



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Bevacizumab (recombinant humanised)

Proprietary Product Name: Avastin

Sponsor: Roche Products Pty Ltd

March 2013

TGA Health Safety
Regulation

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- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to product submission

Submission details

<i>Type of Submission</i>	Extension of indications
<i>Decision:</i>	Approve
<i>Date of Decision:</i>	24 August 2012
<i>Active ingredient:</i>	Bevacizumab (recombinant humanised)
<i>Product Name:</i>	Avastin
<i>Sponsor's Name and Address</i>	Roche Products Pty Ltd PO Box 255 Dee Why NSW 2090
<i>Dose form:</i>	Injection concentrate
<i>Strengths:</i>	100 mg/4 mL and 400 mg/16 mL
<i>Container:</i>	Vial
<i>Pack size:</i>	1
<i>Approved Therapeutic use:</i>	Avastin (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.
<i>Route of administration:</i>	Intravenous infusion
<i>Dosage (abbreviated):</i>	15 mg/kg once every 3weeks
<i>ARTG Numbers:</i>	99755, 99757

Product background

Bevacizumab is a recombinant humanised (rch) monoclonal antibody that binds to and inhibits human vascular endothelial growth factor (VEGF). It is produced in Chinese Hamster Ovary cells. Inhibition of VEGF prevents new blood vessel formation, thereby inhibiting tumour growth and metastasis.

Bevacizumab is registered in Australia for the first line treatment of epithelial ovarian, fallopian tube and primary peritoneal cancer, in combination with carboplatin and paclitaxel. It is also registered for the treatment of several other cancers (breast, lung, colorectal, renal and glioma).

This AusPAR describes the application by Roche Australia Pty Ltd (the sponsor) to extend the approved indications for Avastin to include the following:

AVASTIN (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.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) in February 2005. Applications have been approved in the European Union (EU) (24 October 2012) and Switzerland (17 December 2012).

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. The full clinical findings can be found in Attachment 2.

Introduction

Background and rationale

Earlier evidence has shown that the VEGF family plays a central role in ovarian cancer pathogenesis and progression. This led to the development of a comprehensive development programme for bevacizumab in ovarian cancer.

An application to extend the use of bevacizumab in combination with carboplatin and paclitaxel for the front line treatment of patients with epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer was approved by the TGA in February 2012¹. The current application focuses on the use of bevacizumab in the recurrent setting.

Scope of the clinical dossier

The clinical data comprised full reports together with tabular summaries of the pivotal Study AVF4095g, also known as OCEANS, which was a multicentre, randomised, Phase III study of Avastin in combination with carboplatin and gemcitabine chemotherapy for the treatment of patients with recurrent, platinum sensitive epithelial ovarian carcinoma, primary peritoneal carcinoma, and fallopian carcinoma. Full reports of efficacy and safety in relation to this pivotal trial are provided.

Also submitted is data in relation to reviews of studies demonstrating adverse effects seen with the “off-label intraocular” use of bevacizumab for the treatment of macular degeneration. This involves two company study reports and four published papers to support changes in the PI: details of the PI revisions in relation to this issue are beyond the scope of this AusPAR.

¹ The AusPAR for this application is located at <http://www.tga.gov.au/pdf/auspar/auspar-bevacizumab-120806.pdf>

Paediatric data

There are no specific paediatric clinical data in the submission.

Good clinical practice

All aspects of good clinical practice have been observed.

Pharmacokinetics

No new studies were provided.

Pharmacodynamics

No new studies were provided.

Efficacy**Dosage selection for the pivotal study**

A dose of bevacizumab of 15 mg/kg every 21 days is equivalent to a dose of 5 mg/kg per week and is the most commonly used dose of bevacizumab that has been shown to be effective in clinical trials across multiple tumour types. This dose was also studied in two single arm Phase II studies in ovarian cancer by the Gynaecological Oncology Group (GOG), demonstrating definite activity of bevacizumab as a single agent. This was thus the dose chosen for the subsequent first line Phase III trial conducted by the GOG of bevacizumab in combination with carboplatin and paclitaxel; this regimen has also been chosen by the GOG for the pivotal study in this submission (AVF4095g) in the recurrent setting.

It should also be noted that the combination chemotherapy regimen for this pivotal trial was based on the results of earlier studies in which patients with platinum sensitive recurrent disease received gemcitabine (Gemzar) and carboplatin. Results of this study showed an improvement in response rates and progression free survival (PFS) with this drug combination compared with single agent carboplatin. These data have subsequently been approved in the United States and Europe thereby establishing gemcitabine in combination with carboplatin as a standard second line combination for the management of ovarian cancer.

Summary of studies

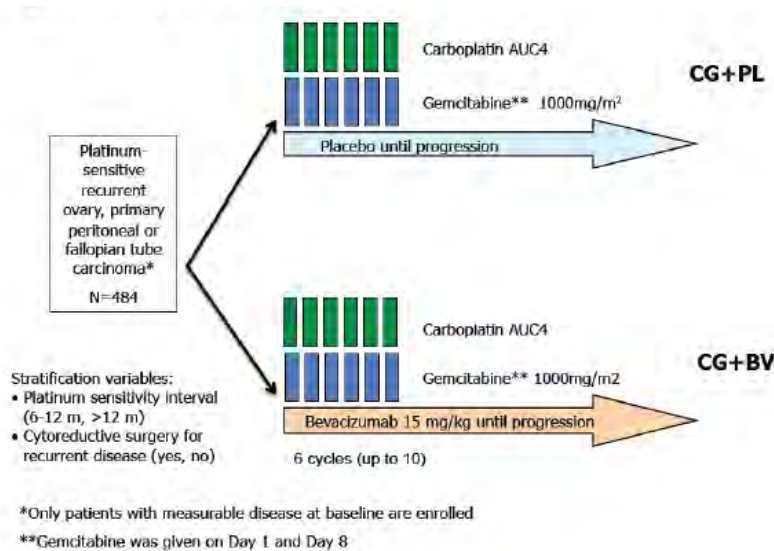
A single study is presented in this submission, being the pivotal Phase III trial AVF4095g which was designed to support an extension of the indication for bevacizumab in combination with carboplatin and gemcitabine for the treatment of patients with recurrent, platinum sensitive epithelial ovarian cancer, fallopian tube cancer and primary peritoneal cancer. The study was sponsored and conducted by Genentech Inc. and enrolled 484 patients over 33 months in 96 sites in the United States. The first patient was enrolled in April 2007 and the last enrolled in January 2010, with a clinical cut-off date for efficacy endpoints on the 17th September 2010.

The pivotal study was a randomised, double blind, placebo controlled, multicentre Phase III study evaluating the efficacy and safety of IV carboplatin (area under the curve (AUC) dose of 4 mg/mL.min² on Day 1, every 21 Days) and IV gemcitabine (1000 mg/m² on Days

² From the AVF4095g study report: the carboplatin dose was calculated to reach a target AUC of concentration multiplied by time according to the Calvert formula with use of an estimated glomerular filtration rate (GFR);

1 and 8, every 21 Days) plus concomitant and extended bevacizumab (IV dose of 15 mg/kg on Day 1, every 21 Days). This was compared to carboplatin and gemcitabine plus concomitant and extended placebo in women with recurrent, platinum sensitive epithelial ovarian cancer, fallopian tube cancer and primary peritoneal cancer. The design of the study is presented in Figure 1.

Figure 1. Study AVF4095g schema



Key efficacy results from the pivotal study are summarised in the Delegate's overview, under the section on *Overall Conclusion and Risk/benefit Assessment*, below.

Evaluator's summary and conclusions on clinical efficacy for the proposed indication.

The data from a reasonably sized study have clearly shown that the addition of bevacizumab to combination chemotherapy of carboplatin and gemcitabine is associated with a statistically significant increase in PFS of four months, and also a significantly increased overall response rate (ORR). Nevertheless, at this time the data is not yet supported by the improvement in overall survival (OS), but as the data is relatively immature, with only 29% of patients having died at the time of final data cut-off, further follow up would be appropriate. Nevertheless, all sensitivity analyses and sub-group evaluations confirm the apparent benefit of the addition of bevacizumab to chemotherapy in these patients.

Even though the median duration of PFS improvement is only of the order of four months, in the context of recurrent disease in patients whose survival will be limited, this prolongation of PFS can be considered clinically meaningful.

Safety

Studies providing evaluable safety data

Safety data for this evaluation comes from the pivotal study AVF4095g. Safety data was recorded up to the 17 September 2010 from a total of 480 safety evaluable patients.

for the purposes of this protocol, the GFR was considered to be equivalent to the creatinine clearance (CrCl): Calvert Formula for carboplatin (AUC) dosing: Total dose (mg) multiplied by target AUC (in mg/mL/min) multiplied by [GFR (in mL/minute) + 25].

Safety data collected during the study was reviewed by an independent external Data Monitoring Committee (DMC) which periodically monitored previously determined safety signals and made recommendations regarding continuation of the study.

Evaluator's summary and conclusion on clinical safety

The safety profile demonstrated from this pivotal trial was generally in line with that presently recognised for patients receiving bevacizumab. Bevacizumab is associated with a higher incidence overall and higher Grades of adverse effects than placebo. The most common of these adverse effects included arterial thrombotic events, at least Grade III hypertension, proteinuria, and non-CNS bleeding. It was also noted that a small number of patients experienced reversible posterior leukoencephalopathy syndrome (RPLS) on bevacizumab in this study, which had not been previously recognised as a common adverse effect for with agent.

The proportion of patients requiring bevacizumab discontinuation given adverse events (AEs) was also clearly higher on the bevacizumab therapy, most often related to hypertension, proteinuria, epistaxis and a small number of occasions of RPLS. Only one patient had experienced death as a direct result of bevacizumab therapy.

Overall, it would appear that while there is a significant spectrum of adverse effects associated with bevacizumab, these most often are manageable. Nevertheless, caution would be required in decisions regarding prescription of bevacizumab, particularly in the context of patients whose malignancy is quite far advanced which would therefore require greater care in administration and management of adverse effects.

Safety in relation to intraocular administration of bevacizumab

Off-label administration of intraocular bevacizumab for the treatment of age related macular degeneration has been occurring for approximately five years. There has been no organised assessment of this in relation to potential safety. Roche Pty Limited has undertaken a safety review of data presented to the company together with those from a literature search.

Evaluator's conclusion

The data have led to new statements being placed in the proposed PI involving adverse reactions reported in the post-marketing setting. These include an outline of data from the studies showing evidence of increasing incidence of ocular inflammation and selected systemic events, including haemorrhagic stroke and overall mortality. The data presented is accurate in relation to the reported studies and appropriate for inclusion in the PI.

List of questions

Please advise when the final analysis of OS in study AVF4095g is expected and commit to submitting this data when available³.

³ In response, the sponsor advised that the final OS analysis is anticipated at the end of 2013 with approximately 353 deaths (73% of patients). The company commits to submit the final OS analysis, when available.

Clinical summary and conclusions

Benefit risk assessment

Assessment of benefits

The efficacy results from the pivotal study AVF4095g have demonstrated a significant improvement in PFS for patients receiving bevacizumab in combination with carboplatin and gemcitabine compared to chemotherapy alone, with an improvement in median PFS of four months. This had statistical significance of $p < 0.0001$. These primary efficacy results were consistent across various patient sub-groups, which included Eastern Cooperative Oncology Group (ECOG) performance status⁴, histologic sub-type, stratification variables and age. Various sensitivity analyses also confirmed the robustness of the data. Evidence of a significant improvement in ORR was also obtained, with an ORR of 79% for patients receiving bevacizumab compared to 57.4% for those receiving placebo (p value < 0.0001).

Overall survival data remains immature and does not show a significant difference, although at the time of data analysis, 32.3% of patients receiving placebo died compared to 26% patients in the bevacizumab arm. This study was well conducted involving a reasonably sized patient population. Confirmation of the degree of activity determined by the improvement in PFS will await analysis of OS on a more mature analysis.

Assessment of risks

Safety data from the pivotal study has revealed that the incidence of at least Grade III AEs was higher in the bevacizumab arm, being 89.5%, compared to the placebo arm (82.4%). Adverse events of special interest were observed at a higher rate in the bevacizumab treated patients: the incidence of AEs of any Grade was: bevacizumab 94.3% versus placebo 85%, and for Grade III-IV AEs, the incidence was bevacizumab 73.7% versus placebo 61.8%. These AEs included arterial thromboembolic events of any Grade, at least Grade III hypertension, proteinuria, non-CNS bleeding, and RPLS. Overall, these events were consistent with previous experience of bevacizumab in other tumour types, although the incidence of RPLS was a little higher than previously reported. It is also noted that the incidence of AEs leading to study drug discontinuation was higher in the bevacizumab arm, being 19.8%, compared to 4.7% for placebo, with the most common being Grade III or higher hypertension, proteinuria, epistaxis and RPLS. Only one patient experienced a fatal intracranial haemorrhage as a result of bevacizumab therapy.

The safety data confirmed the AEs profile of bevacizumab previously reported and indicates that this is an agent which needs to be managed with care. This is even more pertinent in patients with relatively advanced Stage 3 disease who have already failed first line therapy and therefore are facing further therapy with relatively limited survival prospects.

Assessment of benefit-risk balance

The pivotal study has demonstrated that the addition of bevacizumab to chemotherapy, carboplatin and gemcitabine, is associated with a significant improvement in PFS for patients with recurrent ovarian, fallopian tube and primary peritoneal carcinomas. An improvement of four months in PFS for the bevacizumab patients is pertinent in the clinical setting, but not to a large degree. The toxicity profile demonstrated in this study with bevacizumab is, while generally well recognised, not insignificant in its extent, and therefore requires careful management in this patient population.

⁴ Eastern Cooperative Oncology Group (ECOG) status: These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

The evaluator considers that the benefit-risk balance is in favour of approval of bevacizumab for the proposed indication: in combination with carboplatin and gemcitabine for the treatment of patients with recurrent, platinum sensitive epithelial ovarian, fallopian tube or primary peritoneal carcinoma. Nevertheless, follow up with mature OS data would be most pertinent to ensure that there is sufficient evidence to support the routine clinical incorporation of bevacizumab into patients receiving chemotherapy for recurrent ovarian malignancies.

The data presented with regards to proposed additions to the PI in relation to intraocular use of bevacizumab, and in particular potential adverse effects that have been recognised from recent retrospective reviews, is appropriate and in accord with what has been reported⁵.

Recommendation regarding authorisation

The evaluator considers it appropriate to support approval for the proposed indication of bevacizumab in combination with carboplatin and gemcitabine for treatment of patients with recurrent, platinum sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer.

The proposed additional statements with regards to adverse effects arising from the unapproved intravitreal use of bevacizumab are appropriate and in accord with recent retrospective reviews.

The evaluator notes that bevacizumab in combination with carboplatin and paclitaxel has been proposed as a new indication for first line treatment of patients with epithelial ovarian, fallopian tube or primary peritoneal cancer⁶. This is based on data from two studies including the pivotal study GOG0218 and supportive study B017707. It is noted that both studies demonstrate a significant improvement in PFS, while this is more clearly demonstrated in the pivotal study GOG0218. It is also noted that the dosage of bevacizumab in the former study was 15 mg/kg every 3 weeks, compared to the supportive study B017707 where the dosage of bevacizumab was 7.5 mg/kg every 3 weeks. Data from both of these studies, however, still does not reveal a significant advantage in terms of OS.

These data effectively support the fact that there is definite efficacy for combining bevacizumab with chemotherapy in ovarian cancer. The lack of evidence of definite improvement in OS awaits determination of more mature data. The evaluator still feels it appropriate to support approval for the proposed indication in patients with recurrent, platinum sensitive ovarian, fallopian tube and primary peritoneal cancers.

Note: Details of the evaluator's recommendations regarding revisions to the proposed PI are beyond the scope of this AusPAR.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

⁵ Details of PI revisions are beyond the scope of this AusPAR.

⁶ This indication was under evaluation at the time the clinical evaluation for the current application was prepared. The application for first line treatment received TGA approval in February 2012 (AusPAR available at <http://www.tga.gov.au/pdf/auspar/auspar-bevacizumab-120806.pdf>)

Safety specification

Subject to the evaluation of the clinical aspects of the safety specifications (SS) by the TGA's Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns, as specified by the sponsor in the EU RMP, is as follows (Table 1):

Table 1. Ongoing safety concerns.

Important identified risks	Bleeding/haemorrhage
	Pulmonary haemorrhage
	Arterial thromboembolic events (ATE)
	Hypertension
	Proteinuria
	Congestive heart failure (CHF)
	Wound healing complications
	Gastrointestinal perforations
	Reversible posterior leukencephalopathy syndrome
	Neutropenia
	Venous thromboembolic events (VTE)
	Fistula (other than gastrointestinal)
	Thrombotic microangiopathy
	Pulmonary hypertension
	*Ovarian failure
*Hypersensitivity/infusion reactions	
Important potential risks	Embro-foetal development disturbances
	Physeal dysplasia
	Peripheral sensory neuropathy
	Cardiac disorders (excluding CHF and ATE)
	Osteonecrosis of the jaw (ONJ)
Important missing information	Safety profile of the different treatment combinations in patients with non-squamous NSCLC

	Long-term effects of bevacizumab when used in the paediatric population
	Patients with renal impairment
	Patients with hepatic impairment

* Previously classified in the EU RMP Version 9.0 as important potential risks.

Pursuant to the evaluation of the clinical aspects of the SS and in the absence of concerns raised from the clinical evaluation conducted by the OMA, the above summary of the Ongoing Safety Concerns is considered acceptable.

Pharmacovigilance plan

Routine pharmacovigilance activities⁷ as well as ongoing post-authorisation studies are proposed to monitor the safety of bevacizumab. This was acceptable.

Risk minimisation activities

The sponsor has assessed that routine risk minimisation activities are sufficient for all important identified risks, all important potential risks and areas of important missing information.

Considering that Avastin will be used primarily under the care of specialists experienced in managing cancer patients, the evaluator considered the use of routine risk minimisation as proposed is acceptable.

Summary of recommendations

The OPR provides this recommendation to the Delegate in the context that the submitted RMP is supportive to the application:

- Approval should be conditional on the implementation of a RMP identified as the EU-RMP Version 10 (7 July 2011) and with the Australian RMP Addendum Version 2.0 (September 2011).

Several revisions to the PI were recommended (details of these are beyond the scope of this AusPAR)

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

⁷ Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

See 3.1.2 *Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)*

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical**Efficacy**

- The efficacy of bevacizumab in the proposed indication is based on a single randomised, double-blind, placebo controlled trial conducted in the USA (AVF4095g). Subjects were randomised to receive either carboplatin, gemcitabine and placebo (“placebo group”) or carboplatin, gemcitabine and bevacizumab (“bevacizumab group”). Subjects were platinum-sensitive, defined as relapse greater than 6 months after last platinum treatment. Randomisation was stratified by degree of platinum sensitivity (relapse 6-12 months and > 12 months after last platinum treatment) and cyto-reductive surgery for recurrent disease. The doses of carboplatin and gemcitabine were the same in both groups: carboplatin AUC 4 mg/mL.min on Day 1 every 21 Days and gemcitabine 1,000 mg/m² on Days 1 and 8 every 21 Days (median 6 cycles). The bevacizumab dose was 15 mg/kg every 3 weeks until disease progression or unacceptable toxicity. The median duration of treatment was 8.6 months with bevacizumab and 7.4 months with placebo.
- The majority of subjects had epithelial ovarian cancer (83% in the bevacizumab group and 86% in the placebo group). The median age of subjects was 60 years in the bevacizumab group and 61 years in the placebo group. ECOG performance status was 0 or 1.
- The primary efficacy endpoint was investigator-determined PFS. Progression free survival was assessed using modified RECIST⁸ criteria. Bevacizumab significantly increased PFS by a median 4 months based on the stratified analysis (Table 2). Similar results were achieved in the unstratified analysis and an analysis of independently assessed PFS. There was support from other endpoints. Complete responses were considerably lower in the independent assessment (1.2% for placebo and 0.8% for bevacizumab) than the investigator assessment (9.1% for placebo and 17.4% for bevacizumab).
- Bevacizumab did not significantly increase OS but the trend was in favour based on preliminary data after 29% of subjects had died and median duration of follow-up of 2 years. The final analysis will be done after 73% of subjects have died, which is anticipated by the end of 2013.
- In the subgroup analysis, the significant increase in PFS in the bevacizumab group was seen in patients with epithelial ovarian cancer but not in patients with fallopian tube or primary peritoneal cancer. There were insufficient patients with these other cancers to show a significant difference between treatment groups; however, the trend

⁸ RECIST (Response Evaluation Criteria In Solid Tumors) is a set of published rules that define when cancer patients improve (“respond”), stay the same (“stable”) or worsen (“progression”) during treatments. The criteria were published in February, 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute of the United States, and the National Cancer Institute of Canada Clinical Trials Group.

was in favour of bevacizumab. The three cancers are reported to be histologically equivalent by the International Federation of Gynecology and Obstetrics (FIGO).

Table 2. Efficacy Results. Trial AVF4095g. Investigator Determined – Intent-to-Treat

	Placebo Group n=242	Bevacizumab Group n=242	Hazard Ratio or Difference [95% CI] ¹ p-value
Progression-Free Survival median (months)	8.4	12.4	0.48 [0.39, 0.61] p<0.0001 ¹
ORR % Complete Partial	57.4 9.1 48.3	78.5 17.4 61.2	21.1 [13.0, 29.2] p<0.0001 ²
Duration of Response median (months)	7.4 n=139	10.4 n=190	0.53 [0.41, 0.70] p<0.0001 ¹
Overall Survival median (months)	29.9	35.5	0.75 [0.54, 1.05] p=0.09 ¹

Stratified hazard ratio of bevacizumab versus placebo determined by Cox regression. Difference in ORR is bevacizumab – placebo. Medians are Kaplan-Meier estimates. ¹ Log-Rank. ² Cochran-Mantel-Haenszel. ORR: Objective Response Rate (Complete Response + Partial Response).

Safety

- The safety of bevacizumab in the proposed indication was assessed in 247 bevacizumab subjects and 233 placebo subjects from the pivotal trial AVF4095g. The median duration of follow-up was 9.6 months (range 1-34 months) for bevacizumab and 8.4 months (range 1-29 months) for placebo. The greatest difference in incidence occurred for the following adverse effects: hypertension (bevacizumab 41% versus placebo 9%), epistaxis (bevacizumab 54% versus placebo 14%), headache (bevacizumab 49% versus placebo 30%) and proteinuria (bevacizumab 17% versus placebo 4%).
- The incidences of severe hypertension, proteinuria and thrombocytopenia were significantly higher with bevacizumab than placebo. There was a greater incidence of serious AEs with bevacizumab than placebo (35% versus 25%). Two bevacizumab subjects died due to AEs, one due to intracranial haemorrhage and one due to sepsis. One placebo subject died due to an AE (myocardial infarction).
- In general, AEs experienced with bevacizumab in the pivotal trial were consistent with the known safety profile of bevacizumab.

Clinical evaluator's recommendation

The clinical evaluator recommended approval of the new indication.

Risk management plan

- The OPR has agreed to EU-RMP Version 10 (7 July 2011) with Australian Addendum Version 2.0 (September 2011).
- Based on the clinical data submitted with this application, the SS is adequate. There were some PI recommendations.

Risk-benefit analysis**Delegate considerations**

The pivotal trial showed that the addition of bevacizumab to carboplatin and gemcitabine resulted in a significant increase in PFS of median 4 months in patients with recurrent, platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer. The combination of carboplatin and gemcitabine is one of several treatment options for recurrent, platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer. There is no standard treatment⁹.

The trial included only small numbers of subjects with fallopian tube or primary peritoneal cancer and a statistically significant increase was not achieved in these cancers. However, the trend was in favour. Fallopian tube and primary peritoneal cancer are rare. Histologically, these cancers and epithelial ovarian cancer are similar¹⁰ and it is likely that the PFS benefit applies to all three cancers. The benefit in PFS was supported by a significant increase in overall tumour response rate. The median increase in OS was similar to the increase in PFS; however, the data were immature.

The safety of bevacizumab in the proposed indication was consistent with the use of bevacizumab in other indications. Bevacizumab has some very serious adverse effects and patients receiving this drug need to be carefully monitored. The Delegate proposed to include increased precautionary statements in the PI (details of these are beyond the scope of this AusPAR).

The median increase in PFS of 4 months was not large in this patient population which has a median survival of 2-3 years. The increase is of borderline clinical significance when viewed in the context of the significant toxicity of the drug. Confirmation of the benefit of bevacizumab would need to await the final OS analysis. Quality of life was not assessed.

The Delegate supports the clinical evaluator's recommendation to approve bevacizumab for the proposed indication, conditional on review of the final OS analysis when available.

Proposed action

The Delegate proposed to approve bevacizumab (Avastin) injection for the new indication:

- In combination with carboplatin and gemcitabine, treatment of patients with recurrent, platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer.

⁹ Clinical Practice Guideline: epithelial ovarian, fallopian tube, and primary peritoneal cancer. Developed July 2010, by consensus of the Alberta Provincial Gynecologic Oncology Tumour Team. <http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-gyne005-epithelialovarian.pdf>

¹⁰ *ibid.*

Approval will be subject to finalisation of the PI.

Proposed conditions of registration:

- Submission of the final analysis of OS in trial AVF4095g when available.
- Implementation of EU-RMP Version 10 (7 July 2011) with Australian Addendum Version 2.0 (September 2011) and subsequent revisions as agreed with the TGA Office of Product Review.

Details of the Delegate's proposed revisions to the PI are beyond the scope of this AusPAR.

Advice requested from ACPM

The Delegate proposed to seek general advice on this application from the ACPM.

Response from sponsor

The sponsor concurs with the Delegate's proposed action to approve the application for the extension of indication to include:

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Avastin (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.

The proposed dosing regimen for this indication is:

The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an IV infusion as follows:

Treatment of recurrent disease

Avastin should be given in combination with carboplatin and gemcitabine for 6 cycles (up to 10 cycles), followed by continued use of Avastin as single agent until disease progression.

The sponsor clarified the following aspects of the Delegate's overview:

Efficacy:

- (fifth bullet point) information concerning sub-group analysis: As formal hypothesis testing on the subgroup analyses was not conducted, the sponsor considered it inappropriate to draw conclusions on the statistical significance for sub-groups.

Safety:

- (second dot bullet point): only one of the two bevacizumab subjects who died due to adverse events was treatment emergent (that is, within 30 days of last study treatment); the subject who died from sepsis was not considered treatment related.

The sponsor also provided responses to recommended PI revisions; details of these are beyond the scope of this AusPAR.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy and safety considered these products to have an overall positive benefit-risk profile for the indication:

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

In making this recommendation the ACPM advised that the indication should be revised to align with the population in the trials submitted and hence limited to patients that have not received prior bevacizumab treatment.

The ACPM expressed concern that the sponsor has not submitted all the available data on OS and that the TGA request further detail.

The ACPM agreed with the Delegate on the proposed amendments to the PI and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following;

- a statement in the *Clinical Trials* section of the PI to more accurately and completely reflect the study design and outcomes.

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following;

- a submission of the available results on OS.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Avastin injection concentrate, containing bevacizumab (rch) 100/4 mL and 400 mg/16 mL, for the following indication:

AVASTIN (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.

The full indications are now:

Metastatic Colorectal Cancer.

Avastin (bevacizumab) in combination with fluoropyrimidine based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer.

Locally recurrent or metastatic Breast Cancer.

Avastin (bevacizumab) in combination with paclitaxel is indicated for the first-line treatment of metastatic breast cancer in patients in whom an anthracycline-based therapy is contraindicated (see Clinical Trials).

Advanced, metastatic or recurrent, non-squamous Non Small Cell Lung Cancer (NSCLC).

Avastin (bevacizumab), in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent, non-squamous, non-small cell lung cancer.

Advanced and/or metastatic Renal Cell Cancer.

Avastin (bevacizumab) in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or metastatic renal cell cancer.

Grade IV glioma.

Avastin (bevacizumab) as a single agent, is indicated for the treatment of patients with Grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy.

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal cancer

Avastin (bevacizumab) in combination with carboplatin and paclitaxel for the first line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer.

Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer.

Avastin (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.

Specific conditions of registration applying to these goods

- The implementation in Australia of the EU RMP version 10.0 dated 7 July 2011, with Australian Addendum Version 2.0 dated September 2011, and any subsequent revisions, as agreed with the TGA and its OPR.
- The final analysis of OS in trial AVF4095g will be submitted when available.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the current Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

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