Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Bevacizumab

Proprietary Product Name: Avastin

Sponsor: Roche Products Pty Ltd

March 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- 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.

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
AE	adverse event
ALT (SGPT)	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST (SGOT)	aspartate aminotransferase
ATE	arterial thromboembolic event
CA-125	cancer antigen 125
CHF	congestive heart failure
CI	confidence interval
CL	clearance
CR	complete response
CRC	colorectal cancer
CT	chemotherapy
CT+BV	chemotherapy plus bevacizumab
CTCAE	common toxicity criteria adverse events
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EORTC	European Organization for Research and Treatment of Cancer
FACT	Functional Assessment of Cancer Therapy
FOSI NCCN/FACT	Ovarian Symptom Index
FTC	fallopian tube cancer
GCIG	Gynecologic Cancer InterGroup

Abbreviation	Meaning
GCP	good clinical practice
GHS	Global Health Status
GI	gastrointestinal
GIP	gastrointestinal perforation
HADS	Hospital Anxiety and Depression Scale
HR	hazard ratio
HRQoL	Health related quality of life
HTN	hypertension
ICH	International Conference on Harmonization
iDMC	independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intent to treat
IV	intravenous
IVRS	Interactive voice response system
LVEF	left ventricular ejection fraction
MCID	minimum clinically important difference
MRI	magnetic resonance imaging
MUGA	Multiple gated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	NCI Common Terminology Criteria for Adverse Events
NPT	non-protocol specified anticancer therapy
ORR	objective response rate

Abbreviation	Meaning
OS	overall survival
PD	progressive disease
PK	pharmacokinetic
PK - DDI PK drug	drug interaction
PFI	Platinum free interval
PFS	Progression free survival
PLD	pegylated liposomal doxorubicin
PPC	primary peritoneal cancer
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient reported outcome
PS	performance status
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
QLQ	Quality of Life Questionnaire
RECIST	response evaluation criteria in solid tumours
RPLS	reversible posterior leukoencephalopathy syndrome
SLD	sum of longest diameter
$t_{1/2}$	terminal half life
ULN	upper limit of normal
VTE	venous thromboembolic event

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	19 November 2014
Active ingredient:	Bevacizumab
Product name:	Avastin
Sponsor's name and address:	Roche Products Pty Ltd 4-10 Inman Road DEE WHY NSW 2099
Dose form:	Solution for injection
Strengths:	100 mg/ 4 mL and 400 mg/ 16 mL
Container:	Single dose vial
Pack size:	One
Approved therapeutic use:	*Avastin (bevacizumab) in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens, and have not received any prior anti-angiogenic therapy including bevacizumab.*
Route of administration:	Intravenous (IV) infusion
Dosage:	The recommended dose of Avastin administered as an IV infusion in the treatment of *Recurrent disease-Platinum resistant* Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer is as follows: 10 mg/kg body weight given once every 2 weeks when administered in combination with one of the following agents – paclitaxel or topotecan (given weekly) or pegylated liposomal doxorubicin. Alternatively, 15 mg/kg every 3 weeks when administered in combination with topotecan given on days 1-5, every 3 weeks. (*See CLINICAL TRIALS Study MO22224 f*or descriptions of the chemotherapy regimens). It is recommended that treatment be continued until disease progression.
ARTG numbers:	99755 and 99757

Product background

This AusPAR describes the application by the sponsor, Roche Products Pty Ltd, to register Avastin (bevacizumab) for the following indication

> *Avastin (bevacizumab) in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens.*

Avastin in combination with chemotherapy is currently approved for metastatic Colorectal Cancer, locally recurrent or metastatic Breast Cancer, advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer (NSCLC), advanced and/or metastatic Renal Cell Cancer, Grade IV Glioma, and Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (first-line and for recurrent platinum-sensitive disease).

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) in February of 2005.

At the time the TGA considered this application, a similar application had been approved in the European Union (EU; on 31 July 2014) and was under consideration in Canada, Switzerland and the USA.

Product information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

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. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

Impact of ovarian cancer

Ovarian cancer is a disease that globally affects nearly a quarter of a million women each year. It is the eighth most common cancer in women and the seventh leading cause of cancer death among women, responsible for approximately 140,000 deaths globally each year. It has the highest mortality rate of all gynaecological cancers. In Australia in 2008, 1,272 cases of ovarian cancer were diagnosed, making it the second most common

gynaecological cancer in Australia, ranking tenth in terms of the most commonly diagnosed cancers in women. Ovarian cancer was the most common cause of gynaecological cancer death with 848 deaths in 2007, ranking seventh in terms of all causes of cancer deaths among women.[1]

Treatment

Initial

The definitive diagnosis and staging of ovarian cancer is by surgery and cytological or histological examination of tissue samples. The FIGO surgical staging system is used for ovarian cancer. Because the disease tends to be asymptomatic in early stages or associated with vague, nonspecific symptoms, the majority of patients are diagnosed with advanced-stage disease. Despite the high sensitivity of ovarian cancer to initial treatment with platinum and taxane based combination chemotherapy, which is the standard of care in the frontline setting, the majority of women (more than 80%) diagnosed with advanced-stage disease will have a recurrence of their cancer.

Treatment after recurrence

Following front-line therapy, approximately 20% of women will have a first platinum-resistant recurrence within < 6 months after completing platinum therapy. Once the disease returns, a complete remission is very unlikely and women face repeated therapeutic interventions as long as the disease is responsive or can be stabilised by treatments before going on to end-of-life supportive care. Recurrence is incurable and treatment measures are essentially palliative. Recurrent disease is classified into three groups: platinum-sensitive if the disease recurs more than 6 months after previous platinum therapy; platinum-resistant if the disease recurs less than 6 months after previous platinum therapy; and platinum-refractory if the disease progresses during induction platinum therapy. In the latter two groups, platinums are generally deemed toxic and not sufficiently useful to be part of the treatment plan. This classification is highly prognostic and is important in determining optimal chemotherapeutic treatment options. Treatment is with single agent, non-platinum chemotherapeutic agents such as pegylated liposomal doxorubicin (PLD), topotecan and paclitaxel. Overall, the prognosis for platinum-resistant recurrence is poor, with response rates to current therapies at best ranging from 10% to 20%, with few durable responses, median progression-free survival (PFS) ranging from 2 to 5 months, and median overall survival (OS) ≤ 12 months. Hence, there is still an ongoing need to find novel treatments that maximise PFS and improve symptoms in patients with platinum-resistant ovarian cancer.

Activity of Bevacizumab in ovarian cancer

Bevacizumab has been approved in the EU and Australia, but not in the USA and Canada, for initial treatment and for the treatment of recurrent, platinum-sensitive disease on the basis of studies showing a clinically significant increase in Progression-Free Survival (PFS) with significant toxicity but no increase in Overall Survival (OS).

Bevacizumab has also shown activity in recurrent platinum-resistant disease in three Phase II studies. In the first, Study GOG-0107D[2], both platinum-sensitive and platinum-resistant patients were included with a response rate (RR) of 20% (13 of 62), a median

[1]Cancer Australia. Report to the nation - ovarian cancer 2012, Cancer Australia, Surry Hills, NSW, 2012
[2]Burger RA, Sill MW, Monk BJ, et al. Phase II Trial of Bevacizumab in Persistent or Recurrent Epithelial Ovarian Cancer or Primary Peritoneal Cancer: A Gynecologic Oncology Group Study. J Clin Oncol. 2007; 25(33):5165-5171

PFS of 4.7 months and OS of 17 months. In a second study, Study AVF2949g[3], of only platinum-resistant patients (n=44), 7 (15%) patients responded but the trial was stopped because 5 patients experienced bowel perforation, one which was fatal. This adverse event was associated with three or more prior treatments. In the third trial[4], using a combination of bevacizumab and daily oral cyclophosphamide, reported 17 partial responses (24%) in 70 patients with recurrent disease after two prior treatments (one platinum). The median Time to Progression (TTP) was 7.2 months and an OS of 16.9 months. However 4 patients experienced a GI perforation or fistula.

Comment:

The trial of Garcia et al[4] was not referred to in the Clinical Overview.

Rationale for use of Bevacizumab in phase III study of recurrent, platinum-resistant ovarian cancer

The basis for this Phase III study was the promising activity of bevacizumab seen in the recurrent disease setting, both with platinum-sensitive and platinum-resistant disease.

Comment and conclusion:

The Phase II studies above in recurrent platinum-resistant disease show bevacizumab has activity in a clinical situation in which there are few therapeutic options and in which the symptoms are often severe and distressing. Although the occurrence of bowel perforation with this agent is of concern, the incidence of this event should be reduced by not enrolling patients in the study who have more than two prior treatments.

For these reasons the evaluator found the rationale acceptable.

Contents of the clinical dossier

The clinical dossier documented a development program of a pivotal trial relating to the proposed extension of indications.

The submission contained the following clinical information:

- Report BO17706, PopPK AVITA, 'Population Pharmacokinetic Analysis BO17706 ', March 28, 2008. This report was a post-hoc analysis (Bayesian feedback) of the pharmacokinetics data from 100 patients in Study BO17706 that evaluated bevacizumab in the treatment of metastatic pancreatic cancer
- Report 1031796, 'Population Pharmacokinetic Analysis of Bevacizumab. Final Analysis Report ', January 9, 2008.This report added data from 224 patients to that in a previous report that included 533 patients. The cancers were those for which bevacizumab was or became an approved indication, namely breast, renal cell, colorectal and non-small cell lung cancers. Bevacizumab pharmacokinetics were characterised by a 2-compartment model with first order elimination, the data having been analysed using non-linear effects modelling (NONMEM)
- Pivotal study report, Study MO22224 (AURELIA), entitled '*A multi-centre, open-label, randomised, two-arm phase III trial of bevacizumab plus chemotherapy versus chemotherapy alone in patients with platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal cancer. Report No. 1054737, August 2013.*'

[3]Cannistra SA, Matulonis UA, Penson RT, et al. Phase II Study of Bevacizumab in Patients With Platinum-Resistant Ovarian Cancer or Peritoneal Serous Cancer. 2007; 25(33):5180-5186.
[4]Garcia AA, Hirte H, Fleming G, et al.: Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. J Clin Oncol 26 (1): 76-82, 2008

Comment:

No PK data in patients with ovarian cancer was provided. Instead it was argued in the application that since the PK results for bevacizumab were comparable in the cancers previously studied and approved (metastatic CRC, breast cancer, renal cell cancer and Grade IV gliomas), no PK data were needed in ovarian cancer. This could be argued for the first line treatment of ovarian cancer patients with bevacizumab combined with carboplatin and paclitaxel since most patients have initial surgery with tumour removal to a maximum extent (minimum residual disease). However in recurrent disease, both platinum-sensitive and platinum-resistant, malignant ascites is often present. In the pivotal study in this application, 31.3% of all patients at baseline had ascites. The concern is that these patients may be at higher risk of toxicity from bevacizumab because of possible accumulation of the drug in the ascitic fluid (a third space) with leakage back into the systemic circulation. This concern that no PK data were available for patients with malignant ascites was raised by the evaluator in the evaluation of bevacizumab for first line therapy and a statement to this effect was placed in the Product Information (PI). This issue is considered again in the *Safety* section of this evaluation report and in *Clinical questions* to the sponsor.

Paediatric data

The submission did not include paediatric data. The TGA Form 'Paediatric Development Plan 'indicated the sponsor has a waiver from presenting a Paediatric Investigation Plan in the EU (EU Class Waiver # P/63/2010) on the grounds that the requested indication is not applicable to the paediatric population.

Good clinical practice

Local regulations/declaration of Helsinki

The investigators were to ensure that this study was conducted in full conformity with the principles of the 'Declaration of Helsinki' or with the laws and regulations of the country in which the research was conducted whichever afforded the greater protection to the individual. The study was to adhere to the principles outlined in 'Guideline for Good Clinical Practice ICH Tripartite Guideline (January 1997)' or with local law if it afforded greater protection to the patient. For studies conducted in the EU/EEA countries, the investigator was to ensure compliance with the EU Clinical Trial Directive (2001/20/EC). In other countries where 'Guideline for Good Clinical Practice' exists Roche and the investigators were to ensure adherence to the stated provisions.

Informed consent

It was the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The investigator or designee was also required to explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

Independent ethics committee

The protocol and any accompanying material provided to the patient (such as patient information sheets or descriptions of the study used to obtain informed consent) as well as any advertising or compensation given to the patient, were to be submitted by the investigator to an Independent Ethics Committee. Approval from the committee had to be obtained before starting the study, and was to be documented in a letter to the investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of the Independent Ethics Committee approval had also to be submitted by the investigator to the Committee in accordance with local procedures and regulatory requirements.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 1 shows the studies relating to each population pharmacokinetic (PK) topic and the location of each study summary.

No PK studies were performed on patients with ovarian cancer and no changes are proposed to the PK section of the Product Information. The justification for not conducting PK studies in the population of patients with recurrent platinum-resistant ovarian cancer was the same as that used in the previous applications to register the indications for first-line treatment of EOC, and the treatment of recurrent platinum-sensitive disease. In summary the justification was the similarity of the PK parameters of bevacizumab when used to treat a variety of solid cancers such as metastatic colon cancer, metastatic renal cancer and breast cancer. As well, the PK properties of bevacizumab in the treatment of patients with renal cell cancer were consistent with a model based on an extensive data base of PK data in a Population PK Analysis. The latter had been submitted to the TGA with the application for first line treatment of EOC.

Table 1. Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
Population PK analyses	Healthy subjects	N/A
	Target population	N/A
	Other To develop a population PK model describing the PKs of bevacizumab by pooling 10 clinical trials (Phase I, II and III). To test whether the PK of bevacizumab in subjects with metastatic pancreatic cancer is comparable to the previously analyzed populations.	Population PK Analysis of Bevacizumab Final Analysis Report 1031796 Population PK Analysis BO17706

N/A=not applicable

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

No pharmacokinetic data were provided with this application. Justification included:

1. The PK parameters of bevacizumab found in a variety of solid tumours were similar and would be expected to apply to the present clinical population.

2. The predictions from Population PK modelling and the actual PK parameters found in patients with pancreatic cancer treated with bevacizumab (Populatione PK Analysis BO17706) were comparable.

PK Deficiencies - Sponsor should comment (see *Clinical questions*):

1. The PK parameters for bevacizumab in patients with malignant ascites may differ from patients with solid tumours who have no ascites (see Pharmacokinetics in patients with malignant ascites, Attachment 2).
2. A possible clinical effect of the reduced rate of clearance of bevacizumab by 40% from co-administered anti-cancer drugs as shown in the Population PK Analysis Report 1031796 has not been considered.
3. The Australian PI presents the results of the population PK analysis showing effects of low albumen and high tumour burden on the PK parameters of bevacizamub including clearance but does not mention co-administered anti-cancer drugs that slow the rate of clearance of bevacizumab.

Pharmacodynamics

Studies providing pharmacodynamic data

No pharmacodynamic (PD) data were included in the present application. The Australian PI gives the following information about those PD effects that are related to the anti-cancer action of bevacizumab. No information is provided on those PD effects responsible for the drug's toxicity. '*Avastin inhibits the binding of VEGF to its receptors, Flt 1 and KDR, on the surface of endothelial cells. Neutralising the biologic activity of VEGF reduces the vascularisation of tumours, thereby inhibiting tumour growth. Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced*.'

Evaluator's conclusions on pharmacodynamics

No pharmacodynamics data were submitted.

Dosage selection for the pivotal studies

The sponsor' Summary of Clinical Efficacy (SCE) gives the following justification for the selection in the pivotal Study MO22224 of a dose of bevacizumab of 10 mg/kg every two weeks (q2w) or 15 mg/kg every three weeks (q3w).

'*This dosage was selected to be within the linear pharmacokinetic range resulting in serum bevacizumab concentrations in excess relative to circulating VEGF concentrations (3–20 mg/kg every 2 or 3 weeks, or 1.5-10 mg/kg/week).*

The dose of bevacizumab 10 mg/kg IV q2w or bevacizumab 15 mg/kg IV q3w, which is equivalent to a dose of 5 mg/kg/week, is the most commonly used dose of bevacizumab that has been shown to be effective in clinical trials across multiple tumour types (e.g. non-small cell lung cancer, metastatic breast cancer, advanced renal cell carcinoma, metastatic carcinoma of the colon or rectum, and front-line and recurrent treatment of EOC, FTC, and PPC) [references were given in the SCE).

Phase II trials GOG-170D and AVF2949g, in ovarian cancer patients demonstrated that a dose of bevacizumab equivalent to 15 mg/kg q3w had activity in the recurrent setting. Furthermore, it is the currently approved dose in the front-line and recurrent platinum-sensitive ovarian cancer settings the EU and Australia '. (Note: These indications for ovarian cancer are not approved in the USA).

Comment:

After the above text in the SCE are the following sentences '*Bevacizumab should be administered in combination with chemotherapy until PD or unacceptable toxicity. Bevacizumab may be continued as a single agent if chemotherapy is discontinued earlier.*'

The first usage is acceptable, but the second is ambiguous since the wording allows bevacizumab to be continued if the patient were receiving chemotherapy plus bevacizumab, and then the chemotherapy was stopped early, say for toxicity. The CSR on the other hand specifically stated that only patients in the chemotherapy alone arm were to cross over on disease progression to receive monotherapy with bevacizumab. The sponsor needs to confirm that only patients in the chemotherapy alone arm cross-over to receive bevacizumab monotherapy (see Clinical questions below).

Efficacy

Studies providing efficacy data

One pivotal study report, Study MO22224 (AURELIA), entitled 'A multi-centre, open-label, randomised, two-arm phase III trial of bevacizumab plus chemotherapy versus chemotherapy alone in patients with platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal cancer. Report No. 1054737, August 2013 was submitted

Evaluator's conclusions on clinical efficacy

Avastin to treat patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens

The sponsor's Clinical Overview did not provide a section of Conclusions, only one of Benefits. The sponsor's Summary of Clinical Efficacy (SCE) gives a Conclusions section. Any differences from the latter are identified in the following.

Primary end-point

- The regimen of bevacizumab in combination with chemotherapy (paclitaxel, topotecan, or PLD) resulted in a statistically significant and clinically important improvement in investigator-assessed PFS from a mean value of 3.4 months (95% confidence interval (CI) 2.10-3.75) in the chemotherapy (CT) arm to 6.8 months (95%CI 5.62-7.79), with a stratified hazard ratio (HR) = 0.384; 95% CI: 0.300, 0.491; log-rank p-value < 0.0001. Subgroup and sensitivity analyses, including simulated Independent Review Committee (IRC) results, supported these results.

Note: Addendum: As a result of requests to the sponsor, corrections of incorrect dates of trial events found and submitted by the sponsor, and an independent blinded radiological review of assessments of progressive disease (PD) by investigator's, the figures above have changed a little but the benefit and significance of the improvement seen with chemotherapy plus bevacizumab (CT+BV) has been maintained. The changes were as follows:

- *PFS After correction of dates of event for 1 patient:* PFS 3.4 months (95%CI 2.10-3.75) and 6.7 months (5.62-7.79) in the CT+BV arm; HR 0.379 (0.296-0.485), log-rank p value<0.0001
- *Time to Treatment Failure (TTF)* (time from randomization to discontinuation of treatment for any reason, including progressive disease or death or withdrawal of treatment due to adverse events/unacceptable toxicity, withdraw consent, symptomatic deterioration, or other reason considered progressive): **TTF** 3.4 months (interquartile range 1.8-5.5) in the CT arm and 5.4 months (interquartile range 3.4-9.3) in the CT+BV arm; HR 0.422 (95% CI: 0.333, 0.536; log-rank p-value < 0.0001)
- *PFS using data from the Independent Review Committee after reviewing PD as assessed by investigators:* PFS 3.9 months (95% CI: 3.4, 5.2) in the CT arm and 8.1 months (95% CI: 6.9, 9.6) in the CT+BV arm; HR of 0.484 (95% CI: 0.370, 0.632; p < 0.0001).

Secondary end-points

- A statistically significant and clinically meaningful improvement in objective response rate (ORR) was observed in the small number of responders. The ORR was increased from 12.5%, n=18, [CI 7.1% to 17.9%] in the chemotherapy alone arm to 28.2%, n=40,[CI 20.8 to 35.6%] in the bevacizumab combination arm, with a p value of 0.001 (unstratified).
- The ORR of the 72 patients who received monotherapy with bevacizumab after disease progression to bevacizumab monotherapy cannot be assessed without further data from the sponsor (requested).

Comment:

This outcome was not presented in the CSR.

Note: Addendum – The sponsor responded that these data were not available due to the study design.

- The median duration of objective response was 5.4 months (CI (3.81-9.23 months) in the CT arm and 9.4 months (6.60-11.63 months) in the CT+BV arm. Although the p value was 0.02 the overlapping CI intervals weakens any conclusion of the benefit of BV as measured by this outcome.

Comment:

This outcome was not included in the conclusions in the SCE.

- Analysis of overall survival at one interim and at the final analysis found these analyses did not meet statistical significance. At the time of the final OS analysis when 73% of patients had died, the median duration of survival was 13.3 months (CI 11.89-16.43 months) in the CT arm and 16.6 (CI 13.70-18.99 months) in the CT+BV arm, with a HR (stratified) of 0.88 (CI 0.69-1.14), and a p value of 0.35 (log-rank).

Note: Addendum - After the inclusion of the dates of death of 2 additional patients by the sponsor, the following results were obtained: 276 (73.7%) rather than 274 (73.1%) patients had died. The median duration of survival was unchanged in each arm and the HR was 0.87 (95%CI 0.678-1.116), and a p value of 0.27 (log-rank).

- The following four instruments used in the assessment of the Health Related Quality of Life (HRQoL) failed to show any significant clinical benefit of combining bevacizumab with chemotherapy – the functional, the symptom and the Global Health Scales of European Organization for Research and Treatment of Cancer (EORTC) quality of life (QLQ)-30[5]; the functional scale, and 8 of 9 symptoms in the ovarian cancer module

[5] EORTC QLQ-30: A questionnaire designed to measure the quality of life of patients with ovarian cancer.

(OV28) instrument; the 19 symptoms in the Functional Assessment of Cancer Therapy–Ovarian Cancer symptom index (FOSI) instrument and the Hospital Anxiety and Depression Scale (HADS) scale.

Comment:

This conclusion differs from that in the sponsor's Clinical Overview, SCE and company study report (CSR). The applicant selected one outcome (abdominal/GI symptom OV28), ignored the approximately 28 other negative symptom outcomes in the FOSI and OV28 instruments, made the one outcome the only secondary objective for HQoL and placed all the other negative outcomes in an 'Exploratory Outcomes' category, contrary to the trial protocol.

Safety

Studies providing safety data

The pivotal study, MO22224, provided evaluable safety data.

For the safety analyses, the data cut-off date for this report was 25 January 2013. The safety analyses were based on the safety population. The denominator used in the analyses was the number of patients who actually received each treatment rather than the treatment to which patients were randomized. The primary safety analyses were conducted to evaluate the safety of bevacizumab plus the chemotherapy in comparison to chemotherapy alone. In the CT arm, if the patient had received crossover bevacizumab monotherapy, only data on or prior to the crossover were included in the primary analyses. The data after the crossover for these patients were summarized separately for evaluation of safety parameters for the crossover bevacizumab monotherapy period (see After cross-over treatment, Attachment 2).

The definition and reporting requirements of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting Topic E2 was followed.

Patient exposure

Exposure to treatment drugs in the CT and the CT+BV arms were evaluated and compared and the median number of cycles and dose intensity for each chemotherapy agent evaluated. Dose intensity indicated the actual amount of chemotherapy that a patient received compared with the expected dose relative to the length of time the patient was on study chemotherapy.

For the CT and CT+BV arms, the median duration of treatment was 10.3 and 19.9 weeks respectively, and the median number of cycles was 3.0 and 6.0.

For *paclitaxel*, the median number of cycles was 4.0 and 6.0 cycles in the CT and CT+BV arms, respectively. The percentage of patients who received 7 cycles or more was lower in the CT arm (12.7%) than in the CT+BV arm (33.3%). The median total paclitaxel dose was 2055.0 mg in the CT arm compared with 2794.0 mg in the CT+BV arm. The median dose intensity was 91.8% in the CT arm compared with 87.8% in the CT+BV arm.

For *topotecan*, the median number of cycles was twice as high in the CT+BV arm as compared with the CT arm (CT: 3.0 cycles versus CT+BV: 6.0 cycles). The median total topotecan dose was also twice as high in the CT+BV arm as compared with the CT arm (CT: 43.2 mg versus CT+BV: 87.7 mg). The median dose intensity was 75.0% in the CT arm compared with 84.0% in the CT+BV arm.

For *PLD*, the median number of cycles was 3.0 and 4.0 cycles in the CT and CT+BV arms, respectively. The median total PLD dose was 230.0 mg in the CT arm and 277.0 mg in the CT+BV arm. The median dose intensity was similar between treatment arms (CT: 100% versus CT+BV: 99.5%).

Bevacizumab exposure

Only patients in the CT+BV arm received bevacizumab prior to disease progression. The median number of treatment cycles was 6.0 cycles (range: 1 to 32). The median duration of bevacizumab treatment was 22.1 weeks, and the median dose intensity was 94.4%. The median total dose of bevacizumab was 6750.0 mg.

Of 72 patients in the CT arm who received crossover bevacizumab monotherapy after documented disease progression (optional cross-over phase), the median number of cycles received was 4.5 cycles (range: 1 to 19). The median duration of bevacizumab treatment was 11.6 weeks, and the median total dose of bevacizumab was 4194.0 mg.

Comment:

Dose-intensity (DI) was not provided for the latter group.

Safety issues with the potential for major regulatory impact

The main safety issue with the potential for rejecting this application is the absence of safety data needed to arrive at a conclusion on risk-benefit, especially since the proposed treatment did not demonstrate an increase in OS or an improvement in quality of life. The missing data have been requested under *Clinical questions* and will not be listed again here.

Postmarketing data

The sponsor's Clinical Overview states '*Periodic Safety Update Report (PSUR)/Recent Periodic Benefit-Risk Evaluation Report (PBRER) data are consistent with the SmPC and previous PSURs/PBRERs. The post-marketing reports are provided in Module 5.3.6 Post-Marketing Experience.*'

Comment:

Module 5.3.6 of the sponsor's submission stated that Reports of Post Marketing Experience were not applicable (NA). Section 6 of the sponsor's Summary of Clinical Safety (SCS) has a review of the Postmarketing experience as follows.

The postmarketing experience with bevacizumab was based on safety data contained in nine previously scheduled Periodic Safety Update Reports (PSURs). The total number of patients exposed to bevacizumab in the postmarketing setting or in clinical trials over the 8 year period covered by the Periodic Safety Update Reports (PSURs) is estimated to be approximately 1,339,560 patients.

During the 9 year period from 26 February 2004 to 25 February 2012, a total of 53,586 adverse events (AEs), of which 44,427 were serious, were reported in 28,252 patients (2.1%). In 3,411 cases (0.3%), the outcome was fatal. Data for each PSUR reporting period and for the cumulative 8 year period were submitted. Overall, the incidence of patients reporting AEs, the proportion of AEs considered serious and the incidence of patients with AEs leading to death has remained stable over this period.

The most frequently reported serious adverse events in patients treated with bevacizumab during the reporting period 26 February 2011 to 25 February 2012 were GI disorders (19.0%), general disorders and administration site conditions (10.5%), infections and infestations (9.2%), vascular disorders (7.8%), and nervous system disorders (7.3%).

Comment:

The tables do not identify AEs by preferred terms but by System organ Classes (SOCs). It is important to know the frequency of the drug-related AE by preferred terms in the SOCs GI disorders, vascular disorders and nervous system disorders so that a comparison can be made with the frequency of these AEs in the pivotal trial. The sponsor will be asked to provide this. The postmarketing information given in the current PI lists mainly rarely reported AEs and AEs of unknown frequency.

Evaluator's conclusions on safety

Drug exposure in the pivotal study

- Patients in the CT+BV arm received treatment for twice as long and received twice as many cycles as those in the CT arm, except for those receiving PLD.
- The median number of treatment cycles of bevacizumab before cross-over treatment was 6 and after cross-over, 4.5. Dose-intensity after cross-over was not provided.

Adverse events

- The overall incidence of adverse events (Grade 2–5 collected) was 87.3% in the CT arm compared with 91.1% in the CT+BV arm. The incidence of Grade 3 to 5 adverse events was 53.0% in the CT arm compared with 59.2% in the CT+BV arm before cross-over and 26.4% from bevacizumab treatment after cross-over. The incidence of patients who experienced serious adverse events was 27.1% in the CT arm compared with 31.3% in the CT+BV arm before cross-over, and 16.7% from bevacizumab treatment after cross-over.
- Grade 2–5 adverse events showing at least 10% higher incidence in the CT+BV arm than the CT arm were hypertension (CT: 5.5% versus CT+BV: 19.0%), proteinuria (CT: 0.6% versus CT+BV: 12.3%) and peripheral sensory neuropathy (CT: 7.2% versus CT+BV: 17.9%). Those showing at least 5% higher incidence in the CT+BV arm than the CT arm were mucosal inflammation (CT: 5.5% versus CT+BV: 12.8%), infection (CT: 4.4% versus CT+BV: 10.6%), palmar-plantar erythrodysaesthesia syndrome (CT: 5.0% versus CT+BV: 10.6%), neutropenia (CT: 25.4% versus CT+BV: 30.7%) and epistaxis (CT: 0 versus CT+BV: 5.0%). The only Grade 2 to 5 adverse event that showed a difference of at least 5% higher incidence in the CT arm was anaemia (CT: 26.5% versus CT+BV: 19.6%).
- Grade 5 adverse events occurred in 5 patients (2.8%) in the CT arm and 6 patients (3.4%) in the CT+BV arm before cross-over and in one patient (1.4%) after cross-over. A total of 6 patients in the CT arm and 9 in the CT+BV arm died due to adverse events. The difference was that Grade 5 AEs were limited to the study period up to 30 days after last treatment whereas the total number included patients in the study follow-up.
- The incidence of adverse events leading to withdrawal of study treatment was 8.8% in the CT arm compared with 43.6% in the CT+BV arm. The most frequently occurring adverse events leading to withdrawal of study treatment with chemotherapy or bevacizumab were peripheral sensory neuropathy, palmar-plantar erythrodysesthesia syndrome, fatigue, proteinuria and neutropenia.
- More patients discontinued treatment in the paclitaxel plus bevaciamab compared to the paclitaxel arm (16% versus CT+BV 45%) than with topotecan and pegylated liposomal doxorubicin (PLD) chemotherapy.
- The incidences of adverse events of special interest were higher in the CT+BV arm (21.8%) as compared to the CT arm (5.1%). Individual AEs of special interest are

summarised in Adverse events of special interest Pivotal study (Attachment 2). The incidence of GI perforations was 1.7% (n=3) in the CT+BV arm. One patient in the CT arm developed a fatal peritonitis. One patient experienced posterior reversible encephalopathy syndrome (PRES) in the CT+BV arm and another possible before cross-over and a third after cross-over treatment with bevacizumab.

Comment:

The figure of 3 patients in the CT+BV arm (SCS and CSR) should be 4, if a probable case is included (see Comment, Gastrointestinal perforation, Attachment 2).

- The incidence of serious adverse events reported were higher in the CT+BV arm for patients ≥ 65 years of age (38.6%), compared to those 65 or less (26.6%). These included fatigue, alopecia, mucosal inflammation, peripheral sensory neuropathy and hypertension
- Addition of bevacizumab to paclitaxel and PLD increased the frequency of serious AEs by approximately 8%. Peripheral sensory neuropathy was more frequently reported in the paclitaxel cohort and palmar-plantar erythrodysesthesia syndrome in the PLD cohort
- The safety of bevacizumab in combination with chemotherapy could not be assessed in patients with ascites, since this sub-group was not separately assessed for safety.

Although a comparison of the incidence of AEs, particularly those of special interest, showed a similar incidence in the pivotal study and in other reported clinical trials of different tumour types, a comparison with the incidence in postmarketing reports could not be made as these data were not provided.

First round benefit-risk assessment

First round assessment of benefits

The benefit of bevacizumab in the proposed usage was:

- A clinically important prolongation of Progression Free Survival (PFS) and a significant increase in the overall response rate in this patient population.

However

- No significant clinical benefit was demonstrated in Overall Survival (OS) in the CT+BV treatment arm compared to the CT arm.
- No improvement in the QOL was demonstrated in any of the parameters assessed, although a benefit was demonstrated in the frequency of paracenteses of malignant ascites in the CT+BV group.

Why was OS not increased when the PFS was prolonged?

A detailed discussion on this issue is beyond the scope of this evaluation, as the possible reasons remain speculative. In brief it is noted that:

- Survival of the 72 patients progressing on the CT arm may have benefited in terms of survival after cross-over treatment with bevacizumab, so that the OS of the CT group approached that of the CT+BV group. No response data for this group was provided to support this effect
- Patients received greater exposure (more cycles) of chemotherapy when administered with bevacizumab compared to chemotherapy alone. Administration of bevacizumab may have therefore allowed the delivery of longer treatment, although the dose intensity was similar to that seen from chemotherapy alone.

One outstanding question is whether PFS was an appropriate end-point under international guidelines for a study of this type. The Committee for Medicinal Products for Human Use (CHMP) Guideline on the Evaluation of Anticancer Medicinal Products in Man December 2005, page 17, states '*If major differences in toxicity are expected in favour of the control regimen, OS should normally be selected as the most appropriate primary endpoint. Similarly, if there are no evidence based next line therapies available and if the period of time from disease progression to death is expected to be short, OS is considered to be the most appropriate endpoint; in most cases even if crossover is foreseen according to protocol. In cases where alternative endpoints are considered to adequately capture patient benefit, the choice has to be justified and scientific advice is recommended. PFS is an acceptable endpoint in situations where it is expected that further lines of treatment with effect on OS may importantly hamper the detection of a relevant treatment effect on OS.*' Regarding the latter point, no evidence is available indicating bevacizumab has activity in ovarian cancer that has progressed after treatment with bevacizumab combination therapy.

First round assessment of risks

- The risks of increased frequency, more severe and more serious AEs in the usage of bevacizumab in combination with chemotherapy for the requested indication were confirmed in the pivotal study. The incidence was as reported in previous studies in different tumour types. The incidence of patients experiencing Grade 2 to 5 AEs was similar in the CT and the CT+BV groups of patients but those receiving chemotherapy plus bevacizumab experienced an 6.2% more severe (Grade 3 to 5) AEs. As well, 50% more patients died of the effects of AEs in the CT+BV group (n=9) than in the CT group (n=6).
- The number of withdrawals due to AEs was very much larger (43.6%) in the CT+BV group than in the CT group (8.8%). Reasons may include the longer time of treatment with bevacizumab (twice, on average), and the continuing treatment with bevacizumab after disease progression. After cross-over, the incidence of AEs from patients receiving bevacizumab was less than before cross-over but after cross-over additional chemotherapy was not given with bevacizumab.
- The incidence of peripheral sensory neuropathy and of palmar-plantar erythrodysesthesia syndrome was increased by the addition of bevacizumab to placlitaxel and PLD chemotherapy respectively.
- Older patients (over 65 years) were a greater risk of adverse effects of bevaciuzmab and chemotherapy.

Patients with ascites (one-third of the patient population) are at potential risk of experiencing a greater incidence of severe and serious AEs as no safety data and no PK studies were provided in this sub-group.

*Addendum***:** Data provided by the sponsor (see 17. Adverse Events in the Sub-group of Patients with Ascites Attachment 2) showed this was not the case.

First round assessment of benefit-risk balance

The benefit-risk balance of bevacizumab used in combination with chemotherapy for the indication requested needs to take into account the following considerations:

- the PFS with CT +BV alone was 6.8 months; that is the additional treatment with BV doubled the PFS of 3.4 months found in the CT group

- the duration of OS with CT+BV was 16.6 months; during this time patients received CT+BV treatment for a median duration of 5 months, a treatment with serious and potentially life threatening consequences
- no significant increase in OS and no significant improvement in the QOL was demonstrated for patients receiving CT+BV compared to CT alone
- missing data that the sponsor has been asked to provide requires assessment to reach a conclusion about the benefit-risk balance.

First round recommendation regarding authorisation

A recommendation regarding authorisation can only be made after the information requested in *Clinical questions* has been evaluated in the context of the present evaluation.

Clinical questions

Pharmacokinetics

1-2. Justification for not providing PK data in the present evaluation

Two main arguments were presented to justify the lack of PK data in the patient population to be treated in this new indication for Avastin.

1. The PK parameters of bevacizumab found in a variety of solid tumours were similar and would be expected to apply to the present clinical population.

   However about one-third of subjects in the pivotal study in this application had ascites at base-line. Ascites would be still present when bevacizumab was administered, raising the question whether this would alter the PKs of bevacizumab by creating a third-space from which bevacizumab could slowly re-enter the systemic circulation or penetrate more directly the gastrointestinal tract, increasing the risk of toxicity.

1.1 Please justify the absence of data on the PK of bevacizumab in patients with malignant ascites, and give reasons why ascites as a third pharmacological space would not be a safety risk in such patients when treated with Avastin.

2. *Pharmacokinetic studies in the present population of patients were claimed to be unnecessary because the PK parameters of bevacizumab had been shown to be similar in a variety of other cancers as shown in the Population PK Analysis of Bevazicumab, Report 1031769 and confirmed for pancreatic cancer in Population PK Analysis BO17706.*

   However this claim of similar PK parameters of bevacizumab in different cancers in patients with different covariates is not supported by a number of conclusions in the up-dated Report 1031796. The possible clinical effects of covariates on PK parameters such as clearance rates of bevacizumab are an example. It is possible that the dose of bevacizumab may need to be reduced to decrease the risk of serious adverse effects in patients who receive the drugs named above, co-administered with bevacizumab.

2.1: Please explain why the conclusions of Report 1031796 as stated above differ from the statements in the sponsor's Clinical Overview, page 18 that states *'A population PK assessment for the influence of combination therapy on bevacizumab disposition has been reported for various chemotherapies and other anti-cancer agents (e.g., erlotinib, trastuzumab, and rituximab). Results show that there were no differences in CL observed between patients treated with single-agent bevacizumab and patients treated with bevacizumab co-administered with chemotherapies (including paclitaxel) or other anti-cancer agents, suggesting that chemotherapies and anti-cancer agents do not alter*

bevacizumab PK when coadministered with bevacizumab.', and also on page 18, Section 3.1, dot point 7 that states *'The cumulative PK-DDI data to date for bevacizumab given in combination with various chemotherapy and other anti-cancer agents across tumour types do not suggest a potential for a PK-DDI between bevacizumab and chemotherapy or other anti-cancer agents.'*

Similarly, the sponsor's Summary of Clinical Pharmacological Studies is wrong in the conclusions, claiming a 17% increase in half-life of bevacizumab with named anti-cancer drugs, instead of the correct 40%.

Was this because the earlier Population PK model was used and not that in Report 1031796? It is noted that Report 1031796 is part of the justification for not providing PK data in this patient population.

2.2: On the basis of the findings of a 40% increase in the half-life of bevacizumab, should the initial dose of bevacizumab be less than your recommended dose in patients who are to be co-administered carboplatin, gemcitabine, paclitaxel, topotecan or doxorubicin (pegylated liposomal)?

Efficacy

3. Continuing treatment with bevacizumab after disease progression

The reasons for selecting the dosage of bevacizumab in the pivotal Study B022224 are given in the sponsor's submission except for the following: *'Bevacizumab should be administered in combination with chemotherapy until PD or unacceptable toxicity. Bevacizumab may be continued as a single agent if chemotherapy is discontinued earlier.'*

The first usage is acceptable but the second is ambiguous since the wording allows bevacizumab to be continued if the patient were receiving chemotherapy plus bevacizumab, and then the chemotherapy was stopped early, say for toxicity. The CSR on the other hand specifically stated that only patients in the chemotherapy alone arm were to cross over on disease progression to receive monotherapy with bevacizumab.

Please confirm that only patients with PD in the chemotherapy alone arm crossed-over to receive bevacizumab monotherapy. If patients who were randomised to the CT+BV arm had the CT discontinued early and received BV, please indicate how many of the 72 patients were in this group. Also provide the assessment of response for all patients (n=72) who received monotherapy, in total and in the two groups previous CT only and previous CT+BV if such was the case.

4. The use of CA 125 to assess response

The use of cancer antigen 125 (CA 125) in the pivotal trial as described in the CSR and the trial protocol followed the guidelines of the Gynaecological Cancer Group[6] except that, as stated in the CSR in assessing PFS, CA 125 was not used to determine progressive disease.

The following is in the abstract of that paper '*The criteria for defining progression are now acceptable in clinical trials of recurrent disease as they have since been validated (*[information redacted] *personal communication, 2010). The GCIG requests that data from all clinical trials using these definitions are made available to GCIG trial centers so that continual validation and improvement can be accomplished.* ***These definitions were developed from analyzing patients receiving cytotoxic chemotherapy and have not yet been validated in patients receiving molecular targeting agents***' (evaluator's emphasis).

[6] Rustin GJS, Vergote I, Eisenhauer E et al, Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG): Int J Gynecol Cancer 2011;21: 419-423

Please address the questions (1) whether the definitions have since been validated in patients receiving molecular targeting agents and (2) whether the personal communication referred to in the paper has been published in a peer-reviewed journal. If neither or either is the case, justification for the use of these guidelines is needed.

5. Acceptability of statistical analysis plan (SAP) amendment 2

The reason given for Statistical Analysis Plan (SAP) Amendment 2 by the applicant is *that 'The plan emphasizes analyses that would meet the expectations of Regulatory Agencies in their review processes for approval of the new indication.'*

The amendment was made 11 months after the close of the clinical data-base of the trial. Until this time, the SAP had been the same in all the amended protocols and assessments of the various endpoints would have been made by the investigators following these trial protocols up to closure of the clinical data-base. It is therefore possible that results or early impressions of these assessments may have led to the SAP Amendment 2, which was not part of the original study design. Therefore selection bias in the changes to the SAP cannot be excluded.

In all the trial protocols, Quality of Life (QOL) was to be assessed by investigators during the course of the trial using multiple HRQoL instruments, including the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ) ovarian cancer module with 28 items (OV28). Such assessments would have been completed at the time of clinical data-base cut-off (25 January 2013), after which no more assessments for QOL were done. The above changes to the SAP (Amendment 2) were made 1 month later on 19 December 2012. In that period, the results of the investigators' assessments of trial patients' QOL using all instruments would have been in whole or in part or potentially available for scrutiny. For the sponsor then to decide that the results from all instruments were no longer to be part of the secondary objectives as pre-defined in the protocols and used throughout, and to regard these outcomes as exploratory only rather than secondary objectives, then to select only the Quality of Life Questionnaire-OV28 abdominal/(GI) symptom scale to be a secondary objective for QOL introduces the strong possibility of data selection and bias.

The evaluator therefore conclude that it would be unsafe to accept this change and intends to evaluate QOL as determined by all instruments as a secondary objective of the trial as planned, and as stated in the trial protocols.

If the sponsor does not agree with this decision, please give reasons.

6. Need for further information on QOL

Insufficient information has been provided on the assessment of the QOL in this study. Given the failure to show an increase in overall survival in patients treated with bevacizumab, the assessment of QOL is of vital importance in determining patient benefit if any from treatment with bevacizumab. Please provide the following information on QOL:

1. What was the proportion of evaluable patients who completed QoL questionnaires over the course of the treatment (that is, longitudinal data) for both arms.
2. Please fill in the table to demonstrate the number of patients with evaluable QoL questionnaires for the following groups.

2.1 The proportions of patients with evaluable baseline and follow-up QoL questionnaire outcomes of those patients

a. experiencing adverse events on bevacizumab compared with those who had an AE in the control arm?

b. experiencing adverse events on bevacizumab compared with those who were on bevacizumab who did not experience an AE leading to discontinuation?

2.2 Please provide the QoL outcomes for all those on bevacizumab at the last time point prior to progression compared with those in the control arm at the last time point prior to progression?

2.3 Did any of the QoL tools measure symptom burden?

7. Obscure meaning of captions on two tables

The captions of Table 114, CSR, (Patient Disposition and Reason for End of Treatment - Chemotherapy Alone: by November 14, 2011 Randomized Patients - Paclitaxel Assigned at Randomization) and that of Table 111, CSR (Patient Disposition and Reason for End of Treatment - Chemotherapy (Paclitaxel): by November 14, 2011 Randomized Patients - Paclitaxel Assigned at Randomization) are confusing. Please explain the meaning of these captions.

8. Assessment of response of malignant ascites to treatment

Frequency of paracenteses performed on patients while on-study was summarised by treatment period for patients with ascites at baseline, as well as patients without ascites at baseline. No formal statistical analysis was performed, but the frequency of paracentesis was substantially reduced among patients treated with CT+BV.

A footnote to Table 26 CSR, states that one patient had multiple paracenteses but the number of paracenteses was not given. In assessing these data, it is important to know how many paracentesis procedures were performed on each patient throughout the study.

Please provide this information.

9. The effect if any of discontinuation from treatment on progression free survival

Please provide the median and interquartile time to treatment failure for both arms (that is, incorporating discontinuations due to adverse events, toxicity, disease progression and so on)? Also please provide a Kaplan-Meier (K-M) curve for PFS for those patients who remained on active treatment up until the time of their disease progression, that is, taking into account discontinuations due to toxicity and adverse events.

10. The number of patients who received prior anti-angiogeneic therapy

Please explain the difference between the Interactive voice response system (IVRS) and electronic case report form (eCRF) recorded numbers for those who had received prior anti-angiogenic therapy and justify which is more likely to be accurate? In what percentage was the prior treatment unknown due to blinding from the previous trial?

11. PFS in subgroups of patients

1. Was there an improvement in PFS with bevacizumab/PDL cf PDL alone?
2. Was there an improvement in PFS for those with ascites at baseline with addition of bevacizumab to treatment?

12. Independent review of scans

Please clarify whether an independent review of scans was undertaken as specified in the protocol amendment, and if not, provide a justification for this not being done.

Safety

13. Absence of data on the relationship of trial drug administration to the occurrence of adverse events

While causal relationship was provided for AEs of special interest, this information was not provided for AEs as a whole in the CSR, the sponsor's Clinical Overview, the sponsor's Summary of Clinical Safety and the SAP Amendment 2. The wording in *Overall Adverse Events* however indicates that all AEs reported as above (as in the CSR) were to be taken as treatment-related. Please give reasons for this omission.

14. Grouping of grades of AEs

The grades of AEs were grouped as Grades 2 to 5, Grades 3 to 5, and Grade 5. Please indicate where the data for the adverse events and serious adverse events for each arm, according to following grading can be found: Grade 1 to 2, Grade 3 to 4, Grade 5. If the data have not been presented in this way, please provide two tables with these data.

15. Absence of assessments of laboratory tests

No results for laboratory tests were presented. However the listing of AEs (Listing 709,) included the preferred terms that are defined from laboratory tests, such as neutropenia, and Grade 3 gamma-glutamyl transpeptidase (GGT) increase. Presumably the investigators used their local data to define such events and then reported them as AEs, with causality. To assess the risk-benefit of the proposed treatment in this group of patients, the AEs related to haematology, liver function and renal function needs to be considered. Please provide these data, including possible relationship to bevacizumab administration.

16. Adverse event of special interest – abscess and fistula

The difference in incidence between the two arms, CT and CT+BV, of this AE is striking for an AE known to be associated with bevacizumab treatment. Two of the events were assessed by investigators as unrelated to bevacizumab treatment. The lack of relationship to bevacizumab would be more convincing if information were given whether the patients were receiving treatment at the time of first occurrence of the AE, what the chemotherapy agent(s) was, and whether the patients' disease was responding, stable or progressing.

Please provide this information.

17. Adverse events in the sub-group of patients with ascites

Addition of bevacizumab to paclitaxel and PLD increased the frequency of serious AEs by approximately 8%.

No assessment of the frequency of serious AEs in the subgroup of patients with ascites was reported. This is important since 31.3% of patients had ascites when receiving chemotherapy and no pharmacokinetic studies were done on these patients to determine whether the PK parameters of bevacixumab were altered, especially whether the ascites formed a third space with prolongation of drug clearance.

Please provide the frequency and nature of the serious AEs in this subgroup of patients.

18. Why was a Grade 4 event (GI haemorrhage) not classified as a Grade 5 event?

Patient [information redacted] was the patient with the Grade 4 GI haemorrhage. The event is not listed in the Listings or Narratives of Grade 5 Events (Patient Deaths) but is in Listing 715, in which the Primary Cause of Death is given as 'Ovarian cancer progression' with the Medical Dictionary for Regulatory Activities (MedDRA) term 'Ovarian Cancer'. Please explain why this death should not be classified as Grade 5, resulting from the AE of GI bleeding and why if GI bleeding was still occurring at the time death, this was not the

cause of death rather than 'ovarian cancer'. The arbitrary time of a 30 day cut-off does not change the cause of death.

19. Frequency of the preferred terms in the following SOC- GI disorders, vascular disorders and nervous system disorders

Table 20, Summary of Adverse Events by System Organ Class in Patients Receiving Bevacizumab: Post-Marketing Data, in the sponsor's Summary of Clinical Safety, does not give the preferred terms for the AEs reported.

To allow a comparison of frequency of these AEs with that in the pivotal study, please provide the frequency of preferred terms for the following SOCs referred to in the PMD – GI disorders, vascular disorders and nervous system disorders.

20. Information on other trials

Aside from those submitted to the TGA with this submission or previous submissions by the sponsor for bevacizumab in ovarian cancer, is the sponsor aware of any other trials that have been or are being conducted comparing the addition of bevacizumab to standard treatment in patients with advanced ovarian cancer?

Second round evaluation of clinical data submitted in response to questions

The evaluator's comments on the sponsor's responses are included under *Clinical questions* in Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of bevacizumab in the proposed usage were reduced as follows:

- Time to Treatment Failure (section *The effect if any of discontinuation from treatment on progression free survival*) provided in the responses showed a reduction in benefit when this parameter was compared to the period of Progression Free Survival (PFS)
- The benefit to the PFS of adding bevacizumab to PD chemotherapy, as shown by investigators' assessments was not confirmed by the assessments of the Independent Review Committee.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks in the proposed usage of bevacizumab are reduced in the case of patients with ascites at baseline whose safety profile was shown to be the same as for patients without ascites at baseline.

Second round assessment of benefit-risk balance

The benefit-risk balance of bevacizumab is unfavourable given the proposed usage but would become favourable if the changes recommended below are adopted.

Second round recommendation regarding authorisation

1. The following change to the proposed indication would make the product approvable:

   'Avastin (bevacizumab) in combination with paclitaxel or topotecan is indicated for the treatment of patients who present with ascites associated with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens.'

The recommended change is based on the demonstrated efficacy of the treatment of the one-third of patients with ascites on presentation and the associated relief of symptoms.

Although the PFS is accepted under International Guidelines as a surrogate measure of efficacy, any associated clinical benefit must be sufficient to provide an acceptable risk benefit ratio. The measure of Time to Treatment Failure (TTF) includes important clinical reasons why patients stop treatment that are not considered in the measure of PFS and becomes more important when other clinical benefits from the treatment with bevacizumab are in question. Also the TTF appears closer to the situation in real life oncology practice than the PFS. Treatment of *all patients* did not result in an acceptable risk-benefit because of the short increase of 2 months in the Time to Treatment Failure, from 3.4 to 5.4 months, the response rate of 28.2%, and an Overall Survival of 16.6 months, not significantly different from the 13 months in the chemotherapy alone arm. The toxicity of adding bevacizumab is clearly shown by the much higher frequency of serious adverse events, adverse events unique to the drug and the high rate of discontinuation from adverse events due to bevacizumab, noting that 72 patients out of every 100 receiving added bevacizumab did not respond to the treatment.

Treatment with pegylated liposomal doxorubicin (PD) is not recommended because of the increased frequency of Palmar-Plantar Erythrodysaesthesia Syndrome with BV (PD arm 12.7%; PD+BV arm 27.4%), the overall high frequency of Gd 5 AEs in the PD+BV arm (6.3% PD alone; 8.1% PD+BV) and the failure to show any benefit in the PFS for patients treated with bevacizumab added to PD chemotherapy (Independent Review of PFS).

2. Changes to the Product Information were also recommended to the Delegate but the details of these are beyond the scope of this AusPAR.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan Avastin EU RMP v14.0 (data lock point 2 August 2013) and an Australian Specific Annex (Version 4.0 dated November 2013) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 3.

Table 3: Ongoing safety concerns

Important identified risks	Bleeding / hemorrhage Pulmonary haemorrhage Proteinuria Arterial thromboembolic events (ATE) Hypertension Congestive heart failure Wound healing complications Gastrointestinal perforations Posterior reversible encephalopathy syndrome Neutropenia Venous thromboembolic events (VTE) Fistula (other than gastrointestinal) Thrombotic microangiopathy Pulmonary hypertension Ovarian failure Hypersensitivity reactions / infusion reactions Gall bladder perforation Peripheral sensory neuropathy Cardiac disorders (excluding CHF and ATE) Osteonecrosis of the jaw
Important potential risks	Embryo-foetal development disturbance Physeal dysplasia
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 pediatric population Safety and efficacy in patients with renal impairment Safety and efficacy in patients with hepatic impairment

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance for all safety concerns. According to the Australian-specific Annex (ASA) routine pharmacovigilance includes the use of guided questionnaires for the important identified risks 'arterial thromboembolic events' and 'congestive heart failure' and important missing information 'safety profile of the different treatment combinations in patients with non-squamous NSCLC'. These questionnaires are provided as annexes to the RMP and are acceptable.

Risk minimisation activities

Routine pharmacovigilance is proposed by the sponsor to mitigate all safety concerns. No additional risk minimisation is proposed.

Reconciliation of issues outlined in the RMP report

Table 4 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 4: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request	*The sponsor acknowledges this requirement.*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.		
In a previous evaluation the evaluator sought clarification regarding the 'safety monitoring plan' assigned to the important identified risk 'congestive heart failure'. The sponsor provided appropriate clarification in their response and it is noted that the evaluator recommended that the sponsor should include the titles of the studies attributed to this activity within the pharmacovigilance plan in the RMP and/or ASA. This recommendation is maintained.	*The sponsor acknowledges the evaluator's recommendation. Reference to the studies will be included in the ASA.*	This is acceptable. The sponsor should provide the TGA with an updated version of the ASA with their pre-ACPM response.
In the previous evaluation it was also recommended that the ASA should include an attachment setting out all the forthcoming studies (that comprise the pharmacovigilance program) and the anticipated dates for their submission in Australia to clarify these milestones in the Australian context. This recommendation is also maintained.	*The sponsor acknowledges the evaluator's recommendation. A table of studies will be added to the ASA.*	This is acceptable. The sponsor should provide the TGA with an updated version of the ASA with their pre-ACPM response.
The evaluator notes that several milestones relating to studies outlined in the RMP and in previous evaluations have passed. The sponsor is reminded that a summary of the CSR of these	*The sponsor acknowledges the TGA's reminder. Study milestone dates will be revised in future versions of the EU-RMP*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
studies, including pharmacovigilance outcomes, should be outlined in PSURs accordingly. These studies include BO21990 (AVAglio), AVF3991n (ARIES), AVF4349n (VIRGO), AVF4095g, MO19286 (AVEX), ML21823, NSABP C-08 and B02541.	*submitted to TGA.* The sponsor has also provided a list of studies that have been included in PSURs and those to be included in future PSURs.	
In the ASA for the important identified risks 'fistulae (other than GI)' and 'cardiac disorders (exc. CHF and ATE)' a proposed pharmacovigilance activity includes 'data collection in study BO17920 '. According to the RMP, this refers to a study completed in 2010. In the response the sponsor should provide information on whether this activity is completed and should therefore be removed from the pharmacovigilance plan.	*The sponsor confirms BO17920 has been completed and will be removed from the ASA pharmacovigilance plan as a PV activity for the risks 'fistulae (other than GI)' and 'cardiac disorders (exc. CHF and ATE)'.*	This is acceptable. The sponsor should provide the TGA with the updated version of the ASA with their pre-ACPM response.
The evaluator maintains the following recommendations regarding the draft product information made in a previous evaluation for bevacizumab: That the specific term 'physeal dysplasia'should be added to the nonclinical section of the PI to be consistent with the EU Summary of Product Characteristics (SmPC) and communicate this important potential risk. That under 'Precautions-wound healing' a statement such as the following found in the SmPC should be added: *'Serious wound healing complications, including anastomotic complications, have been reported, some of which had a fatal outcome* '.	*The following statement has been proposed for inclusion in the Precautions section of the Avastin PI via Safety-Related Request which is currently under review by TGA:* *'In a 26 week pre-clinical study in cynomolgus monkeys, physeal dysplasia was observed in young animals with open growth plates, at bevacizumab average serum concentrations below the expected human therapeutic average serum concentrations.'* *The following statement has been proposed for inclusion in the Precautions section of*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	the Avastin PI via Safety-Related Request PM-2014-01869-1-4 which is currently under review by TGA: *'Serious wound healing complications, including anastomotic complications, have been reported, some of which had a fatal outcome. '*	

Summary of recommendations

It is considered that the sponsor's response to the TGA's request for further information has adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

Issues in relation to the RMP

There are no outstanding issues in relation to the RMP for this submission. The sponsor has committed to updating the ASA in response to the RMP evaluation report. The updated ASA should be provided to the TGA with the pre-ACPM response.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

Implement Avastin EU RMP v14.0 (data lock point 2 August 2013) + Australian Specific Annex (Version 4.0 dated November 2013) with revisions as agreed.

VI. Overall conclusion and risk/benefit assessment

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

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

The clinical evaluator has reviewed the submitted data, which included:

- Two population PK reports
  - BO17706, PopPK AVITA '*Population Pharmacokinetic Analysis BO17706 '*, March 28, 2008.
  - Report 1031796 '*Population Pharmacokinetic Analysis of Bevacizumab. Final Analysis Report ',* January 9, 2008
- One pivotal Phase III Study MO22224 (AURELIA)

The submitted data was evaluated using TGA adopted European medicines Agency (EMA) guidelines as follows:

- EMA/CHMP/205/95 Guideline on the evaluation of anticancer medicinal products in man
- CHMP/EWP/89249/2004 Guideline on the clinical investigation of pharmacokinetics of therapeutic proteins.

Clinical evaluator's recommendation

The clinical evaluator recommended that the following change, based on the demonstrated efficacy of treating patients with ascites on presentation and the likely associated relief of symptoms, to the proposed indication would make the product approvable:

> *'Avastin (bevacizumab) in combination with paclitaxel or topotecan is indicated for the treatment of patients who present with ascites associated with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens.'*

Pharmacokinetics/pharmacodynamics

No PK studies were submitted on patients with ovarian cancer and no changes are proposed to the PK section of the Product Information.

Summary of PK data

The population PK data have been previously evaluated in other applications for malignancies other than ovarian cancer and the clinical evaluator noted that this had been used to support an earlier application for bevacizumab in ovarian cancer. The clinical evaluator identified two issues potentially arising from the population PK data:

1. The clinical evaluator noted a 40% increase in half-life ($t_{½}$) from 20 to 28 days when bevacizumab was co-administered with chemotherapy. The sponsor responded with a population PK modelled effect on steady-state concentrations of bevacizumab at the proposed dose and did not believe a dose reduction was required.
2. The population PK model is based upon a two-compartment model and the impact of ascites (31% of subjects in this study) has not been studied. It is uncertain what effect this would have upon the reported clearance, and $t_{½}$ of 18 days for a female subject. Based upon a 2-compartment model, albumin levels and body weight were reported to have the greatest clinical effect on clearance with an increase seen in those with low albumin, and with higher body weight. Although the mechanism for ascites in ovarian cancer, at least initially may not be related to a low albumin level, with progressive disease and repeated paracenteses, a low albumin may develop. The

sponsor indicated that the toxicity from any potential sequestration of bevacizumab in the third space would not be significant.

Dosage selection

The proposed dose regimen is consistent with that used in other indications and for previous approvals in ovarian cancer. Bevacizumab could be continued as monotherapy in the combination arm if the chemotherapy was discontinued due to toxicity.

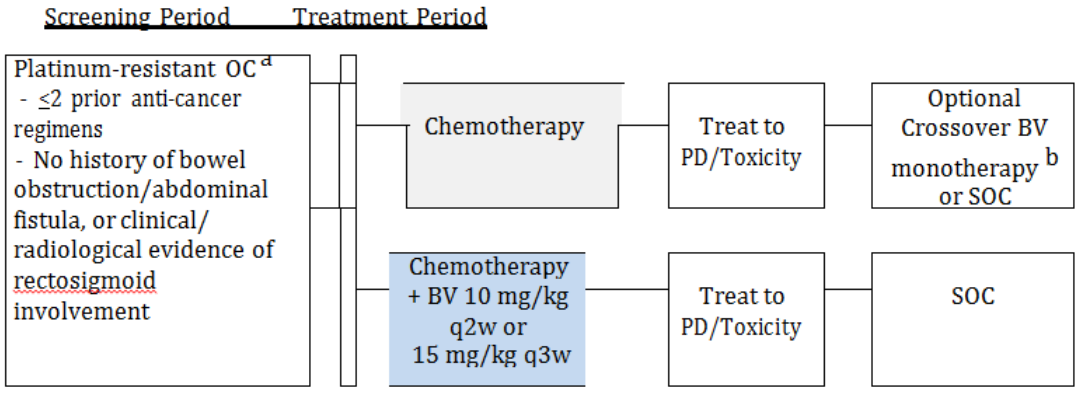
Clinical efficacy

Study MO22224 was an open-label, randomized, two-arm Phase III study carried out in 96 centres in 14 European countries (see Figure 3) comparing bevacizumab (BV) plus chemotherapy (CT+BV) versus chemotherapy (CT) alone to treat recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who received no more than two prior chemotherapy regimens. The vast majority had not received prior anti-angiogenic therapies, including bevacizumab.

Eligibility

Ovarian, fallopian tube or primary peritoneal cancer that recurred within 6 months of previous platinum therapy, but refractory disease was excluded (that is, progression while on therapy). Prior anti-angiogenic therapies were permitted, including participation in a blinded trial, where the therapy was not known. Investigators could choose one of three chemotherapy agents (see Figure 3).

Figure 3: MO22224 Study Design



OC=ovarian cancer; PD=progressive disease; BV=bevacizumab; q2w=every 2 weeks; q3w=every 3 weeks; SOC=standard of care. [a]Epithelial ovarian, primary peritoneal, or fallopian tube cancer. [b]Bevacizumab monotherapy permitted on clear evidence of disease progression Stratification factors: Chemotherapy selected, Prior anti-angiogenic therapy, Platinum-free interval (<3 versus 3-6 months from previous platinum to subsequent PD). Chemotherapy options (investigator's choice): Paclitaxel 80 mg/m^2; Days 1, 8, 15, 22 q4w Topotecan 4 mg/m^2; Days 1, 8, 15 q4w (or 1.25 mg/m^2; Days 1-5 q3w) PLD 40 mg/m^2; Day 1 q4w

Analysis populations

ITT – all who were randomized.

HRQoL – all who completed baseline and at least one post-baseline assessment.

Safety – any dose of either chemo or bevacizumab.

Delegate comment:

There was no Per Protocol population, so it is not known how many patients were lost or key endpoint data were missing in each of the arms.

Cross-over to BV monotherapy from CT arm. The strict criteria governing cross-over, mostly to select patients fit for further treatment with BV, which would also potentially have biased the results in that only those who were more fit would have been allowed to cross over. Note: Bevacizumab monotherapy also occurred in the CT+BV arm when chemotherapy was discontinued due to toxicity but in an unknown number and these cases were not captured or analysed separately as monotherapy.

Primary objective

Progression Free Survival (PFS) as determined by the investigator according to RECIST Version 1.0 or by symptomatic deterioration, whichever occurred first. CA125 concentrations were not used to assess PD in the trial as this had not been validated in patients receiving combination therapy with a molecular targeting agent has not been validated as an indicator of progressive disease.

Secondary objectives

Objective Response Rate per RECIST: PR/CR as determined by investigators. Best objective response was determined and confirmed as described in Attachment 2.

Duration of objective response

per RECIST: For randomised patients who achieved an objective response per RECIST = date of the first occurrence of a CR or PR (whichever occurred first) until the date that PD or death was documented (whichever occurred first). The duration of objective response was not censored at the start of non¬protocol specified anticancer therapy (NPT) or crossover to bevacizumab monotherapy before disease progression.

Overall survival (OS)

= time from randomisation to death from any cause.

Health-Related Quality of Life (HRQoL) Measurements - The HRQoL instruments used to assess HRQoL were:

- The symptom and functional scales, and Global Health Status (GHS)/QoL scale of EORTC QLQ-C30
- European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ) ovarian cancer module with 28 items (OV28)
- Total score from the National Comprehensive Cancer Network (NCCN)/FACT Ovarian Symptom Index (FOSI)
- The depression and anxiety scale from the Hospital Anxiety Depression Scale (HADS)

Delegate comment:

Statistical analysis plan amendments were made at very late stages for example 1 month after the closure of the database when the outcomes for some parameters would be known for example quality of life data. While most changes would have no effect on the outcomes, the clinical evaluator noted the potential for bias to have occurred when post hoc making selected patient reported outcomes (PROs) a secondary outcome, and the remainder exploratory. This is particularly so, when the selected questions focusing on abdominal symptoms from one QoL questionnaire (EORTC-OV28) were made a secondary outcome and all other parts of that questionnaire and outcomes from the other three tools were relegated to being exploratory only. This amendment specifies examining only a change in the disease-related symptoms from treatment (which may have been known at the time of the amendment) but will miss other quality of life issues that may arise from complications of the treatment (such as deep vein thrombosis (DVT) or fatigue). The justification of this being done to be more likely to meet the

'expectations of Regulatory Agencies' reinforces this concern identified by the clinical evaluator.

Baseline demographics were balanced (and the majority of subjects had primary ovarian carcinoma (90%), most commonly serous epithelial carcinoma, most were FIGO Stage IIIC (55.2%), with the second most common FIGO Stage IV (26.2%). The majority (62.4%) of tumours were histologic Grade 3 (poorly differentiated). Most subjects had measurable disease at baseline (79.2%) and baseline CA-125 levels ≥2 × upper limit of normal (ULN) (87.0%). Approximately one-third of randomized patients had ascites at baseline (31.3%).

Previous Treatment and Procedures: All randomised patients had received first-line platinum-based chemotherapy treatment for ovarian cancer. Most patients had a PFI of 3 to 6 months (72.6%) compared with a PFI of <3 months (27.4%). 87% of all randomised patients had received initial surgical management for their ovarian cancer. Less than half of all randomised patients (CT: 42.9% versus CT+BV: 40.2%) had received second-line chemotherapy treatment. Of these patients, the majority (88.0%) had received a platinum-based regimen.

7.5% had received prior anti-angiogenic therapies including bevacizumab at baselin, but due to blinding in clinical trials, the treatment was not known in one third of these subjects.

Delegate comment:

The vast majority of subjects (at least 92.5%) had not been previously treated with anti-angiogenic therapies and this needs to be reflected in the indication, as there are no data to support that re-treating with bevacizumab therapy will be efficacious.

Results for the primary efficacy outcome

At the time of data cut-off of the primary efficacy analysis (14 November 2011), 168 PFS events (92.3%) in the CT arm and 141 PFS events (78.8%) in the CT+BV arm had occurred. The efficacy results for PFS were as follows, for the CT and CT+BV arms respectively:

Number (No.) (%) patients with progression: 168 (92.3%) compared to 141 (78.8%)

No. (%) patients without progression: 14 (7.7%) compared to 38 (21.2%)

Median time to event, months: 3.4 (95% CI 2.10, 3.75) compared to 6.7 (5.62, 7.79)

Hazard Ratio, relative to CT 0.379(95% CI: 0.296, 0.485)

Log-rank p-value < 0.0001

Adding bevacizumab to chemotherapy significantly improves PFS. Sensitivity analyses, taking into account potential impact of missing tumour assessments, discontinuation because of toxicity and non-protocol therapies including cross over to bevacizumab monotherapy consistently supported the primary PFS finding.

While the independent review of the data, requested in the TGA's questions, confirmed a PFS 3.9 months (95% CI: 3.4, 5.2) in the CT arm and 8.1 months (95% CI: 6.9, 9.6) in the CT+BV arm; HR of 0.484 (95% CI: 0.370, 0.632; p < 0.0001), it failed to show any benefit in the PFS for patients treated with bevacizumab added to PLD chemotherapy. The investigator reported improvement in PFS for those on PLD/bevacizumab of 5.1 months versus 3.5 months PLD alone (HR 0.53; 95% CI 0.36, 0.77) was not supported by the independent review which yielded 95% CI for the HR of 0.46 and 1.06. This needs to be stated clearly in the PI and registration for this combination is not supported by the Delegate or the clinical evaluator.

Delegate comment:

This demonstrates the importance of both undertaking and reporting the independent scan review results. The simulated independent review presented in the submitted dossier did not reveal this discordance.

Subgroup analyses (other than by chemotherapy regimen) were difficult to interpret due to small numbers but two groups where no significant benefit was apparent were those with ECOG>2 and those with prior anti-angiogenic therapy.

Other efficacy outcomes

Overall survival (cut-off date 25 January 2013)

No significant difference in median OS : 13.3 months (95% CI 11.89,16.43months) in the CT arm versus 16.6 months (95% CI 13.70,18.99 months) in the CT+BV arm, with a HR (stratified) of 0.87 (CI 0.68-1.12), and a p value of 0.27 (log-rank).

Cross-over

Some 72 patients crossed over from the chemotherapy alone arm due to toxicity or progression; an uncertain number of patients discontinued chemotherapy in the combined arm but continued bevacizumab as monotherapy but these patients were not captured nor analysed separately from those who continued with chemotherapy in this group. Thus the potential impact of cross over is unknown. The median duration of treatment after cross over was 11.6 weeks (which may also be the interval before the first scan detecting progression).

Quality of life

The clinical evaluator did not accept, on the grounds of a high risk of bias, the sponsor's presentation of a QoL data analysis amended to include only abdominal symptoms data (based on an amendment to the Statistical Analysis Plan made after cut-off for closure of the trial). The Delegate is in agreement that this amendment introduced significant potential for bias, as well as potentially missing the impact of treatment and adverse events on general wellbeing.

An additional source of bias is the open label design of the trial where patients knew what they were receiving which may have influenced their responses.

However, compliance was poor across all four assessment tools with missing data in more than 50% (84/182 evaluable) in the CT arm by Week 8/9 (the first time point for comparison with baseline), and only 43/182 with questionnaires available in this arm at week 16/18 compared to 86/179 in CT+BV arm. This is another significant potential source of bias as data from those progressing were not captured[7]. Those who discontinued due to an AE (high rate in CT+BV arm) may have experienced an improvement in QoL with discontinuation and management of symptoms. Thus, quality of life has not been adequately assessed and it is not possible draw any conclusions from the results presented.

Delegate comment:

The information in Table 13 in the PI regarding quality of life needs to be removed.

Paracentesis requirement (exploratory endpoint)

One out of 59 patients with ascites at baseline in the combination arm required paracenteses (>1, but exact number of procedures not presented) compared to 12/54 in the CT alone arm, with half of these needing >1 paracentesis. It was not stated how many

[7] as per TGA adopted EU guideline: CPMP/EWP/1776/99 *Guidelines on Points to consider on missing data*

of these patients had required paracenteses prior to treatment to establish a reduction in the rate as a treatment benefit.

Objective response rate

Some 79.2% had measurable disease at baseline. Of those, the ORR with combination treatment was 28.2% versus 12.5% in the CT alone group. Difference in ORRs of 15.7% (95% CI: 6.5%, 24.8%; p = 0.0007). CR was equal in both arms ie no improvement with addition of bevacizumab, but more subjects experienced a PR with the combination treatment. ORR was not assessed for those who crossed over, nor considered separately for those in the CT+BV who discontinued only the chemotherapy component.

Delegate comment:

> The failure to improve CR rates may well explain the failure to effect a statistically significant improvement in OS with inclusion of bevacizumab.

Duration of objective response

The CI overlapped and the numbers were relatively small so little can be drawn from this analysis.

Efficacy summary

Adding bevacizumab to chemotherapy in this population led to a statistically significant increase in partial response rates but no additional complete responses. This led to a statistically significant improvement in PFS but did not translate into a statistically significant gain in OS. An independent review of the scans confirmed the overall PFS findings but did not confirm that those on PLD plus bevacizumab had a statistically significant increase in PFS. Some 92.5% had not had prior anti-angiogenic therapy. The quality of life data were incomplete and therefore it is not known whether this was accompanied by an improvement in quality of life, although there was a decrease in the number of patients requiring paracenteses.

Safety data

The pivotal efficacy trial, MO22224, provided the safety data for analysis. Only Grade 2-5 treatment-emergent adverse events were reported, and there was no summary presentation of data for those adverse events considered related to the study treatment. When the clinical evaluator requested this information, the sponsor did not prepare a response but directed the evaluator to the 80 pages of individual patient AE data to determine causality. Laboratory tests, including haematology, serum chemistry, and urinalysis were performed by local laboratories, with the adverse events reported in the CRF but no data included in the clinical database for the CSR and thus are not available for evaluation.

Special adverse events of interest (commonly recognised side effects of bevacizumab) were analysed separately. These included all Grade 2 or greater posterior reversible encephalopathy syndrome (PRES), ATE (arterial thromboembolic event), central nervous system (CNS) bleeding, GI perforation, fistula or abscess, and febrile neutropenia; and Grade 3 or greater hypertension (HTN), proteinuria, wound healing complication, non-CNS bleeding, venous thromboembolic event (VTE), congestive heart failure (CHF), and peripheral sensory neuropathy.

Delegate comment:

> The safety reporting has captured, analyzed and presented limited data from a randomised Phase III trial. While there have been multiple randomised controlled trials, including in ovarian cancer, there is a risk with this approach that new or rare adverse events will not be recognised. This is especially important as neither

topotecan nor PLD in combination with bevacizumab has been previously evaluated. The total AEs have not been reported as Grade 1 AEs were not recorded which renders the *All Grade Reactions (≥ 10% difference between the study arms in at least one clinical trial)* heading in Table 14 in the PI inaccurate; it is likely for this trial that more AEs would have reached the >10% threshold for inclusion' had Grade 1 AEs been recorded. The heading requires amendment in the PI (to Grade 2-5), as it is not an accurate summary of this trial, as Grade 1 events were not recorded in this trial.

Duration of therapy

For the CT and CT+BV arms, the median duration of treatment was 10.3 and 19.9 weeks respectively, and the median number of Cycles 3.0 and 6.0 respectively. Only patients in the CT+BV arm received bevacizumab prior to disease progression. The median number of treatment cycles was 6.0 cycles (range: 1−32). The median duration of bevacizumab treatment was 22.1 weeks. Of 72 patients who received crossover bevacizumab monotherapy after documented disease progression (optional cross-over phase), the median number of cycles received was 4.5 cycles (range: 1−19). The median duration of bevacizumab treatment was 11.6 weeks.

Patients completed more cycles of chemotherapy when receiving bevacizumab with paclitaxel (median 6 compared to 4) and topotecan (median 6 compared to 3), but those on PLD received only a single additional cycle compared to chemotherapy alone, suggestive of less benefit with the combination (either decreased efficacy and/or increased toxicity cf other regimens). The investigator-reported improvement in PFS for those on PLD/bevacizumab of 5.1 months versus 3.5 months PLD alone (HR 0.53; 95% CI 0.36, 0.77) was not supported by the independent review which yielded 95% CI for the HR of 0.46 and 1.06. This independent review result is consistent with the minor median single cycle increase achieved, and the patient numbers in these two groups were adequate for analysis (51 events CT and 49 CT+BV) by the independent committee.

Delegate comments:

1. The Delegate and clinical evaluator are in agreement that efficacy has not been established for the combination of PLD and bevacizumab (see also Safety concerns below).
2. It is not possible to determine that there was a benefit from crossing over to bevacizumab after chemotherapy as the median treatment duration reported is likely to be the interval before the first scan after cross-over (that is, 3 months). Furthermore, only those with good performance status were permitted to cross over. No claims are being made for any such benefit of monotherapy which is appropriate but it underscores the loss of important information for OS from allowing cross over when there was an uncertain benefit with doing so. The Delegate is uncertain that cross over would be an explanation for the failure to demonstrate a statistically significant OS.

Adverse events

All AEs presented in the dossier were treatment-emergent with no presentation or discussion of treatment-related AEs by the sponsor. The safety section of the PI needs to be updated with the AEs from this trial where they exceed those currently reported in the PI.

AEs occurring in ≥ 20% of patients in either arm were fatigue (CT: 26.5% versus CT+BV: 27.4%), anaemia (CT: 26.5% versus CT+BV: 19.6%) and neutropenia (CT: 25.4% versus CT+BV: 30.7%).

Grade 2–5 AEs with >5% greater incidence in the CT+BV arm were:

- hypertension (19.0% versus 5.5%)
- proteinuria (12.3% versus 0.6%)
- peripheral sensory neuropathy (17.9% versus 7.2%).
- mucosal inflammation (12.8% versus 5.5%)
- infection (10.6% versus 4.4%)
- palmar-plantar erythrodysaesthesia syndrome (10.6% versus 5.0%)
- neutropenia (30.7% versus 25.4%)
- epistaxis (5.0% versus 0%)

The only Grade 2–5 adverse event that showed a difference of at least 5% higher incidence in the CT arm was anaemia (CT: 26.5% versus CT+BV: 19.6%).

Grade 3–5 AEs

Before Cross-over Treatment: CT+BV 59.2% compared to 53.0% in the CT arm.

With ≥2% higher in the CT+BV arm: hypertension, palmar-plantar erythrodysaesthesia syndrome, and general physical health deterioration.

With ≥2% higher in the CT arm: leucopenia, abdominal pain, ascites, vomiting, fatigue and dyspnoea.

After cross-over to bevacizumab monotherapy, 26.4% experienced a Grade 3-5 AE, including 1 case of PRES (Grade 4) and a death from GI haemorrhage.

Delegate comment:

> This case of PRES needs to be included in the Precautions section of the PI, including that it occurred when treating ovarian cancer.

Deaths

Most deaths were due to progressive disease. There were 9 deaths reported from AEs in the CT+BV arm and while 6 were reported in the CT arm; one of these occurred after crossing over to bevacizumab monotherapy. The Delegate considers this a bevacizumab-related death (and should not be included with the CT group). These treatment related deaths should be stated in the Clinical Trials section (as was done for the first line ovarian cancer section in the PI). Thus there were 5 deaths due to CT-related AEs and 9 from CT+BV, with a further death after crossing to BV.

Serious adverse events

SAEs were both more frequent and more severe in the CT+Bev arm (31.3% vs 27.1%).

Grade 5	3.4% compared to 2.8%
Grade 4	5.6% compared to 3.3
Grade 3	15.6% compared to 13.3%

Known bevacizumab-related complications such as fistulae (2.2% versus 0) and hypertension (2.2% versus 0) occurred more frequently, while vomiting occurred more frequently in the CT alone group. The PI contains a lower figure for the risk of fistulae and this will need to be updated with the rate observed in this trial.

Discontinuations (total)

Chemotherapy discontinuation at the cut-off date for the primary analysis of PFS

- CT: 97.8% versus CT+BV: 92.7% had discontinued chemotherapy treatment

- Discontinuations due to RECIST defined disease progression were more common in the CT arm 72.0% versus 39.7% while unacceptable toxicity, adverse events and 'other' (such as physician's choice) were much more common reasons in the CT+BV arm 43.6% versus 15.3 %.

Bevacizumab discontinuation

- 86.0% in the CT+BV discontinued bevacizumab treatment: 42.5% due to disease progression and 25.7% due to adverse events or unacceptable toxicity.

Discontinuations due to AEs (before cross over)

- 43.6% in the CT+BV compared to 8.8% in the CT arm experienced Grade 2–5 adverse events that led to withdrawal of study treatment with chemotherapy or bevacizumab. The following were all higher with CT+BV:

peripheral sensory neuropathy	4.5% compared to 1.7%
palmar-plantar erythrodysaesthesia syndrome	3.4% versus 0.6%
fatigue	3.4% compared to 0%
HTN	2.8% compared to 0%
neutropenia	2.2% versus 0%
proteinuria	2.2% versus 0%

Discontinuation rates of the combination treatment were most common in patients receiving paclitaxel and bevacizumab (29% more likely to discontinue the combination compared to paclitaxel alone (45% versus 16.4%)), 18% for the PLD plus bevacizumab arm (21% versus 3.2%cf PLD alone) and 13% higher in the topotecan group (21% versus 3.2%).

AEs in the CT+BV arm that occurred with $\geq$ 5% frequency than the CT arm were as follows for each of the three drugs:

Paclitaxel: neutropenia (+5%), fatigue (+6.7%), peripheral sensory neuropathy (+6.2%), nail disorders (+11.6%).

Topotecan: 0

PLD:- Palmar-Plantar Erythrodysaesthesia Syndrome (+6.5%).

- 27.4% discontinued bevacizumab due to Grades 2-5 AEs patients: 8.4% gastrointestinal, 6.1% vascular disorders (including HTN crisis n=6), and 4.5% renal and urinary disorders.

Delegate comment:

Just over half of those starting the bevacizumab and chemotherapy are able to continue treatment until disease progression or death. Topotecan and BV combination appears to be the best tolerated, although the median number of cycles was the same as for paclitaxel.

Clinical laboratory tests

No information was provided except for haematological AEs of special interest; bleeding and febrile neutropenia. The following is taken from the Round 2 Clinical Evaluation Report:

Delegate comment:

This is a very limited and unsatisfactory presentation of safety data for evaluation, particularly for combinations of treatments previously untested and currently approved in combination. In an open label trial, the reliance upon investigator

opinion as to the importance of laboratory abnormalities introduces the potential bias for abnormalities and AEs to go unreported and uncaptured for example those contributing to less specific symptoms such as fatigue, which was a prominent AE in this trial.

AEs of special interest

- ≥Grade 2 PRES, ATE (arterial thromboembolic event), CNS bleeding, GI perforation, fistula or abscess, and febrile neutropenia
- ≥Grade 3 or greater hypertension (HTN), proteinuria, wound healing complication, non-CNS bleeding, VTE, CHF, and peripheral sensory neuropathy

Before cross-over treatment

- 21.8% in the CT+BV arm experienced an AE of special interest compared to 5.1% of patients in CT arm. The following were observed at a higher rate in bevacizumab-treated patients by the percentage shown for the following categories:
  - ≥ Grade 2*: GI perforation* (+1.1%), *fistula and abscess* (+2.2%), PRES (+0.6%)(n=1)
  - ≥ Grade 3: HTN (+6.7%), peripheral sensory neuropathy (+1.7%), proteinuria (+2.2%), ATE (+1.1%), and wound healing complications (+1.1%).

After cross-over treatment

Of the 72 patients who received monotherapy with bevacizumab after disease progression, the frequency of special interest AEs was less that the in the Before Cross-Over group, except for PRES with a frequency of 4.2% (n=1).

SAEs by sub-group

SAEs were increased in those over 65 and PI changes have been made by the sponsor in response to the clinical evaluator to reflect this. However, the actual statistics need to be included to demonstrate the risk: 38.6% versus 26.6%.

The clinical evaluator also sought information about those with ascites. Although their baseline level of AEs was higher, there did not appear to be an increase when treated with bevacizumab as well.

Safety discussion

An increase in AEs is to be expected when adding in a therapy. The addition of bevacizumab to chemotherapy led to more treatment related deaths, higher rates of discontinuation, a greater number of and more severe SAEs and the introduction of risks specific to bevacizumab such as fistula formation, hypertension and proteinuria. The increase in AEs was highest with paclitaxel AEs and was lowest with topotecan. Addition to PLD increased the risk of hand-foot syndrome and there were a number of deaths recorded with PLD alone and in combination with bevacizumab.

The absence of collection of laboratory data and reliance upon the abnormalities to be reported only if causing symptoms or necessitating treatment changes, lacks rigour, especially for new combinations, where such information is not known.

In general, the Clinical Trial section and Precautions section of the PI lack detail and do not adequately quantify risks for example that the trial population was selected on the basis that the GI perforation rate was too high for those with >2 lines of prior chemotherapy needs to be included. Presentation of the absolute statistics for SAEs in the >65 year old women may deter some from considering the risk balanced against there being no change in survival.

Efficacy and safety summary

Overall, the addition of bevacizumab to chemotherapy led a 15.7% increase in partial response rates (but no CRs) as determined by RECIST criteria, a statistically significant increase in PFS but no statistically significant increase in overall survival. The time to treatment failure, which incorporates other factors for discontinuing therapy rather than progressive disease or death, is a valid tool for assessing the impact of treatment, especially where the discontinuation rate is high: and there was an increase of 2 months from 3.4 to 5.4 months, with an overall response rate of 28.2%. Discontinuations due to adverse events, toxicities, physician decision were high (43.6%) in those receiving bevacizumab.

The quality of life data collection was incomplete and thus did not permit an assessment of any specific or general symptomatic improvement; consequently, the meaningfulness of this PFS, or indeed the harm from AEs to patients' wellbeing are unknown. The Anticancer Guidelines adopted by the TGA indicate that PFS, where there is no OS, should ideally be supported by quality of life data.

There was no statistically significant improvement in PFS in those receiving PLD with bevacizumab on independent review, which is consistent with the evaluation finding of only a marginal increase in the number of treatment cycles completed (3 versus 4).

A subgroup who appeared to derive benefit were those presenting with ascites, with lower numbers in the bevacizumab plus chemotherapy group requiring paracenteses. The clinical evaluator recommended restricting the approval to this particular group where there appeared to be clearer evidence for a symptomatic and clinically meaningful benefit.

Subjects with platinum-resistant ovarian cancer have few effective options remaining for palliative treatment. The potential 3.4 month gain in PFS with bevacizumab will be spent on active treatment to achieve this. Evaluable quality of life data would have assisted the patient's decision as to whether the side effects of the treatment with bevacizumab are outweighed by the potential for there to be no disease progression for a median of 3.4 months. The sponsor limited the analysis of quality of life data to abdominal symptoms and demonstrated an improvement (albeit with large amount of data missing), although 35% of subjects were without abdominal symptoms at baseline. The Delegate considers that some patients would be prepared to take the risk of suffering adverse events risk, to have a period of better control of their disease, following an informed discussion.

The sponsor is requested to make the changes to the safety profile and to include a brief summary sentence of the key safety (deaths, SAEs and discontinuations) beneath the efficacy table to ensure a balanced presentation of the risks for the prescriber to convey to the patient. The PI currently contains statements about specific adverse event risks without rates to support these which does not provide sufficient detail for prescribers to inform patients so they can make an informed choice (for example Use in the Elderly). An updated Consumer medicine Information (CMI) will need to be reviewed, and the TGA's Advisory Committee on Prescription Medicines' (ACPM's) advice on its content is sought.

This population had not been pre-treated with anti-angiogenic therapies and it cannot be assumed that re-treatment would yield the same median PFS improvement. This is reflected in the Delegate's modified indication.

Both the Delegate and the clinical evaluator consider that the efficacy and safety of treatment with bevacizumab and pegylated liposomal doxorubicin (PLD) have not been demonstrated satisfactorily for the proposed usage, as evidenced by the following:

1. The failure of an independent review to demonstrate increased PFS for patients treated with bevacizumab added to PLD chemotherapy
2. The median treatment duration being increased by only a single further cycle before discontinuation due to either disease progression, death or adverse events

3. The adverse safety profile with the combination with BV
    a. increased deaths in the PLD+BV 8.1% compared to 6.3% PLD alone
    b. frequency of palmar-plantar erythrodysaesthesia with BV+PLD 27.4% versus 12.7% PLD alone for this cohort
4. the absence of supportive QoL data to indicate any patient-reported benefits with this treatment to offset the above concerns.

Consideration of registration of the combination of PLD+BV requires the demonstration of adequate safety and efficacy through further randomised studies.

Risk management plan

There were no outstanding issues identified in the second round report by the RMP evaluator.

A number of recommendations for the RMP have been provided by the RMP evaluator and the sponsor should address these matters in the Pre-ACPM Response and follow up where appropriate with the TGA.

Risk-benefit analysis

Delegate's considerations

Data deficiencies/limitations

There are no laboratory data measurements recorded; investigator reported classification of AEs has been relied upon.

The QoL data were insufficient due to low completion rates, especially in the chemotherapy alone arm.

The PI currently does not include statistics to explain adequately the risks to prescriber or patients of undertaking treatment in this population.

Summary of issues

Adding bevacizumab to paclitaxel or topotecan increased the response rate by 15.7%, which were partial responses or stable disease only (no complete responses) improved PFS by 3.3 months (statistically significant) but not OS. No improvement in either PFS or OS was seen on independent review.

Those receiving pegylated liposomal doxorubicin (PLD) managed only a median of 1 extra cycle with bevacizumab, and the independent review of the scans revealed no statistically significant increase in PFS or OS with this combination, so registration is not supported.

Quality of life data were missing, so whether there is specific and/or general symptomatic improvement or harm to wellbeing is unknown.

Deaths, SAEs and AEs were more common with the study treatment.

Proposed action

The Delegate had no reason to say, at this time, that the application for Avastin should be approved for the proposed indication. The following amended indication could be considered for registration:

> *Avastin (bevacizumab) in combination with paclitaxel or topotecan is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian,*

fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens, and who have not received any prior anti-angiogenic therapy including bevacizumab.

Conditions of registration

Implement Avastin EU RMP v14.0 (data lock point 2 August 2013) and Australian Specific Annex (Version 4.0 dated November 2013) with revisions as agreed.

Request for ACPM advice

Whether the improvement in PFS alone is sufficient to support registration for the Delegate's modified indication.

Questions for the sponsor

The sponsor is requested to confirm the number of cases of PRES in the study, including those that developed after crossing over to bevacizumab monotherapy and to incorporate these into the PI, stating specifically that they occurred in this trial population.

Please provide a justification for the proposed PI change restricting to physicians who treat cancer.

Response from sponsor

Comment on the delegate's proposed action

The Delegate's Pre-ACPM preliminary assessment for the application is:

> '*I am not in a position to say that Avastin should be approved for the proposed indication. However the following indication could be considered for registration: 'Avastin (bevacizumab) in combination with paclitaxel or topotecan is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens, and who have not received any prior anti-angiogenic therapy including bevacizumab*.'

The sponsor concurs with the Delegate's recommendation to limit the indication to patients who have not received prior anti-angiogenic therapy. The sponsor does not concur with the Delegate's recommendation to remove pegylated liposomal doxorubicin (PLD) from the indication as a chemotherapy treatment option in combination with Avastin. The sponsor proposes the following modified indication for registration:

> '*Avastin (bevacizumab) in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens, and who have not received any prior anti-angiogenic therapy including bevacizumab*.'

The following statement is made in the Delegate's Overview, under *Summary of Issues*:

> '*Adding bevacizumab to paclitaxel or topotecan increased the response rate by 15.7%, which were partial responses or stable disease only trio complete responses) improved PFS by 3.3 months (statistically significant) but not OS. No improvement in either PFS or OS was seen on independent review*.' The sponsor wishes to highlight this statement is incorrect. Improvement in PFS was confirmed by independent review and is discussed below.

Benefit/risk assessment

Study MO22224 was designed to evaluate the efficacy and safety of bevacizumab (BV) in combination with chemotherapy (CT) for recurrent platinum-resistant ovarian cancer with the main objective to compare progression-free survival (PFS) of patients randomised to selected CT (paclitaxel, topotecan, or PLD) or to selected CT plus BV. The data from MO22224 are the best efficacy results to date of any currently available treatment options in the setting of recurrent platinum-resistant disease and the sponsor considers the benefit/risk profile of BV use in this setting to be positive.

The results of the investigator-assessed PFS, which was the primary endpoint, showed a 62.1% reduction in the risk of a PFS event when BV was added to any CT, that is, paclitaxel, topotecan or PLD, (hazard ratio [HR] 0.379; 95% CI: 0.296, 0.485; log-rank p-value 0.0001), with a corresponding increase of 3.3 months in median duration of PFS. Moreover, the results of the retrospective independent review committee (IRC) for all randomised patients confirmed the clinically meaningful and statistically significant improvement observed in investigator-assessed PFS when BV was added to any CT (HR 0.484; 95% CI: 0.370, 0.632; log-rank p 0.0001). These results are of significant clinical relevance because it is the first time a prolongation in PFS has been observed in this extremely poor prognosis disease setting with limited treatment options. The robustness of the PFS result was supported by all the sensitivity analyses and the majority of subgroups (MO22224 clinical study report (CSR) and IRC statistical analysis plan (SAP)).

The improvement in the PFS primary efficacy endpoint was also supported by secondary endpoints: a statistically significant and clinically meaningful improvement in overall response rate (ORR), with a difference in ORR of 15.7% in favour of the BV arm when BV was added to any CT (95% CI: 6.5%, 24.8%; p 0.0007); and a reduction in the risk of death of 13% (HR 0.870; 95% CI: 0.678, 1.116; log-rank p 0.2711), with a corresponding 3.3 month improvement in median overall survival (OS) (from 13.3 months in the CT arm to 16.6 months in the CT BV arm), though this was not statistically significant. The improvement in median OS compared favourably to the median OS reported in prior trials of the CT agents used in this trial (paclitaxel, topotecan, and PLD) which ranged from 8.3 to 14.1 months (36 to 61 weeks). [8]

In this platinum-resistant patient population, the safety profile of BV when added to CT was consistent with that seen in trials of BV across tumour types. Although safety analyses suggest that BV may exacerbate certain adverse reactions associated with the CT agents used in this study, such as palmar-plantar erythrodysaesthesia (PPE) syndrome with PLD; peripheral sensory neuropathy (PSN), nail disorders, or alopecia with paclitaxel, these adverse reactions are well known to prescribers and no new safety signals were observed for BV in this study. Importantly, MO22224 demonstrated that well selected platinum-resistant recurrent ovarian cancer patients can safely and effectively be treated with BV without additional concerns regarding GI perforation.

For health-related quality of life (HRQoL) outcomes the abdominal/GI symptoms scale of the EORTC QLQ-OV28 module was the only pre-specified secondary endpoint, however the other scores of the EORTC QLQ-OV28 and the scores of the EORTC QLQ-30, the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) Symptom Index (FOSI) and the Hospital Anxiety and Depression Scale (HADS) were analysed and descriptive results of change from baseline were provided in the CSR. No notable difference was observed between treatment groups demonstrating that the addition of BV did not negatively impact the overall HRQoL of patients but did provide relief for abdominal/GI symptoms, one of the most important symptoms of ovarian cancer. Further discussion of the HRQoL data is provided later on is this response.

[8]Naumann R et al. Management Strategies for Recurrent Platinum-Resistant Ovarian Cancer. Drugs 2011; 71 (11): 1397-1412

Retention of PLD as a treatment option

The Sponsor considers the efficacy and safety data in MO22224 to be supportive of the use of BV in combination with PLD, topotecan or paclitaxel. The exploratory PFS analysis by CT cohort showed improved PFS in all 3 cohorts with the addition of BV. Of note, previous randomised Phase II/III trials of single-agent PLD have shown median PFS ranging from 2 to 5 months.[8] In the MO22224 PLD cohort, median PFS was improved from 3.5 months in the PLD alone arm (in line with published data for PLD) to 5.1 months in the PLD + BV arm and the unstratified HR was 0.53 (95% confidence interval [CI]: 0.36, 0.77). As mentioned above, when BV is added to CT (paclitaxel, topotecan, or PLD) in the treatment of patients with recurrent platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, the statistical and clinical improvement in the primary efficacy endpoint was confirmed by the IRC assessed PFS. The results of the retrospective IRC for all randomised patients confirmed the clinically meaningful and statistically significant improvement observed in investigator-assessed PFS when BV was added to any chemotherapy (HR 0.484; 95% CI: 0.370, 0.632; log-rank p 0.0001).

OS was one of the secondary objectives in MO22224. The OS analysis, though not statistically significant, showed a reduction in the risk of death of 13% (HR 0.870; 95% CI: 0.678, 1.116), when patients were treated with BV in combination with PLD, topotecan or paclitaxel compared with CT alone. The exploratory OS analysis by CT cohort showed HRs ranging from 0.64 to 1.07. There is no clear reason for the observed numerical differences between CT cohorts. Considering the widely overlapping CIs, the numerical differences may have occurred by chance. The demographic and baseline characteristics were generally well balanced across treatment arms overall and within CT cohorts because of stratified randomisation by the CT cohort. However, a possible explanation may be that the OS results are confounded by post-progression therapy and by likely differences in subsequent therapy between the CT cohorts. In particular, the exploratory PFS analysis by CT subgroups suggested that the median PFS was extended beyond 6 months in the paclitaxel + BV arm; thus, some patients in the paclitaxel cohort may potentially have been considered platinum-sensitive again and benefited from further platinum-based therapy; this could have potentially led to an improved numerical OS outcome in the paclitaxel + BV arm compared with either the topotecan or PLD cohorts.

With regard to safety in the PLD cohort, the rates of Grade 2 to 5 adverse events (AEs) in the PLD cohort (PLD: 85.7%; PLD + BV 90.3%) are comparable with those of the Grade 2-5 AEs in the overall safety population (CT: 87.3%; CT + BV: 91.1%). The sponsor acknowledges that 9 out of 11 Grade 5 AEs occurred in the PLD cohort (4 in the PLD alone arm and 5 in the PLD + BV arm). The rates of Grade 5 AEs in the two treatment arms, although numerically higher in the PLD + BV cohort due to one additional event, are comparable (PLD: 6.3%; PLD + BV: 8.1%), indicating that BV in combination with PLD did not lead to a higher risk of treatment-related deaths than PLD alone. Furthermore, the investigators' assessments of relationship of the Grade 5 AEs to study treatment further substantiates that the combination of PLD and BV did not demonstrate a safety concern for BV. As described in the CSR narratives for these patients, in the PLD alone arm 2 of the 4 Grade 5 AEs were assessed as possibly related to PLD, while in the PLD + BV arm, only 1 of the 5 AEs was assessed as possibly related to study treatment. It is important to note that one Grade 5 sepsis in the PLD + BV arm occurred after the patient had started subsequent non-protocol therapy with doxorubicin, topotecan, and paclitaxel following PD.

The sponsor acknowledges that there is a higher incidence of PPE in the PLD cohort (PLD: 12.7%; PLD + BV: 27.4%) with the majority of events Grade 2 in severity. The safety result from MO22224 suggests that BV could exacerbate PPE which is a common adverse reaction with PLD treatment. To capture this outcome the sponsor has proposed the following update to the *Adverse Effects* section of the Product Information (PI): *'Some of the adverse reactions are reactions commonly seen with chemotherapy however Avastin may*

exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysaesthesia syndrome with pegylated liposomal doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, and nail disorders or alopecia with paclitaxel.'

With regard to the clinical evaluator's suggestion to limit the indication statement to patients with ascites only, the sponsor would like to emphasise that the data on the effect of BV in patients with ascites is limited. An exploratory analysis in MO22224 showed a reduction in the requirement for paracentesis among patients treated with CT + BV suggesting a clinical benefit of a reduction in ascites in these patients. However, there were only few patients and no formal statistical analysis was done. Moreover, there is no data that would indicate that patients without ascites will not benefit from BV treatment. In fact, the analysis on PFS by baseline risk factor (CSR erratum) shows that patients benefit from BV treatment regardless of the presence of ascites at baseline; no ascites at baseline HR 0.47 (95% CI: 0.35, 0.62) versus with ascites at baseline HR 0.38 (95% CI: 0.25, 0.58). For these reasons, the sponsor considers the recommendation to limit treatment with BV to patients with ascites only cannot be justified.

Patients with platinum-resistant disease are often heavily pretreated and have limited treatment options. Thus, access to more treatment agents for this patient population would enable the clinician to determine the best possible choice for each patient based on toxicity profile and dosing schedule convenience. With regard to the safety profile of each CT regimen, treatment of patients with paclitaxel known to be at an increased the risk of PSN and patients with pre-existing peripheral neuropathy common toxicity criteria (CTC) Grade 2 or higher were excluded from the paclitaxel cohort per protocol exclusion criteria. PLD and topotecan remain important treatment options for patients with previous taxane-induced neuropathy. On the other hand, patients who are at risk of haematological toxicities may not have optimal treatment with topotecan, thus other CT regimens that are available should be considered.

In summary, the efficacy and safety data of BV in combination with PLD, topotecan, or paclitaxel support a positive benefit-risk assessment in patients with recurrent platinum-resistant ovarian cancer. Given the poor prognosis in this patient population, the limited treatment options and the PFS benefit seen in all cohorts, BV in combination PLD with either topotecan or paclitaxel should be available as treatment options for patients with platinum-resistant recurrent ovarian cancer.

HRQoL data collection

The Delegate has raised concerns regarding the validity of the HRQoL data collected. Due to the fact that the HRQoL analyses were planned in the SAP prior to the first database lock, including the definition of the EORTC QLQ-OV28 abdominal/GI symptoms scale as the primary QOL analysis (due to the clinical importance of this scale), the sponsor believes that the analysis of the HRQoL was adequately pre-specified and that the focus should be on the abdominal/GI symptoms scale with the other QOL endpoints treated as exploratory. Discussion is provided below supporting the validity of the HRQoL results and their adequacy to support the PFS results.

The abdominal/GI symptoms scale of the EORTC QLQ-OV28 was pre-specified as the primary QoL analysis on 13 January 2012 prior to the database lock. This scale was prioritised based on the clinical importance of abdominal symptoms in ovarian cancer[9,10] and recommendations for the control of cancer-related symptoms in the late stages of this

[9]Olson S et al. Symptoms of Ovarian Cancer. Am Coll Obs Gyn 2001; 98 (2): 212-217
[10]Price M et al. Physical symptoms, coping styles and quality of life in recurrent ovarian cancer: A prospective population-based study over the last year of life. J Gyn Oncol 2013; 130: 162-168

cancer[11,12]. The independent academic group which oversaw Study MO22224 (Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens [GINECO]) also chose to test difference in response on the abdominal/GI symptoms scale of the EORTC as the primary hypothesis in their independent analysis of the HRQoL data.[13]

The correlation between HRQoL and the study's objective clinical measure (PFS) was analysed[14] to assess potential bias, given the open-label study design and potential bias that may result from knowledge of treatment allocation. Specifically, the association of symptom progression with disease progression (PD) was assessed. Within a 6 week window around PD, scores of the abdominal/GI symptom scale increased in patients, indicating a worsening from the previous assessment in both the CT + BV and CT arms of the study. Symptoms worsened to the same magnitude around PD in both arms indicating correlation with progression. Exploratory analysis in reduction of paracentesis in the ascites subgroup also correlated with clinically meaningful changes on the abdominal/GI symptom scale. Additionally, responses on the other HRQoL measures were evaluated to assess potential systematic trends that may have resulted from the open-label design. No treatment effect was observed on the HADS or FOSI QoL measures. These results further support that patients' knowledge of treatment assignment did not influence responses.

The completion of HRQoL measures is affected by the poor and deteriorating health status of the patients, particularly in late stage oncology trials with poor prognosis such as platinum-resistant ovarian cancers with a median PFS of 2 to 5 months and a median OS 12 months.[15,16] Completion rates similar to MO22224 have been reported including in the validation study of the EORTC QLQ-OV28 (86% at baseline and 72% for the second assessment).[17] In another gynecological cancer study, the drop in completion rates observed over time was similar to MO22224.[18] In MO22224, the completion rate was calculated for all the patients who did not die, were not withdrawn from the study, did not enter the safety follow-up period, did not start non-protocol-specified anti-cancer therapy (NPT), or did not switch from the CT arm to the CT + BV arm at the start of the assessment window. Since the completion of the HRQoL assessments after PD was not mandatory, patients who completed HRQoL assessments after PD were excluded as well. Completion rates between the CT and CT + BV arms were similar at baseline (89.0% versus 88.3%), Week 16/18 (63.4% versus 64.8%), Week 24 (52.9% versus 55.0%), and Week 30 (54.2% versus 60.3%). The difference observed in the completion rates between the CT and CT + BV at Week 8/9 reflect the faster deteriorating health status of a higher number of the patients in the CT arm before month 3 as shown in the Kaplan-Meier plot of PFS. In summary, the main difference observed in the completion rate of HRQoL was due to the

[11]Ledermann J et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals Oncol 2013; 24 (Supplement 6): vi24–vi32
[12]Friedlander M et al. Symptom Control in Patients With Recurrent Ovarian Cancer. Measuring the Benefit of Palliative Chemotherapy in Women With Platinum Refractory/Resistant Ovarian Cancer. Int J Gyn Cancer 2009; 19, (S2), S44-S48
[13]Stockler M et al. Patient-Reported Outcome Results From the Open-Label Phase III AURELIA Trial Evaluating Bevacizumab-Containing Therapy for Platinum-Resistant Ovarian Cancer. J Clin Oncol 2014; epub ahead of print http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.51.4240
[14]Sloan J et al. Analysis and Interpretation of Results Based on Patient-Reported Outcomes. ISPOR 2007; 10 (Supp 2), S106-S115
[15]Naumann R et al. Management Strategies for Recurrent Platinum-Resistant Ovarian Cancer. Drugs 2011; 71 (11): 1397-1412
[16]Gordon A et al. Recurrent Epithelial Ovarian Carcinoma: A Randomized Phase III Study of Pegylated Liposomal Doxorubicin Versus Topotecan. J Clin Oncol 2001; Vol 19, (14) 3312-3322
[17]Greimel E et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Europ J Cancer 2003; 39, 1402-1408
[18]Cella D et al. Health-related quality of life outcomes associated with four cisplatin-based doublet chemotherapy regimens for stage IVB recurrent or persistent cervical cancer: A Gynecologic Oncology Group study. Gyn Oncol 2010; 119, 531-537

differences in PD at this time point. Lastly, the independent academic group GINECO which oversaw the study decided not to make the completion of HRQoL mandatory after PD considering the potential burden to patients. This decision was made before the release of the '*Reflection Paper on the use of patient reported outcome measures in oncology studies*' by the EMA (22 May 2014).

Safety data limitations

The sponsor provides a response here to the Delegate's comments regarding the safety data collected in MO22224. At the time MO22224 was designed in 2009, the general safety profile of BV across various indications was already well established. The data from three pivotal ovarian cancer trials, GOG-0218, BO17707/ ICON7 and AVF4095g (OCEANS), which have all been submitted to the TGA and supported registration of BV in the first-line and recurrent platinum-sensitive disease settings, provided insight into the safety profile specific to ovarian cancer. In MO22224, it was decided to collect only Grade 2 to 5 AEs because Grade 1 events were not considered highly clinically relevant in the studied population. With regard to the lack of data on clinical laboratory tests, the sponsor acknowledges this limitation given the method of reporting laboratory parameters specified in the protocol. The aggregate analysis of safety results of MO22224 included all treatment emergent Grade 2 to 5 AEs regardless of causality assessment. The sponsor believes that the aggregate analysis of safety results of MO22224 is robust and the safety results support a positive benefit/risk balance in this patient population. Laboratory measurements, including haematology, serum chemistry and urinalysis were performed by local laboratories per local standard of care. Laboratory parameters were not collected in the clinical database for this study. Information about AEs leading to dose interruption or reduction by study treatment arms was collected and the results show that the profile of the most common AEs leading to dose interruption or reduction is consistent with the profile of the most common AEs leading to study treatment discontinuation.

Questions asked by the delegate

The sponsor is requested to confirm the number of cases of PRES in the study, including those that developed after crossing over to bevacizumab monotherapy, and to incorporate these into the PI, stating specifically that they occurred in this trial population.

There were two cases of PRES reported in MO22224 study. One patient developed Grade 3 PRES with accompanying high blood pressure during study treatment with PLD and BV. BV treatment was permanently discontinued due to the event and the event of PRES resolved. Another patient developed Grade 4 PRES with accompanying hypertension during BV monotherapy after crossing over from the topotecan treatment arm. BV treatment was permanently discontinued due to the event of PRES and the event resolved with sequelae. Further medical details of these two cases are provided in the narratives in the primary CSR. As requested, the two cases of PRES reported in the study have been described in the proposed PI under the *Precautions* section. As the signs and symptoms, management of the events including discontinuation of BV and outcome of the two events are consistent with the description already included in the *Precautions* section, the sponsor believes that the inclusion of the 2 events in the PI provides sufficient information for the treating physicians.

Please provide a justification for the proposed PI change restricting to physicians who treat cancer.

This PI revision was previously requested by the RMP evaluator during an earlier Avastin application. It aligns the PI with the same statement in the EU SmPC and as stated by the RMP evaluator enhances the safe use of the medicine.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register an extension of indications for a currently registered product.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Avastin, concentrate for intravenous infusion, containing bevacizumab 100 mg/4 mL and 400 mg/16 mL to have an overall positive benefit–risk profile for the amended indication:

> *Avastin (bevacizumab) in combination with paclitaxel, topotecan or pegylated lioposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens, and have not received any prior anti-angiogenic therapy including bevacizumab.*
>
> *Patients should not have a history of bowel obstruction, abdominal fistulae or clinical or radiological evidence of recto-sigmoid involvement.*

In making this recommendation the ACPM was concerned at the modifications made in the statistical analysis of the pivotal trial, particularly on the quality of life assessments and the lateness of the submission to the TGA of the independent statistical analysis.

The ACPM was also of the view that use of bevacizumab in combination with pegylated liposomal doxorubicin (PLD) should not be excluded from the indication on the basis of results from an exploratory analysis. However, the results of the relative efficacy of the different combinations in the clinical trial should be clearly stated in the PI. In addition, the indication should reflect the exclusion criteria of the pivotal trial in order to limit severe adverse events.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

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

- The addition of a statement to the effect that bevacizumab should not be used in patients who have a history of bowel obstruction, abdominal fistulae or clinical or radiological evidence of recto-sigmoid involvement.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. Whether the improvement in progression free survival (PFS) alone is sufficient to support registration for the delegate's modified indication: *Avastin (bevacizumab) in combination with paclitaxel or topotecan is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens, and who have not received any prior anti-angiogenic therapy including bevacizumab*?

The ACPM advised that the addition of bevacizumab to chemotherapy led to a statistically significant and clinically meaningful improvement in PFS survival, but not overall survival

(OS) in this poor prognostic patient group. The ACPM noted that crossover was allowed in the clinical trials and considered this was ethically appropriate, noting however, that this would dilute any OS outcomes. The ACPM considered that PFS rather than OS is the more appropriate outcome in this circumstance.

The ACPM noted the Delegate's proposed indication (see above) omitted pegylated liposomal doxorubicin (PLD). The ACPM acknowledged:

- The study showed there appeared to be less benefit for patients on bevacizumab + PLD [the median extension of treatment duration by 1 cycle of chemotherapy (compared to the median increase of 3 with the other 2 chemotherapy arms)]
- There were 9 deaths in PLD patients (11 in total for the study) but only 1 extra in the PLD + bevacizumab arm
- Increase in side effects with this combination
- The improvement in PFS, on independent review, did not reach statistical significance
- The benefit-risk profile for this combination is more borderline; however, while the ACPM considered that PLD should not be excluded from the indication on the basis of results from an exploratory analysis these differences in benefit should be stated clearly in the PI and the decision should be open to the clinician.

Regarding assessment of quality of life, the ACPM agreed that gastrointestinal symptoms are an effective measure of clinical benefit and therefore are a valid measure of quality of life for this patient group.

The ACPM noted that the ascites subgroup results are also based on an exploratory analysis. The ACPM considered that although it appears those with ascites benefit particularly, overall response rate was also improved in those with measureable disease which did not include ascites. The ACPM therefore advised that treatment should not be limited to patients with ascites.

The ACPM noted that the sponsor had agreed to restrict treatment to patients who had not received prior anti-angiogenic therapies.

The ACPM noted the addition of bevacizumab to chemotherapy increased toxicity with more frequent and severe adverse events (AEs). The ACPM noted that the pivotal trial MO22224 (AURELIA) excluded patients that had a history of bowel obstruction, history of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess or evidence of recto-sigmoid involvement. The ACPM considered that careful selection of patients could lessen severe AEs as was the case in the pivotal trial where the rate of bowel obstruction and fistula formation was low. The ACPM advised that bevacizumab should not be used in these patients in order to limit severe complications and toxicities occurring.

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 this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Avastin containing bevacizumab 100 mg/4 mL and 400 mg/16 mL for the new indication:

> *Avastin (bevacizumab) in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens, and have not received any prior anti-angiogenic therapy including bevacizumab.*

Specific conditions of registration applying to these goods

The Avastin® EU Risk Management Plan (RMP), version 14.0, data lock point 2 August 2013 and Australian Specific Annex (Version 4.0 dated November 2013), included with submission PM-2013-03227-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for main Avastin at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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