PUBLIC SUMMARY DOCUMENT

Product: Bevacizumab, solution for IV use, 100mg in 4mL and 400mg in 16mL, Avastin®
Sponsor: Roche Products Pty Ltd.
Date of PBAC Consideration: November 2013

1. Purpose of Application

To request a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for the treatment, in combination with paclitaxel and carboplatin, of a patient with previously untreated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who is at high risk of disease recurrence.

2. Background

The PBAC had not previously considered bevacizumab for this indication.

Bevacizumab is currently listed on the PBS for the first-line treatment of metastatic colorectal cancer.

3. Registration Status

Bevacizumab solution for intravenous (IV) infusion is TGA approved for treatment of epithelial ovarian, fallopian tube or primary peritoneal cancer for the following indications:

- Bevacizumab, in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with advanced (International Federation of Gynaecology and Obstetrics (FIGO) Stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

- Bevacizumab, in combination with carboplatin and gemcitabine, is indicated for the treatment of patients with recurrent, platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior bevacizumab or other VEGF-targeted angiogenesis inhibitors.

Bevacizumab is also TGA-approved for treatment of 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, and grade IV glioma.

4. Listing Requested and PBAC's View

Section 100 Efficient Funding of Chemotherapy
Private Hospital Authority required
Public Hospital Authority required
Initial PBS-subsidised treatment, in combination with paclitaxel and carboplatin for a maximum of 6 cycles, of a patient with WHO performance status of 0-2 with previously untreated advanced (FIGO Stage IIIB or IIIC) suboptimally debulked (maximum diameter of

any gross residual disease > 1cm) or FIGO stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Private Hospital Authority required
Public Hospital Authority required
Continuing PBS-subsidised treatment for a total of 15 months therapy or until disease progression, whichever occurs earlier, as monotherapy, of a patient with advanced (FIGO Stages IIIB or IIIC) suboptimally debulked (maximum diameter of any gross residual disease > 1cm) or FIGO stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer who has previously received PBS-subsidised treatment with bevacizumab and who does not have progressive disease.

The dose that will be approved is 15 mg per kg every three weeks. Doses greater than or less than 15 mg per kg every 3 weeks will not be PBS-subsidised. The patient's WHO performance status and body weight must be documented in the patient's medical records at the time the treatment cycle is initiated.

The PBAC noted that although paclitaxel and carboplatin may be the most common doublet chemotherapy regimen for ovarian cancer, in clinical practice docetaxel may be used in place of paclitaxel, or cisplatin in place of carboplatin. The PBAC also noted that monotherapy with carboplatin was often used in elderly patients or individuals who were unable to tolerate taxanes. The PBAC considered that it would be inappropriate to mandate paclitaxel with carboplatin as the only chemotherapy regimen to be used with bevacizumab, and recommended that the initial restriction specify only that it should be used in combination with chemotherapy.

For reasons outlined below, the PBAC accepted the sponsor's request to exclude patients with optimally debulked disease.

For reasons also outlined below, the PBAC recommended that the restriction limit PBS subsidised access to bevacizumab to a maximum of 18 cycles of treatment per lifetime and limit the PBS-subsidised bevacizumab dose to 7.5 mg per kg every three weeks. The PBAC noted that the maximum amount for listings under the Efficient Funding of Chemotherapy (EFC) program is calculated to provide sufficient for a single infusion based on the recommended dose and using a patient body weight of 120 kg or a patient body surface area of 2.2 m^2. The PBAC therefore recommended that the maximum amount for the listing of bevacizumab should be 900 mg, (7.5 mg/kg x 120 kg) consistent with the usual EFC) program protocol.

Consistent with the existing listing for bevacizumab and other medicines in the Section 100 Efficient Funding of Chemotherapy Program, the PBAC recommended that the Public Hospital listing should be Authority Required (STREAMLINED).

5. Clinical Place for the Proposed Therapy

Stage III and IV epithelial ovarian, fallopian tube or primary peritoneal cancer is typically treated by cytoreductive surgery followed by chemotherapy. The most frequently used first-line chemotherapy agents are paclitaxel and carboplatin which are usually administered for 6 cycles following cytoreductive surgery.

Bevacizumab is a recombinant humanised monoclonal antibody that specifically binds to and neutralises the biologic activity of vascular endothelial growth factor (VEGF), the key mediator of angiogenesis. By blocking the activity of VEGF, bevacizumab reduces the vascularisation of tumours, and thus inhibits tumour growth and metastasis. The submission claimed that the introduction of bevacizumab in the first-line setting would result in a proportion of patients switching from doublet chemotherapy to the triplet bevacizumab + carboplatin + paclitaxel regimen.

The PBAC agreed with the proposal that patients would switch to a triplet regimen of bevacizumab plus doublet chemotherapy, but did not agree with the proposed limitation to use alongside carboplatin and paclitaxel only.

6. Comparator

The nominated comparator regimen was carboplatin plus paclitaxel (CP). The submission proposed that bevacizumab would be used in addition to carboplatin plus paclitaxel.

The PBAC agreed that doublet chemotherapy alone is the main comparator. The PBAC noted however that, while carboplatin plus paclitaxel is the most commonly used doublet chemotherapy regimen, in clinical practice docetaxel may be substituted for paclitaxel and cisplatin may be used instead of carboplatin.

The PBAC noted also that, in clinical practice, platinum (usually carboplatin) may be used alone.

7. Clinical Trials

The submission presented two randomised trials comparing doublet chemotherapy (CP) with extended use of bevacizumab added to doublet chemotherapy (GOG-0218 and ICON-7). Details are presented in the tables below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
GOG-0218 Burger et al 2011	*Clinical Study Report - GOG-0218:* A phase III trial of carboplatin and paclitaxel plus placebo versus carboplatin and paclitaxel plus concurrent bevacizumab followed by placebo, versus carboplatin and paclitaxel plus concurrent and extended bevacizumab, in women with newly diagnosed, previously untreated, stage III or IV, epithelial ovarian, primary peritoneal or fallopian tube	17 November 2010.

	cancer.	
	Clinical Study Report Addendum - GOG-0218 A phase III trial of carboplatin and paclitaxel plus placebo versus carboplatin and paclitaxel plus concurrent bevacizumab followed by placebo, versus carboplatin and paclitaxel plus concurrent and extended bevacizumab, in women with newly diagnosed, previously untreated, stage III or IV, epithelial ovarian, primary peritoneal or fallopian tube cancer.	Report Number CSR GOG-0218 Addendum, Report date February 2012
	Burger RA, Brady MF, Bookman MA et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer.	New England Journal of Medicine. 2011; 365(26):2473-83.
	Monk BJ, Huang HQ, Burger RA et al. Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: a Gynecologic Oncology Group Study.	Gynecologic Oncology 2013; 128(3):573-8.
ICON-7 Perren et al 2011	*Clinical Study Report – ICON7:* A randomised, two-arm, multi-centre Gynaecologic Cancer Inter Group trial of adding bevacizumab to standard chemotherapy (carboplatin and paclitaxel) in patients with epithelial ovarian cancer.	Report No. 1035868, November 2010.
	Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer.	New England Journal Medicine. 2011; 365(26):2484-96.
	Stark D, Nankivell M, Pujade-Lauraine E et al. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial.	Lancet Oncology 2013; 14(3):236-43.

Key randomised trials included in the submission

	Intervention arm	Comparator arm	Number enrolled in trial
			ITT
GOG-0218, blinded, Stage III or IV disease	6 three-week cycles of carboplatin and paclitaxel 22 three-week cycles of bevacizumab (15 mg/kg)	6 three-week cycles of carboplatin and paclitaxel 22 three-week cycles of placebo	1248
ICON-7, open-label, Stage 1 – IV disease	6 three-week cycles of carboplatin and paclitaxel 18 three-week cycles of bevacizumab (7.5 mg/kg)	6 three-week cycles of carboplatin and paclitaxel	1528

ITT = intention to treat. The subgroup analysis was planned for both trials (stratified randomisation).

Both trials stratified randomisation by stage of disease.

In ICON-7, the progression free survival (PFS) results were based on the standard RECIST definitions of a progression event and the overall survival (OS) results were not confounded by post-progression use of bevacizumab in either arm. ICON-7 was subject to observer bias because the trial was open-label without an independent review panel assessing the RECIST outcomes. The PBAC considered that this may bias the PFS results in favour of bevacizumab.

In GOG-0218, the blinded PFS results were assessed by an independent review panel. However, the PFS results emphasised in the submission were based on a modified intention to treat (ITT) analysis which censored patients who were defined as having a progression event due to elevated CA125 (defined according to Gynecologic Cancer Intergroup (GCIG) criteria) or because they received non-protocol therapy (NPT). The PBAC noted that censoring these patients appropriately limits the analysis to patients with the standard definition of a progression event. However, it introduces bias because the proportions of censored patients differ across the arms of the trial and censored patients are more likely to progress sooner than non-censored patients. Importantly, neither the full ITT analysis (including these patients and their extra progression events) nor the modified ITT analysis (censoring these patients) replicates the more straightforward approach of ICON-7: the protocol-defined composite of progression events in the full ITT analysis includes non-standard and non-validated CA125 events and NPT, whereas censoring patients with either of these events in the modified ITT analysis introduces a form of attrition bias.

The OS results for GOG-0218 were confounded because of continued treatment with bevacizumab after disease progression in the 15.1% of patients in the bevacizumab arm (biased in favour of bevacizumab) and because of cross-over to treatment with bevacizumab after disease progression in 27.7% of patients in the comparator arm (biased against bevacizumab).

Overall, the PBAC did not accept that the results of this trial provided an acceptable basis for its consideration in place of, or in addition to, the results of ICON-7.

The PBAC therefore decided, when judging comparative effectiveness, to rely more heavily on the results of the ICON-7 trial (particularly those presented for the 31 March 2013 data cut-off).

With regard to the assumption of constant proportional hazards and interpretation of hazard ratios for ICON-7, a formal statistical assessment of the assumption of constant proportional hazards was reported. The assessment showed that the assumption was not satisfied. This is consistent with the visual observation of the Kaplan-Meier curves: for example, for the ITT population, the PFS Kaplan-Meier curves for bevacizumab and control cross each other. The PBAC therefore decided to rely on the log rank test and the restricted means rather than hazard ratios when interpreting the results of ICON-7. The PBAC noted that it had no formal statistical basis to determine whether the assumption of constant proportional hazards held for the results of GOG-0218.

The PBAC did not accept the submission's meta-analyses of GOG-0218 and ICON-7 based on hazard ratios as being appropriate. This was because of (1) the concerns noted above with interpreting the results of GOG-0218, and (2) because the assumption of constant proportional hazards was not satisfied for the results of ICON-7 means that it is not appropriate to rely on hazard ratios reported for this trial. In relation to the assumption of constant proportional hazards, the PBAC considered that the general trend of reducing hazard ratio with later cut-off dates suggested (without formal statistical assessment) converging hazards, rather than constant proportional hazards, over time. The PBAC also noted that the hazard ratios for both PFS and OS vary across both trials depending on the date of cut-off of the analysis. The PBAC considered that, given the different median durations of follow-up

across the trials, this raised further difficulties in interpreting the results of any meta-analysis of the two trials.

The PBAC also noted that National Institute for Clinical Excellence (NICE) technology appraisal guidance 284 (*Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer*) indicated that the "…manufacturer did not consider that a meta-analysis was appropriate because GOG-0218 and ICON7 used different doses and durations of bevacizumab, and different study populations." The PBAC noted that this was not consistent with the manufacturer's approach in this submission, which relied extensively on the meta-analysis.

The submission preferred the results for the subgroup analyses of high-risk patients over the ITT results from the trials and only used the high-risk subgroup results in its economic model. The PBAC recalled its general preference for ITT results over subgroup results (e.g. its November 2012 preference for ITT results for trastuzumab in gastric cancer) unless there is sufficient basis to accept a subgroup analysis in a particular circumstance. The PBAC noted the following aspects of this submission's subgroup analyses which contributed to their reliability:

- A biological rationale for treatment effect variation by subgroup was based on bulky tumours and the mechanisms of action of bevacizumab on tumour vascularisation, tumour growth and metastasis. The PBAC noted that this rationale was more convincing with regard to the results of the ICON-7 trial than the GOG-0218 trial, because the GOG-0218 trial showed a reduced treatment effect when moving from the ITT population to the high-risk subgroup.
- The high-risk subgroup was pre-specified in ICON-7 with relevant characteristics included in the stratification of patients at randomisation.
- On 29 September 2013, Oza et al presented a statistical test for interaction (P=0.01 for OS) between the nominated subgroup and its complement subgroup from the ITT population.
- Although ICON-7 raises the issue of multiplicity by separately reporting ten other subgroup analyses (see Figure 3S, Supplementary Appendix, Perren et al, NEJM 2011;365(26):2484-96), the prominence of the high-risk subgroup is emphasised through the way the results for this subgroup were included in this published paper and in the final analysis of the trial presented by Oza et al on 29 September 2013 at the European Cancer Congress.

On balance, the PBAC considered that, given these considerations, the subgroup analysis of ICON-7 provided a more reliable basis than the ITT population to consider the comparative effectiveness of bevacizumab in high-risk ovarian cancer as defined for the requested restriction.

8. Results of Trials

Dose intensity

Bevacizumab 15mg/kg was delivered for up to 22 cycles in the GOG-0218 trial compared with 7.5mg/kg delivered for up to 18 cycles in the ICON-7 trial. The submission stated that the treatment effect in terms of PFS (in the high-risk subgroup) as measured in its meta-analysis of the two trials using hazard ratios did not indicate that bevacizumab dose was a

significant treatment effect modifier (test for interaction p-value=0.93). The submission also stated that no significant treatment effect associated with bevacizumab dose was evident in the corresponding meta-analysis of overall survival for the high-risk subgroup.

The PBAC considered that, as there is no convincing evidence of any additional clinical benefit from using a dose of 15 mg/kg for 22 cycles (a duration of about 15 months as in GOG-0218) compared with a dose of 7.5 mg/kg for 18 cycles (a duration of about 12 months as in ICON-7), the use of the higher dose and the longer duration, with the associated increased risk of adverse events, was not justified.

Progression free survival

The PBAC noted the following data presented by Oza et al on 29 September 2013 at the European Cancer Congress, as the final PFS and OS results from ICON-7 from the 31 March 2013 data cut-off.

Summary of final PFS and OS results for high-risk subgroup of ICON-7

Outcome	Beva + chemo	Chemo	Increment	Log-rank test
Restricted mean PFS	20.0 months	15.9 months	4.1 months	P=0.001
Restricted mean OS	39.3 months	34.5 months	4.8 months	P=0.03

The sponsor's pre-PBAC response also provided pre-publication results of the final PFS and OS results for ICON-7 (31 March 2013 data cut-off, with 46% of patients having died and a median duration of follow-up of 49 months). The final analysis of the ICON-7 trial presented by Oza et al on 29 September 2013 is available here.

Quality of life

The submission relied on European Quality of Life – 5 Dimensions instrument (EQ-5D) results from ICON-7 to conclude that there is no difference in quality of life (QoL) when bevacizumab is added to carboplatin plus paclitaxel. The PBAC considered that this instrument is not sensitive to small changes in quality of life. By contrast, Stark et al, 2013 report quality of life (QoL) results on the global QoL score on the European Organisation for Research and Treatment of Cancer Quality of Life Questionaire (EORTC QLQ-C30), (a more sensitive instrument, range 0-100 points, with 100 being best QoL) for the ICON-7 trial. The results are summarised in the following table.

Mean global quality of life score from EORTC QLQ-C30 for ICON-7

Outcome	Beva + chemo mean (SD)	Chemo mean (SD)	Difference (95% CI)
Baseline (before randomisation)	55.1 (20.8)	58.6 (20.6)	
Week 18 (end of chemotherapy)	59.2 (19.4)	64.4 (20.3)	-5.1 (-7.4 to -2.9)
Week 54 (end of extended bevacizumab)	69.7 (19.1)	76.1 (18.2)	-6.4 (-9.0 to -3.7)

SD = standard deviation; CI = confidence interval

The PBAC considered that, although the submission did not adequately define a clinically important difference in QoL, these results indicate that adding bevacizumab to chemotherapy reduces the improvement in QoL.

Please refer to Section 10 for more details on the data from the ICON-7 trial.

With regard to comparative harms, the number of patients who experienced at least one Grade 3, 4 or 5 adverse event were higher in the bevacizumab arm of ICON-7 and, when excluding laboratory adverse events, were higher also in the bevacizumab arm of GOG-0218. The number of patients who experienced serious adverse events was higher in the bevacizumab arm of ICON-7 and was not reported in GOG-0218. Discontinuations due to adverse events were more common in the bevacizumab arms of both key trials and deaths were numerically more common.

9. Clinical Claim

The submission described treatment with up to 22 cycles of bevacizumab in combination with 6 cycles of paclitaxel and carboplatin as superior in terms of comparative effectiveness and inferior in terms of comparative safety over 6 cycles of paclitaxel and carboplatin alone for patients with Stage IIIB/IIIC sub-optimally de-bulked or Stage IV ovarian cancer.

The PBAC considered that the claim of superior comparative effectiveness with regard to PFS and OS was reasonable, based on the high-risk subgroup results of the ICON-7 trial for up to 18 cycles of bevacizumab.

The PBAC considered the claim of inferior comparative safety to be reasonable.

10. Economic Analysis

A modelled economic evaluation (cost-utility analysis) was presented in the submission, based on the clinical claim of superior efficacy and inferior safety of bevacizumab plus chemotherapy compared with chemotherapy alone. The submission presented a stepped economic evaluation, based on the direct randomised trials and using variables reported in the premodelling studies.

There were three health states in the model – progression-free, progression and death. The Kaplan-Meier estimates of PFS, time to off-treatment (TTOT) and OS were used to predict incremental treatment costs, administration costs and overall effectiveness of the therapies. The population was assumed to enter the model in a progression-free health state and weekly transition probabilities among the health states were estimated using the Kaplan-Meier data of PFS and OS for each treatment arm.

Costs of healthcare resource provision were assumed to accrue every three weeks during TTOT in both arms of the model. The cost of adverse events associated with bevacizumab was assumed to be a one-off cost applied in the first week of model.

The submission presented an Incremental Cost Effectiveness Ratio (ICER) of between $45,000 and 75,000 per Quality Adjusted Life Year (QALY) based on the pooled high-risk subgroup progression-free outcomes of the GOG-0218 and ICON-7 trials for each treatment arm. Pooled overall survival estimates were calculated from the bevacizumab arm of both trials but overall survival estimates came from the comparator arm of ICON-7 alone. These estimates were extrapolated to 10 years from the pooled median follow-up of 26 months in the trials. Utility weights from ICON-7 were used. The high-risk subgroup was used in the model. Adverse event results were included.

The PBAC agreed with the Economic Sub-Committee (ESC) regarding the model that:

- the modelled overall survival gain was overestimated compared with the observed overall survival gain over 60 months for the proposed high-risk subgroup reported by Oza et al (difference in restricted means of 4.8 months)
- the modelled PFS gain was relatively close to the observed PFS gain over 60 months for the proposed high-risk subgroup reported by Oza et al (difference in restricted means of 4.1 months).

The extrapolation method for the model used the OS data from the trials, with shorter durations of median follow-up. The PBAC accepted the ESC advice that the different extrapolation methods generate results showing large variability, with consequent variability in the derived ICER from the economic model. This variability highlighted the problem of immature data

Extrapolation from the pooled median trial follow-up (26.18 months) to 10 years was the key driver of the final ICER. The PBAC noted that the majority of the benefit was derived in the extrapolated period of the model.

The modelled OS curves between the two arms diverge further after the trial median follow-up, suggesting that the modelled treatment effect of bevacizumab increases in the unobserved (extrapolated) period compared to the trial period. The modelled two OS curves do not converge until well into the extrapolated period.

The comparisons of trial-based PFS and OS curves with the modelled PFS and OS curves indicate that the truncation points for extrapolation of PFS at 24 months and OS at 26 months appear to be the time points after which the treatment effects in terms of both PFS and OS decrease rapidly.

The submission presented a number of univariate sensitivity analyses and claims that the model is robust and stable given that the results of the various sensitivity analyses presented. However, the submission failed to perform sensitivity analyses for a number of key variables/assumptions.

Firstly, the model assumed that, in both the base case and sensitivity analyses, there is a continued treatment effect in terms of both PFS and OS beyond the trial duration. 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 including the method of extrapolation in the model were not addressed.

Secondly, the use of OS data from ICON-7 for the chemotherapy arm and the combined GOG-0218 and ICON-7 trials for the bevacizumab arm in the model enlarged the OS benefit observed in the trials. During the evaluation, an additional sensitivity analysis was conducted to examine the impact on the final ICER of using OS data from ICON-7 for both model arms – the ICER increased to between $75,000 and $105,000/QALY from the base case of between $45,000 and $75,000/QALY. The sponsor's Pre Sub-Committee Response argued that a sensitivity analysis using the data for OS from the ICON-7 for both arms yields an ICER of between $45,000 and $75,000/QALY. The PBAC noted that it was not possible for the ESC to verify this ICER independently. The PBAC agreed with the ESC advice that given

the degree of variability in these results, it was unclear to what extent the ICER was driven by treatment effect and the method of extrapolation of survival beyond median follow up in the trial.

Thirdly, 95% confidence limits of progression-free survival and overall survival, as observed during trial period, were not examined in the modelled economic evaluation. The model also did not allow differential QoL data between model arms, despite the likely increase in adverse events associated with the addition of bevacizumab to chemotherapy.

The PBAC considered that, despite its concerns with the model inputs, the model structure was reasonable. The PBAC further noted that the sponsor had proposed a price based on a price reduction to be applied to patients receiving bevacizumab at the TGA-approved dose of 15 mg/kg every three weeks for up to 15 months. The PBAC therefore considered a respecified base case in the modelled economic evaluation under the following conditions:

- retaining the price per milligram rebate as offered
- reducing the dose to 7.5 mg/kg every three weeks
- reducing the treatment duration to up to 18 cycles
- using data from the 31 March 2013 data cut-off for ICON-7 high-risk subgroup only with a median duration of follow-up of 49 months from the ITT population.

Using these parameters resulted in a reduced respecified base case ICER though it remained in the range $45,000-75,000/QALY.

After respecifying the base case, using 49 months truncation date (the median follow up in the ITT population of ICON-7 trial), the PBAC noted that this had reduced the effect of extrapolation on the ICER and associated uncertainty.

The PBAC noted the following outstanding issues with the respecified model:

- No disutility was assumed for bevacizumab in the model. While not accepting that patients on bevacizumab would incur no disutility, the PBAC considered that an appropriate disutility value would be difficult to estimate. Additionally, the PBAC considered that even assuming a high disutility of 0.1 over the duration of treatment, it would make less than $10,000 difference in the ICER.
- Safety in the high-risk subgroup was not captured in the model. The PBAC noted small numbers in most of the adverse events (AEs) presented, and the AE rates were not adjusted for time on treatment, which would be expected to differ across the ITT and high-risk populations.
- The model assumed a continued treatment effect beyond 49 months. Reducing the model duration to 5 years (11 months following the end of median follow up) would increase the ICER (though remaining in the range $45,000-75,000/QALYG). While noting that the higher ICER under the respecified conditions would not accurately reflect bevacizumab's cost effectiveness, this adjustment illustrated the proportion of the ICER which was derived from extrapolation.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 1,000 in Year 5, at an estimated net cost per year to the PBS of $10 – 30 million in Year 5.

The PBAC accepted the Drug Utilisation Sub-Committee (DUSC) advice that the incidence approach to estimate patient numbers only accounted for use in patients who are diagnosed with stage IIIB, IIIC or IV disease. The submission did not account for patients diagnosed with earlier stage disease who progress and become eligible to use bevacizumab, or existing prevalent patients diagnosed in previous years who meet the criteria. This results in a substantial underestimation of eligible patients in the first year and a lesser degree of underestimation in the subsequent years.

The PBAC agreed with the DUSC that, in practice, it is likely bevacizumab will be used in a broader patient population that is outside the restriction. There is likely to be use in patients with stage IIIB or IIIC disease who are optimally debulked. Patients with previously treated stage IIIB, IIIC or IV disease may also receive bevacizumab as second or subsequent line therapy.

The duration of treatment was considered by DUSC to be potentially underestimated. The financial estimates assume patients will cease treatment after a maximum of 22 cycles. The GOG-0218 trial administered bevacizumab at a dose of 15 mg/kg for 22 cycles. The ICON-7 trial administered bevacizumab at a dose of 7.5 mg/kg for 18 cycles. Using the ICON-7 trial data in the duration estimates reduces the proportion of patients continuing beyond 18 weeks and underestimates duration of treatment. In practice, patients may use bevacizumab for longer, including beyond disease progression.

The risk share arrangement (RSA) described in the submission is for a rebate to create a price as the basis for calculating the ICER. This outcome is normally provided through a Special Pricing Agreement (SPA), rather than an RSA. No cap was proposed to manage the risk of use outside of the restriction.

The PBAC advised that the RSA could be constructed to provide a cap on the patient numbers in the submission.

Overall, the PBAC agreed with the DUSC that the submission's estimates of utilisation and cost were underestimated.

12. Recommendation and Reasons

The PBAC recommended the listing of bevacizumab for previously untreated advanced epithelial ovarian, fallopian or primary peritoneal cancer, on the basis that it should be available only under special arrangements under the Section 100 (Efficient Funding of Chemotherapy) Program. The PBAC recommended the special arrangements described in the restriction table below apply (see Recommended Listing).

The PBAC was satisfied that the addition of bevacizumab provides, for some of these patients, a significant improvement in efficacy over chemotherapy alone, however noted that the addition of bevacizumab worsened the safety profile compared with chemotherapy alone.

The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of adding bevacizumab would only be acceptable if (a) the offered price were to be retained, but that the dose and duration of bevacizumab were to be reduced from that proposed in the submission to 7.5 mg/kg and up to 18 cycles, respectively, so that the ICER generated by the economic model, respecified as recommended by the PBAC, falls to about $45,000-75,000/QALY, and (b) the following measures were implemented to contain risks associated with the cost of bevacizumab to the PBS for ovarian cancer:

- a Deed of Agreement to support an SPA as proposed in the submission
- in the absence of any justification for any other rebate amount, an RSA which includes a rebate to the Commonwealth above expenditure caps determined with reference to dose, duration of treatment and number of patients each year as modified to the Government's satisfaction to reflect DUSC Advice on these estimates presented in the submission.

The PBAC noted the high clinical need for treatments for ovarian cancer following surgery, with a lack of new treatments in recent years. The PBAC noted 14 consumer comments from individuals (including three health professionals) and 2 organisations for this item, highlighting the clinical need for new therapeutic options in ovarian cancer.

The submission nominated doublet chemotherapy alone, comprising carboplatin and paclitaxel, as the comparator regimen. The submission proposed that bevacizumab would be added to doublet chemotherapy. The PBAC considered the comparator reasonable, however noted that docetaxel or cisplatin may replace paclitaxel or carboplatin respectively in some regimens. The PBAC noted also that monotherapy with carboplatin or paclitaxel may be used in some instances.

The PBAC noted that the submission presented two trials, GOG-0218 and ICON-7, neither of which demonstrated an incremental overall survival (OS) benefit in their ITT population. In relation to GOG-0218, the PBAC noted the following issues which reduced the Committee's confidence in relying on its results:

- Informative censoring – the PFS results were obtained from a modified ITT analysis which required censoring of patients defined as having a progression event due to elevated CA125 or because they received non-protocol therapy. The PBAC noted that while censoring these patients limited the analysis to the standard definition of a progression event, the proportions of censored patients differed across the arms of the trial. Censored patients were also more likely to progress sooner or later than non-censored patients. Overall, the PBAC considered that this biased the PFS results in favour of bevacizumab.
- Cross-over - 27.7% of patients in the comparator arm crossed over to receive bevacizumab after disease progression. The extent of cross-over was not reported in GOG-0218 for the high-risk subgroup analysis. The PBAC considered that this biased the overall survival results against bevacizumab.
- Continuation beyond progression - 15.1% of patients in the bevacizumab arm continued bevacizumab after disease progression. The PBAC considered that this biased the OS results in favour of bevacizumab.

The PBAC therefore decided, when judging comparative effectiveness, to rely more heavily on the results of the ICON-7 trial which did not raise any of these issues, even though it was conducted as an open-label trial, which may bias the PFS results in favour of bevacizumab. However, a formal statistical assessment of an assumption of constant proportional hazards was reported for ICON-7, which showed that the assumption was not satisfied. The PBAC concluded that the hazard ratios were a poor basis on which to assess the comparative effectiveness of bevacizumab. The PBAC therefore decided to rely on the difference in restricted means as the best, but still suboptimal, means of quantifying the incremental benefit of bevacizumab.

The sponsor's pre-PBAC response provided pre-publication results of the final PFS and OS results for ICON-7 (31 March 2013 data cut-off, 49 months median duration of follow-up with 46% of patients having died, presented by Oza et al on 29 September 2013). The PBAC relied on these final results which were presented for both the ITT population and the high-risk subgroup.

The PBAC did not accept the submission's meta-analyses of GOG-0218 and ICON-7 based on hazard ratios as being appropriate because of the concerns with interpreting the results of GOG-0218 already listed and because not satisfying the assumption of constant proportional hazards for the results of ICON-7 means that it is not appropriate to rely on hazard ratios reported for this trial. Furthermore, the PBAC noted that it had no formal statistical basis to determine whether the assumption of constant proportional hazards held for the results of GOG-0218. In this regard, the PBAC considered that the general trend of reducing hazard ratio with later cut-off dates suggested converging hazards, rather than constant proportional hazards, over time. The PBAC also noted that the hazard ratios for both PFS and OS vary across both trials depending on the date of cut-off of the analysis. The PBAC considered that, given the different median durations of follow-up across the trials, this raised further difficulties in interpreting the results of any meta-analysis of the two trials.

The PBAC also noted that the guidance issued by the National Institute for Clinical Excellence indicated that the "…manufacturer did not consider that a meta-analysis was appropriate because GOG-0218 and ICON7 used different doses and durations of bevacizumab, and different study populations." The PBAC noted that this was not consistent with the manufacturer's approach in this submission, which relied extensively on the meta-analysis.

The PBAC considered that, in view of the issues affecting the GOG-0218 trial and the need to rely on hazard ratios to conduct the meta-analysis, the submission's pooled analyses including the results of GOG-0218 did not form a robust basis for assessing the comparative effectiveness of bevacizumab in ovarian cancer. In reaching this conclusion, the PBAC noted that the TGA had considered that GOG-0218 provided the most reliable basis for registration. However, the PBAC noted that it was relying on more recent data from the 31 March 2013 data cut-off for ICON-7, which were not available to the TGA at the time of registration.

The submission preferred the results for the subgroup analyses of high-risk patients over the ITT results from the trials and only used the high-risk subgroup results in its economic model. The PBAC noted the following aspects of this submission's subgroup analyses which contributed to their reliability:

- A biological rationale for treatment effect variation by subgroup was based on bulky tumours and the mechanisms of action of bevacizumab on tumour vascularisation, tumour growth and metastasis. The PBAC noted that this rationale was more convincing with regard to the results of the ICON-7 trial than the GOG-0218 trial, because the GOG-0218 trial showed a reduced treatment effect when moving from the ITT population to the high-risk subgroup.
- The high-risk subgroup was pre-specified in ICON-7 with relevant characteristics included in the stratification of patients at randomisation.
- On 29 September 2013, Oza et al presented a statistical test for interaction (P=0.01 for OS) between the nominated subgroup and its complement subgroup from the ITT population.
- Although ICON-7 raises the issue of multiplicity by separately reporting ten other subgroup analyses, the high-risk subgroup is emphasised through results for this subgroup in this published paper and in the final analysis of the trial presented by Oza et al on 29 September 2013 at the European Cancer Congress.

On balance, the PBAC considered that, given these considerations, the subgroup analysis of ICON-7 provided a more reliable basis than the ITT population to consider the comparative effectiveness of bevacizumab in high-risk ovarian cancer as defined for the requested restriction.

The PBAC considered that bevacizumab did demonstrate clinical benefit in terms of both PFS and OS for the high-risk subgroup, however accurately quantifying the incremental benefit was difficult. The PBAC considered, based on the 31 March 2013 data cut-off restricted mean results of ICON-7, that patients using bevacizumab with chemotherapy have approximately 4.1 months additional PFS (log-rank P=0.001) and 4.8 months additional OS (log-rank P=0.03) compared with patients using chemotherapy alone.

Although the submission relied on EQ-5D results from ICON-7 to conclude that there is no difference in quality of life (QoL) when bevacizumab is added to carboplatin plus paclitaxel,

the PBAC considered that this instrument is not sensitive to small changes in quality of life. By contrast, using a more sensitive instrument, Stark et al, 2013 for the GOG-0218 trial, indicated small but statistically significantly reduced improvements in quality of life from baseline with the addition of bevacizumab at 18 weeks (end of chemotherapy) and at 54 weeks (end of extended bevacizumab). The PBAC considered that the submission did not adequately demonstrate a clinically important difference in QoL.

The numbers of patients who experienced at least one Grade 3, 4 or 5 adverse event were higher in the bevacizumab arm of ICON-7 and, when excluding laboratory adverse events, were higher also in the bevacizumab arm of GOG-0218. The number of patients who experienced serious adverse events was higher in the bevacizumab arm of ICON-7 and was not reported in GOG-0218. Discontinuations due to adverse events were more common in the bevacizumab arms of both key trials and deaths were numerically more common.

The PBAC therefore concluded that the addition of bevacizumab to chemotherapy worsened quality of life and increased toxicity.

The PBAC considered that, as there is no convincing evidence of any additional clinical benefit from using a dose of 15 mg/kg for a duration of 22 cycles (as in GOG-0218) compared with a dose of 7.5 mg/kg for 18 cycles (as in ICON-7), use of the higher dose and longer duration, with the associated increased risk of AEs, was not justified. The PBAC therefore recommended that PBS subsidy be limited to a dose of 7.5 mg/kg every three weeks for a maximum of 18 cycles. The PBAC considered this to be consistent with the evidence and with prudent prescribing in using the lowest effective dose for the shortest duration.

In relation to the economic evaluation, the PBAC considered that the model structure was reasonable, although the inclusion of inputs from GOG-0218 (included in the pooled data) meant that the resulting ICER could not be relied upon, especially as the model was restricted to a median duration of follow-up which was much less than the 31 March 2013 data cut-off for ICON-7.

The PBAC considered that the base case ICER of $45,000-75,000 was underestimated, noting that the magnitude of the benefit was difficult to estimate and that the majority of the benefit was derived in the extrapolated period of the model. In particular, the PBAC noted that in the modelled economic evaluations presented in the submission and in the pre-PBAC response, the modelled PFS and OS benefit suggested that the treatment effect of bevacizumab on OS increased in the unobserved (extrapolated) period compared to the observed (trial) period. The modelled OS curves did not converge until well into the extrapolated period. The PBAC considered that having the majority of the estimated survival benefit generated during the extrapolated period decreased the reliability of the overall modelled incremental OS estimate. In particular, the PBAC concluded that this was a substantial overestimate compared with that which would be extrapolated from observed OS restricted mean difference of 4.8 months from the 31 March 2013 data cut-off for the ICON-7 high-risk subgroup, noting that the extrapolation would be taken from Kaplan-Meier OS curves which had already converged by 49 months (the median duration of follow-up).

The PBAC noted that the sponsor had proposed a price based on a price reduction to be applied to patients receiving bevacizumab at the TGA-approved dose of 15 mg/kg every three

weeks for up to 15 months. The PBAC considered a respecified base case in the modelled economic evaluation under the following conditions:

- retaining the price per milligram rebate as offered
- reducing the dose to 7.5 mg/kg every three weeks
- reducing the treatment duration to up to 18 cycles
- using data from the 31 March 2013 data cut-off for ICON-7 high-risk subgroup only with a median duration of follow-up of 49 months.

The respecified model resulted in a new base case ICER of $45,000-75,000 per QALY gained, which the PBAC considered acceptably cost effective to provide a basis for a positive recommendation. The PBAC was also reassured that this respecified model was much less sensitive to different approaches to extrapolating the OS from the final ICON-7 dataset than from earlier durations of follow-up.

The PBAC recommended that a risk share agreement be negotiated with the sponsor, with thresholds reflective of the price per milligram offered in the submission, a dose of 7.5mg/kg and a treatment duration of up to 18 cycles.

The PBAC recommended that the initial PBS restriction specify that bevacizumab be used in combination with chemotherapy, without specifying a doublet chemotherapy regimen of carboplatin and paclitaxel as proposed by the sponsor. The PBAC considered that a restriction that specified carboplatin and paclitaxel as the specific doublet chemotherapy regimen would be unduly directive to prescribers, and would preclude the possibility of substitution of docetaxel or cisplatin into the regimen. The PBAC also recommended that the initial restriction should permit monotherapy chemotherapy regimens.

On balance, the PBAC accepted the sponsor's request to exclude patients with optimally debulked disease as being most directly supported by the high-risk subgroup analysis of ICON-7 trial, even though these patients have a similar prognosis to patients with suboptimally debulked disease. However, the PBAC considered that there would be some subjectivity in assessing the optimality of debulking and agreed with DUSC advice that it is likely that bevacizumab would be used beyond this intention of the restriction.

The PBAC advised under section 101(3BA) that it did not consider that bevacizumab for ovarian cancer could be considered interchangeable with any other PBS-listed drugs on an individual patient basis.

The PBAC recommended that the Safety Net 20 Day Rule should not apply.

The PBAC recommended that bevacizumab is not suitable for prescribing by nurse practitioners.

Outcome:
Recommended

Suggested wording for the restriction (final restriction to be finalised):

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Proprietary Name and Manufacturer	
BEVACIZUMAB				
bevacizumab, 100 mg/4 mL injection, 1 x 4 mL vial	900 mg	5	Avastin	RO
bevacizumab 400 mg/16 mL injection, 1 x 16 mL vial	900 mg	5		

Severity:	Advanced FIGO Stage IIIB, IIIC or Stage IV
Condition:	epithelial ovarian, fallopian tube or primary peritoneal cancer
Treatment phase:	Initial treatment
Restriction:	Section 100 – Efficient Funding of Chemotherapy Private Hospital/Private Clinic Authority Required Public Hospital Authority Required *(STREAMLINED)*
Clinical criteria:	The condition must be suboptimally debulked (maximum diameter of any gross residual disease > 1 cm) AND The patient must have a WHO performance status of 2 or less AND The condition must be previously untreated AND The treatment must be commenced in combination with platinum-based chemotherapy AND The treatment must not exceed a dose of 7.5 mg per kg every 3 weeks. AND The treatment must not exceed a lifetime total of 18 cycles of bevacizumab for epithelial ovarian, fallopian tube or primary peritoneal cancer
Prescriber instructions:	The patient's WHO performance status and body weight must be documented in the patient's medical records at the time the treatment cycle is initiated.
Administrative advice:	Note: Special Pricing Arrangements apply

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Proprietary Name and Manufacturer
BEVACIZUMAB			Avastin RO
bevacizumab, 100 mg/4 mL injection, 1 x 4 mL vial	900 mg	11	
bevacizumab 400 mg/16 mL injection, 1 x 16 mL vial	900 mg	11	

Severity:	Advanced FIGO Stage IIIB, IIIC or Stage IV
Condition:	epithelial ovarian, fallopian tube or primary peritoneal cancer
Treatment phase:	Continuing treatment
Restriction:	Section 100 – Efficient Funding of Chemotherapy Private Hospital/Private Clinic Authority Required Public Hospital Authority Required *(STREAMLINED)*
Clinical criteria:	The patient must have previously received PBS-subsidised treatment with bevacizumab for this condition AND The patient must not have progressive disease AND The treatment must not exceed a dose of 7.5 mg per kg every 3 weeks AND The treatment must not exceed a lifetime total of 18 cycles of bevacizumab for epithelial ovarian, fallopian tube or primary peritoneal cancer
Administrative advice	Note: Special Pricing Arrangements apply

13. 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.

14. Sponsor's Comment

Roche acknowledges the PBAC's positive recommendation to list bevacizumab on the PBS for the first-line treatment of patients with high-risk advanced ovarian cancer; however, is not able to accept the conditions of the positive recommendation as requested by the PBAC. The listing of bevacizumab for the front-line treatment of advanced ovarian cancer is important in an area where there has been a lack of new treatment advances and a high unmet clinical

need. A resubmission was submitted for the March 2014 PBAC meeting with the aim of working with the PBAC to achieve a PBS listing for patients at the earliest opportunity.