	
Clinical cut-off 12 December 2012			
Any adverse event	██████████	██████████	██████████
Grade ≥3 adverse events	██████████	██████████	██████████
Serious adverse events	██████████	██████████	██████████
Adverse events leading to discontinuation	██████████	██████████	██████████
Adverse events leading to death	██████████	██████████	██████████
Total deaths	██████████	██████████	██████████
Treatment-related deaths	██████████	██████████	██████████
AESI	██████████	██████████	██████████
AESI Grade 3/4/5	██████████	██████████	██████████
Serious AESI	██████████	██████████	██████████

Statistically significant differences are shown in bold

AESI = adverse event of special interest (gastrointestinal perforations, hypertension and thromboembolic events); Bev = bevacizumab; Chemo = chemotherapy; CI = confidence interval.

Source: Table B.6.8, p52 of the submission.

Benefits/harms

6.10 A summary of the comparative benefits and harms for bevacizumab plus chemotherapy versus chemotherapy alone is presented in the table below.

Table 5: Summary of comparative benefits and harms for bevacizumab plus chemotherapy vs. chemotherapy

Benefits						
	Bev + chemo	Chemo alone	Absolute Difference	HR (95% CI)		
Median OS, months, (95% CI) ^a	██████████	██████████	██████████	██████████		
Median PFS, months, (95% CI) ^b	8.3, ██████████	6.0, ██████████	2.3	0.66 (0.54, 0.81)		
Harms						
	Bev + chemo	Chemo alone	RR (95% CI)	Event rate/100 patients*		RD (95% CI) Additional events/100
				Bev + chemo	Chemo alone	
Serious AEs	██████████	██████████	██████████	51.1	36.5	15 (5, 24)
AESI Grades 3-5	██████████	██████████	██████████	37.6	16.7	21 (13, 29)

^aMedian duration of follow up was 52.2 weeks (clinical cut-off December 2012),

* Median duration of exposure to bevacizumab plus chemotherapy: 20.7 weeks.

Bev+chemo = Bevacizumab plus chemotherapy; OS = overall survival; PFS = progression free survival; RD = risk difference; RR = risk ratio; AEs = adverse events; AESI = adverse events of special interest

Source: Compiled during the evaluation

- 6.11 On the basis of direct evidence presented by the submission, the comparison of bevacizumab plus chemotherapy and chemotherapy alone resulted in:
- Approximately █ months prolongation in median overall survival over a median follow-up of 61 weeks.
 - Approximately 2.3 months prolongation in median progression free survival for over a median follow-up of 52 weeks.
 - Approximately 15 additional patients would experience a serious adverse event, for every 100 patients treated with bevacizumab plus chemotherapy, over a median duration of exposure of 20.7 weeks.
 - Approximately 21 additional patients would experience serious adverse events of special interest, for every 100 patients treated with bevacizumab plus chemotherapy, over a median duration of exposure of 20.7 weeks.

Clinical claim

- 6.12 The submission described the addition of bevacizumab to chemotherapy alone as superior in terms of comparative effectiveness over chemotherapy alone and with a “manageable and acceptable safety profile”, in patients with advanced cervical cancer. The ESC agreed with the commentary that the addition of bevacizumab to chemotherapy is inferior to chemotherapy alone in terms of comparative safety.
- 6.13 The PBAC considered this claim was adequately supported for superior comparative effectiveness in terms of OS and PFS compared with chemotherapy alone. However, the claim of manageable and acceptable safety profile was not adequately supported. While bevacizumab has some clinical benefits to patients, these may be counter-balanced by clinical harms.

Economic analysis

- 6.14 The submission presented a stepped economic evaluation, based on a direct randomised trial (GOG 0240) and extrapolated beyond the trial duration to 7 years, using a Markov model with three health states: progression-free, progression and death. The model structure is summarised below.

Table 6: Summary of model structure and rationale

Time horizon	7 years in the model base case (versus a median follow-up of 14.1 months in the trial)
Outcomes	LYs and QALYs
Methods used to generate results	Cohort expected value analysis using the area under the curve to calculate the outcomes and costs for each arm in the Markov model
Cycle length	Weekly
Transition probabilities	Calculated from observed and extrapolated Kaplan-Meier data for PFS and OS
Discount rate	5% for costs and outcomes
Software package	Excel 2010

LYs= life-years; OS = overall survival; PFS = progression-free survival; QALYs = quality-adjusted life-years.
Source: Constructed during the evaluation

- 6.15 The key drivers of the model are summarised below.

Table 7: Key drivers of the model

Description	Method/Value	Impact
Assumption of continued treatment effect of bevacizumab beyond trial observation and after treatment completion	The submission has assumed a continued treatment effect of bevacizumab in the extrapolated portion of PFS and OS curves, without providing a justification. The ESC noted the addition of bevacizumab showed greater gain in median PFS (█%) than in median OS (█% (Dec 2012 cut-off) or █% (March 2014 cut-off)).	High, favours bevacizumab
Time horizon	7 years, which is longer than the maximum survival follow-up of 4.7 years in the trial (as in the bevacizumab + chemotherapy arm)	Moderate, favours bevacizumab
Time point for truncation of trial-based OS curve and to extrapolate	14.1 months median duration of follow-up in the GOG 0240 trial	Moderate, favours bevacizumab
Type of parametric functions for extrapolation	Gamma distribution in the base case and other parametric distributions in sensitivity analyses. The submission only addressed the issues of goodness of fit to the observed trial data, but failed to discuss the plausibility that the parametric function would also give accurate predictions in the unobserved period.	Low, uncertain
Utility weights associated with each health state, particularly post-progression health state	Post-progression health state: █ in the base case. This appears to be an overestimate. In addition, the 'mapped' utility values used in the submission lack face validity, in that they do not reflect the QoL decrement from baseline during treatment, as observed in GOG 0240. The ESC noted the submission pools utility scores post-progression (applying a single value for those who received bevacizumab and those who did not), which may favour bevacizumab, given the adverse event profile.	Low, favours bevacizumab

OS = overall survival; PFS = progression-free survival; QoL = quality of life.

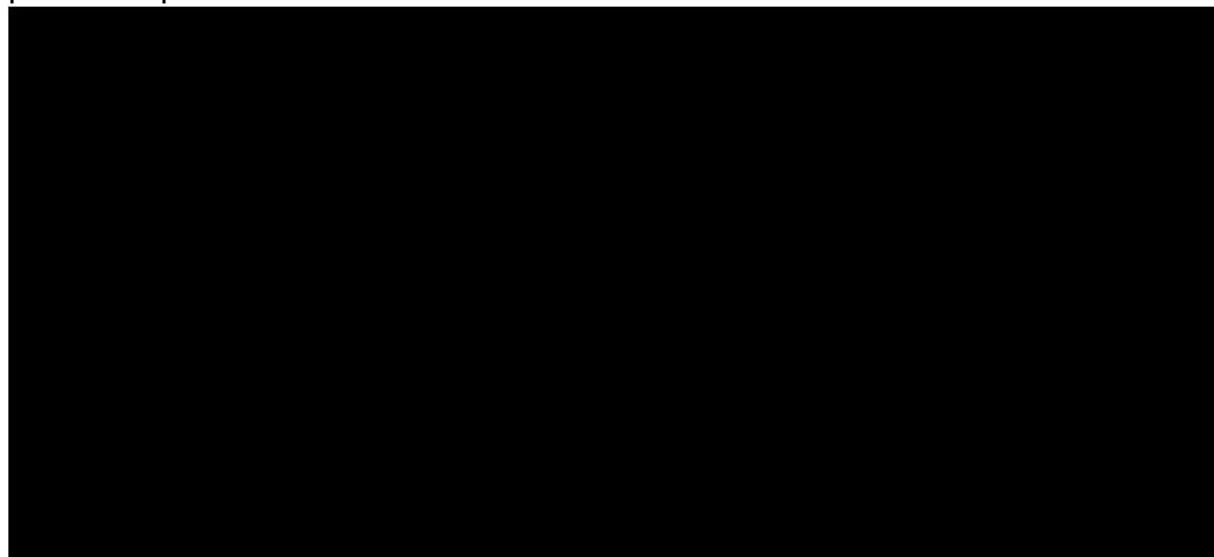
Source: compiled during the evaluation

6.16 The ESC considered that the base case ICER/QALY likely represents a lower boundary of a plausible range of cost-effectiveness for the following reasons (some of which are further discussed below):

- The extrapolation assumed a continued treatment effect beyond trial observation (14.1 months median follow-up) to the 7 year time horizon of the model despite most patients not receiving treatment in the extrapolated component. The ESC considered this assumption was unreliable and likely overstates the benefit of bevacizumab. The ESC considered further extrapolation assuming equal hazard in the post-treatment may be useful, and would likely increase the ICER.
 - The economic model is moderately sensitive to the change of the truncation time point for OS data and this assumption impact the ICER (see figure below). The ESC considered that, while the time point was not unreasonable, the choice of the time point had not been adequately justified in the submission, and noted that the ICER would be higher if a different time point was chosen. If the Kaplan-Meier OS data is truncated at a later time point of 24 months (base case: 14.1 months), the ICER will increase from \$75,000/QALY – \$105,000/QALY to \$105,000/QALY – \$200,000/QALY.

- Type of parametric functions for extrapolation. The ESC noted that Gamma extrapolation was used for both PFS and OS curves. The ESC noted that the good fit of the Gamma extrapolation with the PFS curves but considered that another extrapolation method may be more appropriate for the OS data, such as a log-logistic distribution. The ESC considered that the justification for the use of the gamma function to extrapolate OS was not reasonable, and results in a lower ICER than with other better fitting extrapolations.
- The ESC noted that the utilities are difficult to interpret, and lack face validity (in that they do not reflect the QoL decrement from baseline during treatment, as observed in GOG 0240). Further pooling of utility post-progression was not justified and may not be appropriate in this context. However, the ESC also noted both the commentary and PSCR considered that the impact of changing utility scores in the model is fairly low.

Figure 2: ICER associated with bevacizumab + chemotherapy versus chemotherapy alone when varying the time point of OS Kaplan Meier data truncations



ICER = incremental cost-effectiveness ratio; OS = overall survival; QALY = quality-adjusted life-year

Source: Figure D.6. 1 of the Commentary. Sensitivity analysis performed during the evaluation.

6.17 The results of the stepped economic evaluation are summarised below.

Table 8: Results of the stepped economic evaluation

Stepped economic evaluation	Bevacizumab + chemotherapy versus Chemotherapy alone				
	Incremental costs	Incremental health outcomes		ICER	
		Incremental LYs	Incremental QALYs	Incremental cost per LY	Incremental cost per QALY
Step 1 (trial-based analysis up to 14.1 months)	Revised: \$ [REDACTED]	[REDACTED]	[REDACTED]	Revised: \$ [REDACTED]	Revised: \$ [REDACTED]
Step 2 (parametric extrapolation over a 7 year time horizon)	Revised: \$ [REDACTED]	[REDACTED]	[REDACTED]	Revised: \$ [REDACTED]	Revised: \$ [REDACTED]
Step 3 (inclusion of MRU costs)	Revised: \$ [REDACTED]	[REDACTED]	[REDACTED]	Revised: \$ [REDACTED]	Revised: \$ [REDACTED]
Step 4 (inclusion of AE costs)	Revised: \$ [REDACTED]	[REDACTED]	[REDACTED]	Revised: \$ [REDACTED]	Revised: \$ [REDACTED]
Step 5 (inclusion of utilities to determine QALYs)	Inherent throughout the analysis				
Step 6 (inclusion of [REDACTED]% rebate to ex-manufacturer price of bevacizumab)	Revised: \$ [REDACTED]	[REDACTED]	[REDACTED]	Revised: \$ [REDACTED]	Revised: \$ [REDACTED]

AE = adverse event; ICER = incremental cost effectiveness ratio; LY = life-year; MRU = medical resource use; QALY = quality-adjusted life-year

Source: Table D.5.7, p25, Section D of the submission (items labelled 'Revised' were recalculated during the evaluation using the updated EFC fees, including preparation fee of \$82.67).

6.18 To address the uncertainty associated with extrapolation and the time horizon assumed in the base case of the model, a sensitivity analysis was conducted during the evaluation, using the trial OS data up to the maximum survival follow-up, i.e. 55.9 months (as in the bevacizumab + chemotherapy arm) and also restricting the model time horizon to 55.9 months, the incremental cost-effectiveness ratio (ICER) increases to \$105,000/QALY – \$200,000/QALY from the submission's base case of \$75,000/QALY – \$105,000/QALY. It is acknowledged that in this sensitivity analysis, PFS was still extrapolated from the median follow-up of 12 months for PFS. Nevertheless, the impact of PFS extrapolation on the result of economic evaluation is minimal: increasing the truncation time point for PFS from 12 months to 29 months (the maximum PFS follow-up in the bevacizumab + chemotherapy arm), the ICER only increases to \$105,000/QALY – \$200,000 /QALY from \$105,000/QALY – \$200,000/QALY. It is also acknowledged that at the end of the trial's maximum duration of follow-up, there were still a proportion of patients alive (17% in the bevacizumab arm and 8% in the chemotherapy alone arm, according to the Kaplan Meier OS curves).

6.19 The results of other sensitivity analyses performed during the evaluation, taking into account the proposed [REDACTED]% rebate on the ex-manufacturer price of bevacizumab for advanced cervical cancer and the updated Efficient Funding of Chemotherapy (EFC) fees, are summarised below.

Table 9: Sensitivity analyses performed during the evaluation

Assumptions	Incremental costs	Incremental QALYs	ICER
Base case	\$		\$
Univariate sensitivity analyses			
Parametric function to extrapolate PFS data			
Weibull distribution	\$		\$
Exponential distribution	\$		\$
Log-logistic distribution	\$		\$
Log-normal distribution	\$		\$
Parametric function to extrapolate OS data			
Weibull distribution	\$		\$
Exponential distribution	\$		\$
Log-logistic distribution	\$		\$
Log-normal distribution	\$		\$
Time point of OS data truncation			
24 months	\$		\$
37 months ^a	\$		\$
Time horizon			
14.1 months	\$		\$
3 years	\$		\$
5 years	\$		\$
10 years	\$		\$
Utility associated with progression health state			
0.716	\$		\$
0.62	\$		\$
Costs associated with the progression health state			
\$50 per cycle	\$		\$
\$100 per cycle	\$		\$
5% statutory price reduction for bevacizumab			
Excluding 5% statutory price reduction	\$		\$

PFS = progression-free survival; OS = overall survival

^a Median follow-up by using the method recommended by Schemper and Michael (1996) (see Section D.3 of the Commentary for discussion).

Source: Sensitivity analyses performed during the evaluation

- 6.20 As noted earlier, parametric functions to extrapolate trial-based PFS would have negligible impacts on the ICER. The use of the best fitting (measured by the Akaike Information Criterion) log-logistic distribution to extrapolate OS data from the median follow-up of 14.1 months would increase the ICER by <10%. Despite the model appearing fairly robust for the parametric functions chosen, the parametric functions only indicate the goodness of fit to the observed data during the trial period, and the uncertainties associated with the extrapolated period has not been addressed.
- 6.21 If the Kaplan-Meier OS data is truncated at a later time point of 24 months, the ICER will increase from \$75,000/QALY – \$105,000 /QALY to \$105,000/QALY – \$200,000/QALY. Of note, only a small proportion of patients were censored before 24 months (4.0% in the bevacizumab + chemotherapy arm and 5.3% in the chemotherapy alone arm). Under this circumstance, the trial-based survival estimates are considered to be reliable for extrapolation.

- 6.22 The impacts of 95% confidence intervals, in terms of PFS and OS observed from GOG 0240, on the results of economic model have not been examined in a sensitivity analysis.

Drug cost/patient/course: \$ [REDACTED] (revised \$ [REDACTED], using updated EFC fees)

- 6.23 The average drug cost per patient per course was estimated: 1) assuming a treatment duration of [REDACTED] cycles (based on the time to off-treatment (TTOT) estimates from the GOG 0240 trial); 2) assuming 54.4% of prescriptions being dispensed in public settings and 45.6% in private settings; and 3) incorporating an expected one-off statutory 5% price reduction (to be applied from 1 April 2016) and the proposed [REDACTED]% rebate on the ex-manufacturer price for bevacizumab. The bevacizumab drug cost has been revised during the evaluation to account for the new EFC fees (effective July 2015, including preparation fee of \$82.67)

Estimated PBS usage & financial implications

- 6.24 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the financial impact of listing bevacizumab for the treatment of advanced cervical cancer. The incidence of cervical cancer was based on the Australian Cancer Incidence and Mortality (ACIM) book: Cervical cancer (AIHW 2015), by projecting the incidence data for the period of 2002-2011 over the next 10 years (2012-2022) using a linear function. Expert advice on other epidemiological estimates was sought via a treatment pattern survey and an advisory board meeting to determine the number of incident patients who are likely to receive bevacizumab. The submission further assumed that patients with advanced cervical cancer would start treatment within 3 months of diagnosis, given the poor prognosis of disease; and, therefore, prevalent cases were only considered in the first 3 months of listing.
- 6.25 The 6th Community Pharmacy Agreement which took effect on 1 July 2015, made some changes to the way chemotherapy preparation fees are paid under the Section 100 Efficient Funding of Chemotherapy (EFC) arrangement.

In addition, some chemotherapy compounders will be paid a smaller fee and the DPMA that is published in the schedule will only include that smaller fee.

Under the finalised new arrangements:

- a) The preparation fees paid to compounders who are licensed by the TGA to undertake such compounding are higher than those paid to compounders who are not licensed by the TGA, recognising that TGA licensed compounders incur additional costs in complying with the TGA's licensing requirements, as compared to chemotherapy compounders who are not TGA licensed;
- b) The preparation fee paid to TGA licensed compounders remains the same as under the 5th CPA at \$102.67 (indexed price for 2014/2015);
- c) The preparation fees paid to a s90 Community Pharmacy (incl s92 approved practitioners) and a s94 Approved Private Hospital Authority are the same as those paid to TGA licensed compounders to recognise the specialist nature of preparing chemotherapy medicines;

- d) The preparation fee paid to non-TGA licenced compounders is \$20 less at \$82.67.
- e) Where applicable, the \$20 portion of the preparation fee will be paid directly to the compounder through Australian Healthcare Associates (AHA); and.
- f) The \$20 is not currently captured by the DMPA that is published in the Schedule of Pharmaceutical Benefits.

As the majority of chemotherapy preparations are compounded in settings where the \$102.67 fee applies, this fee should continue to be used in PBAC submissions. The PSCR noted that the revised estimates undertaken during the evaluation use the preparation fee applicable to non-TGA licenced compounders (\$82.67). Applying the TGA licenced compounders preparation fee (\$102.67) will increase the revised Net cost to the PBS/RPBS.

Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Prescriptions ^a					
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS ^b	\$	\$	\$	\$	\$
Revised ^c	\$	\$	\$	\$	\$
Net cost to MBS ^d	\$71,471	\$57,955	\$58,732	\$59,510	\$60,288
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$
Revised^c	\$	\$	\$	\$	\$

^a Assuming prescriptions (including both original and repeat prescriptions) per year as estimated by the submission.

^b Incorporating 5% statutory price reduction and % rebate to the ex-manufacturer price of bevacizumab. Patient co-payments excluded.

^c Using updated EFC fee as in July 2015, including preparation fee of \$82.67 and correcting for reference errors

^d 25% patient co-payments excluded

Source: Compiled during the evaluation

The redacted table above shows that the number of patients treated with bevacizumab is estimated to be less than 10,000 per year at a net cost to the PBS of less than \$10 million per year.

- 6.26 The estimates of financial implications associated with the proposed listing of bevacizumab remain uncertain as they were sensitive to the assumptions drawn from the clinician survey.

Financial Management – Risk Sharing Arrangements

- 6.27 The submission proposed a risk sharing arrangement to apply a % rebate to the ex-manufacturer price of bevacizumab. The submission did not propose a

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

7 PBAC Outcome

- 7.1 The PBAC rejected the request to list bevacizumab for the treatment of patients with advanced cervical cancer on the basis of high and unacceptable cost-effectiveness.
- 7.2 The PBAC accepted the proposed restriction for recurrent, metastatic and persistent disease. The PBAC considered that use with standard platinum-based chemotherapy, either cisplatin (as per TGA approved indication) or carboplatin (current standard of care in Australia) was reasonable. The PBAC noted that topotecan, which was proposed as alternative to platinum-based chemotherapy is only PBS-subsidised for advanced metastatic ovarian cancer.
- 7.3 The PBAC accepted the clinical place for bevacizumab for advanced cervical cancer.
- 7.4 The PBAC agreed that chemotherapy alone (platinum-based chemotherapy plus paclitaxel or topotecan plus paclitaxel for those who are unable to tolerate carboplatin or cisplatin) was the appropriate comparator for bevacizumab in combination with chemotherapy.
- 7.5 The PBAC noted the submission presented the results of a head-to-head trial (GOG 0240) comparing bevacizumab in combination with chemotherapy (cisplatin plus paclitaxel or topotecan plus paclitaxel) to chemotherapy alone (n=452). The PBAC noted the primary outcome was overall survival (OS) and progression free survival (PFS) was a secondary outcome. With regards to OS, the results were statistically significant in the ITT analyses, with a HR of 0.74 (95% CI: 0.58, 0.94) at the December 2012 data cut-off and [REDACTED] at the March 2014 data cut-off. With regards to PFS, the results were also statistically significant in the ITT analyses, with a HR of 0.66 (95% CI: [REDACTED]).
- 7.6 The PBAC noted the results of the comparative harms in the evaluation. The PBAC also noted that 15 additional patients would experience a serious adverse event, for every 100 patients treated with bevacizumab plus chemotherapy, over a mean duration of exposure of [REDACTED] weeks. Further, the PBAC were concerned that the rate of non-gastrointestinal (any grade) fistula/abscess were higher in bevacizumab plus chemotherapy ([REDACTED]%) than chemotherapy alone ([REDACTED]%), while the rate of gastrointestinal perforation (any grade) was substantially higher in bevacizumab plus chemotherapy ([REDACTED]%) than chemotherapy alone ([REDACTED]%), as reported in the TGA Clinical Evaluation Report (p40).
- 7.7 The PBAC considered the gain in median OS of 3.5 months and the gain in median PFS of 2.3 months associated with bevacizumab were clinically modest, , especially in view of significant adverse events including the clinically significant higher incidence of fistula.
- 7.8 The submission described the addition of bevacizumab to chemotherapy alone as superior in terms of comparative effectiveness over chemotherapy alone and with a “manageable and acceptable safety profile”, in patients with advanced cervical cancer. The PBAC considered this claim was adequately supported for superior comparative effectiveness in terms of OS and PFS compared with chemotherapy alone. However, the claim of manageable and acceptable safety profile was not adequately supported. While bevacizumab has some clinical benefits to patients,

these may be counter-balanced by clinical harms.

- 7.9 The PBAC noted the cost utility analysis presented in the submission resulted in an ICER of greater than \$75,000/QALY – \$105,000/QALY. The PBAC, noting the clinical outcomes, considered that this base case ICER/QALY was unacceptably high and was based on QALYs gained resulting from parametric extrapolation of OS and PFS that could not be relied upon. The PBAC noted that base-case ICER/QALY value was much higher than the range of ICER that the Committee has considered cost-effective for treatments of cancer. Further, the PBAC agreed with the ESC that the base case ICER/QALY likely represents a lower boundary of a plausible range of cost-effectiveness. The PBAC noted that the ICER was sensitive to the extrapolation from a median follow-up of 14.1 months to a time horizon of 7 years. The PBAC questioned that trial data was available to 55.9 months however, the submission chose not to incorporate data beyond 14.1 months. The PBAC noted the results of the sensitivity analyses and that the ICER increases to \$105,000/QALY – \$200,000/QALY using the trial OS data up to 55.9 months.
- 7.10 The PBAC considered that the cost of bevacizumab should be reduced to achieve a more acceptable ICER. The proposed dose of bevacizumab was 15 mg/kg, to align with the GOG 0240 trial. The PBAC considered that a possible option to obtain an acceptable price is for the sponsor to rebate the Government [REDACTED]. Alternatively the sponsor may simply reduce the cost/mg of bevacizumab and provide an economic analysis taking into account the adverse event related disutilities. If these changes are made to the model, the PBAC noted that a significant reduction in the price of bevacizumab will be required to result in a sufficiently cost-effective ICER.
- 7.11 The PBAC noted that the estimates of utilisation of bevacizumab were uncertain and the financial estimates were likely overestimated. The PBAC recommended that the sponsor consider obtaining estimates of the cumulative number of cervical cancer deaths in the next 5-10 years taking into account the change in Human papillomavirus (HPV) testing in 2017 and the impact of the HPV vaccine on the National Immunisation Program. Also some justification should be provided in relation to the uptake rates of bevacizumab.
- 7.12 The PBAC considered that a major resubmission would be required to request further consideration of recommending listing of bevacizumab for advanced cervical cancer. The PBAC further considered that the resubmission should define a patient population who would be eligible and have access to treatment and address the concerns of the ESC and the PBAC. The PBAC noted that the incidence of cervical cancer in Indigenous women is twice as high as in non-Indigenous women. The PBAC noted the rate of mortality is five times higher in Indigenous women than in non-Indigenous women. Given the marked discrepancy in mortality between Indigenous women and non-indigenous women, the Committee considered it would be important that the sponsor address the issue of drug access for the Indigenous women.
- 7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

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

Given the high unmet need, Roche is committed to working with the PBAC to provide access at the earliest opportunity to bevacizumab for patients with advanced cervical cancer.