Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for bevacizumab injection

Proprietary Product Name: Avastin

Sponsor: Roche Products Pty Ltd

March 2014

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 <http://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 abbreviations

Abbreviation	Meaning
AE	adverse event
BRiTE	Bevacizumab Reimens: Investigation of Treatment
CI	confidence interval
CRC	colorectal cancer
ECOG	Eastern Cooperative Oncology Group
5-FU	5-fluorouracil
FOLFOX4	oxaliplatin, folinic acid, 5-FU
GCP	Good Clinical Practice
GI	gastrointestinal
HR	hazard ratio
ICH	International Conference on Harmonization
IV	intravenous
mCRC	metastatic CRC
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic
PS	performance status
SAE	serious adverse event
VEGF	vascular endothelial growth factor

I. Introduction to product submission

Submission details

Type of submission:	Major variation (dosage)
Decision:	Rejected (low dose option). Approved (changes to Product Information)
Date of decision:	21 October 2013
Active ingredient(s):	Bevacizumab
Product name(s):	Avastin
Sponsor's name and address:	Roche Products Pty Ltd PO Box 255, Dee Why NSW 2099
Dose form(s):	Solution for Injection
Strength(s):	100 mg/4 mL, 400 mg/16 mL
Container(s):	Single use vial
Pack size(s):	1's
Approved therapeutic use:	Avastin (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer.
Route(s) of administration:	Intravenous (IV)
Dosage:	Dependent on first or second line treatment and type of cancer to be treated. See Product Information (Attachment 1) for details.
ARTG number (s):	99755 and 99757

Product background

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

Bevacizumab is registered in Australia for the treatment of treatment of several cancers including breast, lung, colorectal, renal and ovarian cancer and glioma. Its plasma elimination half-life is 18 to 20 days. Serious adverse effects include haemorrhage,

thrombo-embolism, congestive cardiac failure, hypertension, proteinuria and gastrointestinal perforation.

This AusPAR describes the application by the sponsor to include a low dose option in second line treatment of metastatic colorectal cancer (mCRC). The new dosage proposed is (shown in italics and underlined):

> *5 mg/kg or* 10 mg/kg of body weight given once every 2 weeks or
>
> *7.5 mg/kg or* 15 mg/kg of body weight given once every 3 weeks.
>
> It is recommended that Avastin treatment be continued until progression of the underlying disease. *Patients previously treated with Avastin can continue with Avastin treatment following first progression.*

Changes to the PI were also proposed but details of these are beyond the scope of this AusPAR.

Only clinical data was submitted in support of this application.

The TGA adopted European Medicines Agency (EMA) *Guideline on the Evaluation of Anticancer Medicinal Products in Man* (CPMP/EWP/205/95)[1] and *Points to Consider on applications with one pivotal study* (CPMP/EWP/2330/99)[2] are relevant to this application.

Regulatory status

The product received initial Australian Register of Therapeutic Goods (ARTG) Registration on 2 February 2005.

Similar applications have been approved in the US (23 January 2013), the European Union (EU; 27 May 2013) and New Zealand (19 December 2012).

Product Information

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

II. Quality findings

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

III. Nonclinical findings

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

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

[1] http://www.tga.gov.au/pdf/euguide/ewp020595enrev3.pdf
[2] http://www.tga.gov.au/pdf/euguide/ewp233099en.pdf

Introduction

Clinical rationale

There was no clinical evidence from randomised clinical trials that bevacizumab containing regimens in the second line setting could improve patient outcomes after progression on a bevacizumab-containing regimen in the first line setting. Clinical evidence providing insight into the effect of treatment with bevacizumab beyond first progression was from the BRiTE (Biomarkers for Rapid identification of Treatment Effectiveness) study, a large community-based, non-randomised, observational study, in which 1445 patients who were treated with bevacizumab as part of first line therapy, had bevacizumab as part of second line therapy following disease progression. These patients were associated with improved survival beyond progression compared with patients who did not have bevacizumab. The findings of this study are supported by available data from another observational cohort study (ARIES – Avastin Registry: Investigation of Effectiveness and Safety).

Study ML18147 was designed to examine the effect of adding bevacizumab to cross-over fluoropyrimidine-based chemotherapy in patients with metastatic colorectal cancer (mCRC) who experienced disease progression after first line standard chemotherapy plus bevacizumab. Study ML 18147 was initiated as Study AIO KRK 0504 in 2006 as a non-registrational study by AIO in Germany and Austria. Sponsorship of the study was transferred to Roche in 2008. Several major amendments were made without knowledge of the aggregate results so as not to compromise the integrity of the study. The amendments included a change in the primary endpoint from progression-free survival (PFS) to Overall Survival (OS).

OS was deemed by the sponsor to be a better measure than PFS because it is easily measured, is unambiguous and objective and is a variable that is not subject to the potential biases associated with endpoints requiring clinical judgement. The sample size of the study was increased to adequately power the study for OS as the primary endpoint. Details of any subsequent anti-cancer therapy were obtained during follow-up visits until the end of study so that potential confounding of OS by the use of effective subsequent lines of therapy could be prevented.

FDA raised concerns about potential bias having been introduced as a result of the unplanned modifications to the protocol at the time of change in sponsorship. A number of recommendations were made including use of unstratified log rank test as primary analysis and sensitivity analyses to address the sequential enrolment in the AIO KRK 0504 and ML18147 studies based on data cut-off points. The marketing authorisation holder (MAH) amended the analysis plan accordingly.

Scope of the clinical dossier

The submission contained one study, Study ML 18147 which was a pivotal efficacy/safety study.

Paediatric data

No new data.

Good clinical practice (GCP)

Study ML18147 was conducted in accordance with US FDA regulations, the ICH E6 Guideline for GCP, the Declaration of Helsinki (October 1996), applicable local, state, and federal laws as well as other applicable country laws.

Pharmacokinetics

No new data provided.

Pharmacodynamics

No new data provided.

Efficacy

One pivotal efficacy study was provided; Study ML 18147.

Evaluator's Conclusions on Clinical Efficacy

This was a prospective, randomised, open-label, multinational, controlled, Phase III study. Concerns were raised about potential bias possibly being introduced as a result of the unplanned modifications to the protocol when sponsorship was changed from AIO to Roche in 2008. The concerns were addressed and included the use of unstratified log rank test as the primary analysis. The impact of sequential enrolment in the AIO KRK 0504 and ML18147 studies was also addressed in the analysis plan. The sponsor used the second-order minimisation algorithm to randomise the patients 1:1, to ensure an equal distribution of prognostic factors in the two arms of the study. Randomisation was stratified by the four factors that were described. The majority of patients in the two arms were ECOG PS[3] ≥ 1 at baseline, had received irinotecan based chemotherapy as first line treatment, had progressed on first line treatment within nine months and had received their last dose of bevacizumab as first line treatment within 42 days of randomisation. The primary efficacy endpoint was changed from progression free survival (PFS) to overall survival (OS), which required larger patient populations. The sample size was accordingly increased to power this change. While the traditional endpoint for assessing efficacy in first line chemotherapies for advanced cancer is OS, it is open to confounding by the effects of second line therapies. The study protocol therefore required that monitoring was continued to check on subsequent anti-cancer therapy.

The study met its primary efficacy endpoint of a significant increase in OS in patients treated with bevacizumab in combination with chemotherapy (fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin based chemotherapy regimens) over patients treated with chemotherapy alone. The median duration of survival increase was 1.4 months. The results however were short of the expected 30% improvement in median time to death in the bevacizumab-containing arm. OS analysis stratified by the prognostic factors was consistent with the unstratified analysis. The results were supported by the results of subgroup analyses.

The secondary end point was met, by a statistically significant reduction in disease progression in the bevacizumab plus chemotherapy arm compared with the

[3] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

chemotherapy alone arm. The Objective Response Rate was higher in the bevacizumab plus chemotherapy arm but the small difference between the two arms was not statistically significant.

Subgroup analysis by KRAS[4] mutational status did not provide evidence to suggest a valid treatment difference between patients with wild-type versus mutant KRAS mCRC tumours.

Safety

One pivotal study assessed safety as a primary outcome; Study ML18147.

Patient Exposure

The median duration of exposure in Arm B (bevacizumab+chemotherapy) was longer by a month than in Arm A (chemotherapy alone). There were no significant differences in dose intensity between the two arms. See Table 1 below.

Table 1 Extent of Exposure to Study Drug (Safety Population)

	Chemo n = 409		Chemo + Bev n = 401	
	Treatment duration (months)[a] median (range)	Dose Intensity[b] mean ± SEM	Treatment duration (months)[a] median (range)	Dose Intensity[b] mean ± SEM
Overall	3.22 (0.03-20.07)	–	4.18 (0.03-29.54)	–
Chemotherapy	3.22 (0.03-20.07)	–	4.15 (0.03-29.54)	–
oxaliplatin	2.80 (0.03-12.96)	79.5 ± 1.4	3.49 (0.03-29.08)	74.0 ± 1.6
irinotecan	3.26 (0.03-20.07)	67.5 ± 1.8	4.18 (0.03-25.89)	62.8 ± 2.0
capecitabine	2.63 (0.13-13.36)	78.6 ± 2.1	3.95 (0.23-26.32)	76.6 ± 2.4
5-FU bolus	3.03 (0.03-20.07)	70.9 ± 1.9	3.82 (0.03-29.54)	69.8 ± 1.9
5-FU continuous	3.03 (0.03-20.07)	76.3 ± 1.9	4.18 (0.03-29.54)	71.5 ± 1.7
Bevacizumab	–	–	3.95 (0.03-29.54)	86.3 ± 0.97

SEM = standard error of the mean.

[a] Duration in months from the first dose of study treatment (bevacizumab or chemotherapy) until discontinuation of all study drugs.

[b] Defined as total cumulative dose/planned dose x 100%.

Evaluator's Overall Conclusions on Clinical Safety

All the safety evaluations were performed on the safety population. The duration of exposure was slightly longer in Arm B but the dose intensity of chemotherapy between the two arms was similar. The frequency of adverse events, of any severity, was similar in the two arms of the study. Many of the commonly reported adverse events (diarrhoea, vomiting, neutropaenia, fatigue, abdominal pain and constipation) were in keeping with the adverse event profiles of the chemotherapy agents. Adverse events associated with bevacizumab were examined under '*Adverse events special interest*'. As expected, they were reported more frequently in Arm B (40.6% versus 20.8%). The large disparity was attributed to a higher incidence of Grade 1-2 bleeding/haemorrhage events (mainly epistaxis) in Arm B. The difference between Grade 3-5 '*Adverse events of special interest*' in the two arms was ≤ 2%. The sponsor states that the low rate of difference compared to studies in previously bevacizumab naive patients, suggests that previous exposure to

[4] KRAS=Kirsten rat sarcoma viral oncogene homolog. A type of oncogene, the activating mutations of which play a key role in neoplastic progression, especially in colorectal, pancreatic, and lung cancer

bevacizumab identified adverse events that have probably been managed appropriately. This seems a reasonable assumption. A higher proportion of patients in Arm B discontinued treatment, with most discontinuing chemotherapy as well as bevacizumab. The incidence of deaths not due to progressive disease was similar in the two arms of the study.

List of questions

Safety

The safety population as described in Table 2 '*Summary of Analysis Population in Study ML 18147 (Randomized Patients)*' was 407 patients in the Chemotherapy (Chemo) arm and 403 patients in the chemotherapy + bevacizumab arm. However, the safety population described in Table 8: '*Summary of Overall Safety (Safety Population)*' (see Attachment 2 Extract from the CER) was 409 patients in the chemotherapy arm and 401 patients in the chemotherapy + bevacizumab arm. An explanation for the discrepancy in the two tables is sought.

Table 2 Summary of analysis population in Study ML 18147 (Randomized Patients)

	CHEMO	CHEMO + BEV	TOTAL
No. of Patients Randomized	411	409	820
No. Included in INTENT-TO-TREAT	410	409	819
No. Excluded from INTENT-TO-TREAT	1	-	1
No informed consent date	1	-	1
No. Included in MEASURABLE DISEASE	406	404	810
No. Excluded from MEASURABLE DISEASE	5	5	10
Patients without measurable disease	4	5	9
No informed consent date	1	-	1
No. Included in PER-PROTOCOL	397	383	780
No. Excluded from PER-PROTOCOL	14	26	40
No confirmation of progressive disease after 1st line therapy	7	11	18
No cross-over chemotherapy or failure to receive treatment according to randomization	2	13	15
Failure to receive at least one dose of second-line study medication	4	6	10
No evidence of measurable lesions at baseline	4	5	9
No informed consent date	1	-	1
No. Included in SAFETY	407	403	810
No. Excluded from SAFETY	4	6	10
Did not receive at least one full or partial dose of bevacizumab or CTx	4	6	10

Chemo= Fluropyrimidine based chemotherapy (oxaliplatin or irinotican). Bev= bevacizumab

Sponsor's response

The safety population described in the table '*Summary of Overall Safety (Safety Population)*' indicating 409 patients in the chemotherapy arm and 401 patients in the chemotherapy + bevacizumab arm is the correct population as per the definition in the analysis plan:

The safety analysis population included all randomised patients who received any amount of study treatment, defined as at least one full or partial dose of bevacizumab or chemotherapy. Patients were analysed according to actual treatment received (for example, if patients were randomised to the chemotherapy arm but received at least one dose of bevacizumab they would be analysed in the chemotherapy +Bev treatment arm and if patients were randomized to the chemotherapy +Bev arm but did not receive any dose of bevacizumab they would be analysed in the chemotherapy arm).

The actual randomised patients in the two treatment arms were 407 patients in the chemotherapy arm and 403 patients in the chemotherapy + bevacizumab arm. However two patients who were randomised to chemotherapy + bevacizumab arm did not receive

any bevacizumab, hence when counted as randomised they are included in the chemotherapy + bevacizumab arm but when counted as treated they are included in the chemotherapy arm, thereby explaining the safety population with 409 patients in the chemotherapy arm and 401 patients in the chemotherapy + bevacizumab arm.

The safety population described in the table '*Summary of Analysis Population in Study ML18147 (Randomized Patients)*' assigns patients as they were randomised and not as treated, which is not per the definition of the safety population as defined in the analysis plan.

First round benefit-risk assessment

First Round Assessment of Benefits

The primary efficacy endpoint of a significant increase in OS was met by a prolongation in median survival of 1.4 months.

The secondary endpoint of PFS was met by a statistically significant reduction in the bevacizumab-containing chemotherapy arm.

The secondary endpoint of Best Overall Response was not met because the results were not statistically significant. The difference in response rate between the two arms was small.

Subgroup analysis of the efficacy endpoints by patient KRAS mutational status did not provide any evidence to suggest a valid treatment difference attributable to the use of additional bevacizumab.

First Round Assessment of Risks

The frequencies of adverse event of any severity were similar in the two arms of the study.

The most frequently reported adverse events were in keeping with the known adverse event profiles of the chemotherapy agents.

The difference in frequencies of Grade 3-5 adverse events that were known to be associated with bevacizumab were ≤ 2% between the bevacizumab containing chemotherapy arm and the chemotherapy alone arm.

The incidences of Serious Adverse Events and Deaths not due to progressive disease were comparable between the two arms of the study.

A higher proportion of patients in the bevacizumab containing arm discontinued treatment (15.7% versus 8.8%). Most of the discontinuations in this arm were due to adverse effects associated with bevacizumab.

First Round Assessment of Benefit-Risk Balance

The benefit-risk balance of bevacizumab 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg body weight given once every 3 weeks as the proposed usage in second line treatment of metastatic colorectal cancer, is favourable.

First round recommendation regarding authorisation

The application to amend the Product Information document to include the above dosage regimen for the use of Avastin in second line treatment of metastatic colorectal cancer is recommended.

Second round evaluation of clinical data submitted in response to questions

Nil information provided.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Avastin in the proposed usage are unchanged from those identified in the First Round Evaluation.

Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of Avastin in the proposed usage are unchanged from those identified in the First Round Evaluation.

Second round assessment of benefit-risk balance

The benefit-risk balance of Avastin, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

The application to amend the Product Information document to include the above dosage regimen for the use of Avastin in second line treatment of metastatic colorectal cancer is recommended for approval.

V. Pharmacovigilance findings

Risk management plan

A risk management plan was not required. The proposed postmarket condition of registration relating to pharmacovigilance is detailed below under *Overall conclusion and risk/benefit assessment; Risk Management Plan.*

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

Efficacy

The efficacy of bevacizumab in combination with fluoropyrimidine based chemotherapy in the second line treatment of metastatic colorectal cancer was assessed in a single randomised, open-label, controlled trial conducted in Europe and Saudi Arabia (ML18147). The control group received fluoropyrimidine-based chemotherapy alone. Subjects had progressed after ≥ 3 months of first line bevacizumab plus fluoropyrimidine-based chemotherapy (a standard regimen) and had discontinued first line therapy within 3 months of trial entry. The dose of bevacizumab was 5 mg/kg every two weeks or 7.5 mg/kg every three weeks IV. In both the bevacizumab and control groups, if first line therapy was fluoropyrimidine/ oxaliplatin, second line therapy was fluoropyrimidine/irinotecan and vice versa. Treatment was continued until disease progression or unacceptable toxicity.

The median duration of treatment was 4.0 months bevacizumab/4.2 months chemotherapy (range 0^{+}-30 months) in the bevacizumab group and 3.2 months chemotherapy (range 0^{+}-20 months) in the control group.

The majority of subjects were male (64%) and the median age was 63 years, range 21-84 years. ECOG performance status was mostly 0 or 1 (95%).

The primary endpoint was overall survival (OS). Bevacizumab significantly increased OS by a median 1.4 months (Table 3). An analysis stratified by prognostic factors achieved similar results. Bevacizumab also significantly increased progression-free survival (PFS) by a similar amount (median 1.6 months) but did not significantly increase objective response rate (ORR).

Table 3 Efficacy Results – Trial ML18147– Intent-to-Treat[1]

	Fluoropyrimidine Chemo n=410	Bevacizumab + Fluoropyrimidine Chemo n=409	Hazard Ratio or Difference[2] [95% CI] p-value
Overall Survival median[3] *months*	9.8	11.2	0.81 [0.69, 0.94] p=0.006[4]
Progression-Free Survival median[3] *months*	4.1	5.7	0.68 [0.59, 0.78] p<0.0001[4]
ORR *%* Complete Response % Partial Response %	3.9% 0.5% 3.4%	5.4% 0.2% 5.2%	1.5% [-1.5%, 4.5%] p=0.3113[5]

[1] Less one control group subject without informed consent. Stratified hazard ratio of bevacizumab versus placebo determined by Cox regression. [2] Hazard Ratio: bevacizumab/control; Difference: bevacizumab – control. [3] Kaplan-Meier estimate. [4] Log-Rank Test. [5] χ^2 Test.

The results of the subgroup analyses of improvement in overall survival were generally consistent with the main result. However, there were some subgroups where addition of bevacizumab did not significantly increase survival. Notably this occurred in women and in subjects who progressed after ≤ 9 months first line bevacizumab-fluoropyrimidine chemotherapy. There was no evidence of treatment by sex interaction in the Cox model. In the subgroup of subjects who progressed after ≤ 9 months first line bevacizumab-fluoropyrimidine chemotherapy ("less sensitive subgroup"), the hazard ratio for overall survival was 0.89, 95% Confidence Interval (CI) [0.73, 1.09]. In the subgroup who progressed after > 9 months first line bevacizumab-fluoropyrimidine chemotherapy ("more sensitive subgroup"), the hazard ratio for overall survival was 0.73, 95% CI [0.58, 0.92]. Median survivals for each treatment in the subgroups were not stated and the sponsor was requested to provide these in their Pre Advisory Committee on Prescription Medicines (ACPM) Response.

Safety

The safety of bevacizumab was assessed in Study ML18147. The safety population consisted of 401 bevacizumab fluoropyrimidine chemotherapy subjects and 409 fluoropyrimidine chemotherapy subjects.

There was a slightly greater incidence of severe (Grade 3-5) adverse events with bevacizumab plus chemotherapy than chemotherapy alone; 64% versus 58%. Severe adverse events of notably greater incidence with bevacizumab were neutropenia (16% versus 13%) and mucosal inflammation (3.2% versus 1.0%). Other severe adverse events with greater incidence in bevacizumab subjects included venous thromboembolic events (4.7% versus 2.9%), bleeding (2.0% versus 0.2%) and gastrointestinal perforation (1.7% versus 0.7%).

Adverse events of all grades with notably greater incidence with bevacizumab plus chemotherapy than chemotherapy alone were diarrhoea (59% versus 45%), neutropenia (29% versus 21%), mucosal inflammation (19% versus 11%), pyrexia (18% versus 12%), epistaxis (18% versus 5%) and hypertension (11% versus 6%). These events were consistent with the known safety profile of bevacizumab.

Four bevacizumab plus chemotherapy subjects (1.0%) and three chemotherapy only subjects (0.7%) died due to treatment-related adverse events. The bevacizumab plus chemotherapy deaths were due to upper gastrointestinal haemorrhage, sudden death, cerebrovascular accident and neutropenia and the chemotherapy only deaths were due to intestinal perforation, general physical health deterioration and acute pre renal failure.

The evaluator recommended approval of the modified dose.

Risk management plan

A risk management plan was not required. The proposed postmarket condition of registration is detailed below:

Conditions from the TGA's Office of Product Review (if approved)

Postmarket

This approval does not impose any requirement for the submission of Periodic Safety Update Reports (PSURs). The sponsor should note that it is a requirement that all existing requirements for the submission of PSURs as a consequence of the initial registration or subsequent changes must be completed.

Risk-benefit analysis

Delegate considerations

The benefit of adding bevacizumab 5 mg/kg every two weeks or 7.5 mg/kg every three weeks to *second line* fluoropyrimidine-based chemotherapy in metastatic colorectal cancer after progression on first line bevacizumab-fluoropyrimidine chemotherapy was small; median 1.4 months increase in overall survival and 1.6 months increase in progression-free survival (Study ML18147). The benefit of bevacizumab was larger in a previous second line trial (ECOG E3200) in subjects who had not received bevacizumab first line and who received twice the dose (10 mg/kg every two weeks); median 2.2 months increase in overall survival and 3.0 months increase in progression-free survival (see PI).

The low dose (5 mg/kg every two weeks or 7.5 mg/kg every three weeks) is approved for the *first line* treatment of metastatic colorectal cancer in combination with chemotherapy. In one first line trial AVF0780g), the low dose resulted in greater overall survival than the high dose (10 mg/kg every two weeks); see PI.

Subgroup analysis of Study ML18147 results showed that the overall survival benefit of bevacizumab was greater in subjects who were more sensitive to first line therapy that included bevacizumab (progression after > 9 months of first line therapy). Although the Delegate accepts the exploratory nature of subgroup analyses and that the result may be a chance finding, it is plausible that patients who were more sensitive to first line therapy will also respond better to second line therapy and that patients who were less sensitive may have developed alternative angiogenesis pathways that reduce the benefits of bevacizumab.

The benefit seen with bevacizumab also includes the effects of switching chemotherapy regimens between first and second line treatment, from fluoropyrimidine/oxaliplatin to fluoropyrimidine/irinotecan or vice versa. The contributions from the chemotherapy switch and bevacizumab itself were not determined. When the impact of chemotherapy is taken into account, the overall survival benefit of bevacizumab is likely to be less than the median increase of 1.4 months.

The safety of bevacizumab in Study ML18147 was consistent with that in previous trials. It would be expected that the lower dose of bevacizumab in Study ML18147 would be better tolerated than the high dose in ECOG E3200 but this was not clear from the data. Bevacizumab had some very serious adverse effects including venous thromboembolic events, bleeding and gastrointestinal perforation. Hence, patients receiving this drug need to be carefully monitored. Quality-of-life was not assessed.

The benefit-risk balance of bevacizumab 5 mg/kg every two weeks or 7.5 mg/kg every three weeks in the second line treatment of metastatic colorectal cancer is negative. The small increase in overall survival (median 1.4 months) does not outweigh the increased toxicity of bevacizumab.

The benefit-risk profile is likely to be better in patients who are more sensitive to first line bevacizumab and chemotherapy. The median survival results of the subgroup analysis which the Delegate requested the sponsor provide in their Pre-ACPM Response will provide an indication of the magnitude of the survival benefit and hence an indication of the benefit-risk profile.

In patients less sensitive to first line chemotherapy, the efficacy of bevacizumab may be improved if a larger dose were used (based on Study ECOG E3200), although this is not certain (based on Study AVF0780g). Further study is needed to define the optimum dose of bevacizumab in second line treatment.

If the sponsor's Pre-ACPM Response provides evidence that the benefit-risk profile is positive in subjects more sensitive to first line bevacizumab-chemotherapy treatment,

then approval may be considered. The results of the subgroup analysis of more and less sensitive subjects in Study ML18147 should be included in the product information with a statement that continuation of bevacizumab following first progression is recommended only for patients sensitive to first line bevacizumab-chemotherapy (progression after > 9 months of first line therapy).

Summary of issues

1. Clinical significance.
2. Plausibility of subgroup results of bevacizumab-chemotherapy sensitivity.
3. Benefit-risk balance.

Advice sought

The Advisory Committee on Prescription Medicines (ACPM) was requested to provide advice on the following specific issues:

1. What is the ACPM's opinion of the clinical significance of the increase in overall survival with bevacizumab in Study ML18147? What is the Committee's opinion of the support from the secondary endpoints?
2. How plausible are the subgroup results showing that subjects who were more sensitive to first line therapy that included bevacizumab (progression after > 9 months of first line therapy) are likely to have better overall survival with continuation of bevacizumab in second line therapy?
3. What is the ACPM's opinion of the benefit-risk balance of bevacizumab in the proposed indication? Is the benefit-risk balance improved if continuation of bevacizumab in second line therapy were restricted to subjects who were more sensitive to first line therapy that included bevacizumab (progression after > 9 months of first line therapy)?
4. The ACPM was also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Pre ACPM preliminary assessment

The Delegate considered that the application for the low dose option in second line treatment should not be approved.

Response from Sponsor

Comment on the Delegate's Proposed Action

The sponsor disagrees with the Delegate's conclusion that benefit-risk balance of bevacizumab 5 mg/kg every two weeks or 7.5 mg/kg every three weeks in the second line treatment of metastatic colorectal cancer is negative. ML18147 is the first randomised clinical trial that prospectively demonstrated continued vascular endothelial growth factor (VEGF) inhibition with bevacizumab beyond first progression improves overall survival for patients in second line mCRC. The sponsor considers the median overall survival improvement of 1.4 months observed in Study ML18147 to be clinically meaningful and this benefit is not outweighed by the observed adverse event profile. The purpose of the submission, on the basis of Study ML18147, is to provide the treating physician with flexibility in terms of dose as well as optimal sequencing of available biologics in the continuum of care, allowing potential for maximum number of lines of therapy for patients. The sponsor therefore considers the Delegate's proposal would ultimately restrict treatment options for physicians'.

The sponsor's position is described below in the context of the advice sought of the ACPM by the Delegate.

Comment on the Delegate's Overview

Clinical significance of the increase in overall survival with bevacizumab in trial ML18147 and support from the secondary endpoints

Based on the data provided in the submission, the benefit risk balance of bevacizumab as a second line treatment for patients with progressive mCRC disease who have received a prior bevacizumab containing regimen in the first line setting, is positive. Study ML18147 demonstrated a clinically meaningful improvement in median overall survival (OS) of 1.4 months compared to chemotherapy alone. The OS benefit shown in Study ML18147 is independent of the patient's KRAS status and is consistent with that demonstrated by aflibercept, another antiangiogenic agent recently approved by TGA in the second line setting (Table 7). Study ML18147 also demonstrated a significant prolongation of progression free survival (PFS) when bevacizumab was added to chemotherapy beyond first disease progression.

The safety profile of bevacizumab in ML18147 was consistent with previously reported data from clinical trials of bevacizumab and no new safety signals were observed. In addition, compared with historical data from bevacizumab treatment in the first line or second line mCRC setting, adverse events of special interest (AESIs) to bevacizumab were not increased when continuing bevacizumab beyond progression. ML18147 is the first randomised clinical trial that prospectively demonstrated continued VEGF inhibition with bevacizumab beyond first progression improves overall survival for patients in second line mCRC.

The E3200 study in bevacizumab-naïve patients which was submitted in a previous application and is included in the Australian Product Information (PI) for Avastin, shows that adding bevacizumab (5mg/kg/week equivalent) to a second line fluoropyrimidine regimen is beneficial. The ML18147 study goes further and offers a treatment option for patients who have progressed on bevacizumab plus chemotherapy first line. The results of ML18147 and E3200 confirm that the choice of bevacizumab dose and combination with appropriate chemotherapy agents are beneficial options in a setting of an unmet medical need and provide also the treating physician with flexibility in terms of optimal sequencing of the available biologics, allowing maximum potential number of lines of therapy for patients.

Table 7. Key Phase III Randomised Studies of Effectiveness of Chemotherapy With Anit-VEGF or anti EGFR Biologics as Second-Line Treatment for mCRC

Table 1 Key Phase III Randomised Studies of Effectiveness of Chemotherapy With Anit-VEGF or anti EGFR Biologics as Second-Line Treatment for mCRC

Study Reference	Pop	Treat Line	Regimen	Pts	PFS (median [months])	RR (%)	OS (median [months])	Additional Information
Anti-VEGF biologics								
E3200 [6681]	**ITT**	2nd line	FOLFOX4 +Bev FOLFOX4	293 292	7.5 4.5 HR=0.52 p<0.0001	22.2 8.6 p<0.0001	13.0 10.8 HR=0.751 p=0.0012	Target population had not received prior first-line bevacizumab
VELOUR [10384]	**ITT**	2nd line	FOLFIRI + Afl FOLFIRI + plac	614 612	6.9 4.7 HR=0.76 p<0.00007	19.8 11.1 p=0.0001	13.5 12.1 HR=0.82 p=0.00007	AEs led to discontinuation of treatment in 26.6% of patients in the arm receiving aflibercept with chemotherapy in VELOUR [10384]. For subgroup of patients in the VELOUR study who had received prior first-line bevacizumab treatment (30% of ITT), HR for OS was 0.86 and for PFS 0.56 [10385].
Anti-EGFR biologics								
EPIC [6009]	**ITT**	2nd line	irinotecan + Cet irinotecan	648 650	4.0 2.6 HR=0.69 p ≤0.0001	16.4 4.2 p<0.0001	10.7 10.0 HR=1.00 p=0.71	No survival benefit of adding bevacizumab to irinotecan after 5-FU/oxaliplatin failure.
Anti-EGFR biologics								
EPIC [10391]	**KRAS WT**	2nd line	irinotecan + Cet irinotecan	97 95	4.0 2.8 HR=0.77 p=0.0954	10.3 7.4 p=0.613	10.9 11.6 HR=1.28 p=0.1755	KRAS subgroup results not meaningful due to small numbers of KRAS evaluable patients.
20050181 [10386]	**KRAS WT**	2nd line	FOLFIRI + Pan FOLFIRI	303 294	5.9 3.9 HR=0.73 p=0.004	35 10 p=0.0001	14.5 12.5 HR=0.85 p=0.12	For subgroup of patients who had received prior first-line bevacizumab treatment (19% of ITT), HR for OS was 0.86 and for PFS 0.66. Differences in median OS (15.7 v 12.5 months) and median PFS (5.8 vs 3.7 months) did not reach statistical significance (p>0.05) [10430].
PICCOLO [10387]	**KRAS WT**	≥2nd line	irinotecan + Pan irinotecan	230 230	5.5 4.7 HR=0.78 p=0.01	34 12 p<0.0001	10.4 10.5 HR=0.091 p=0.44	No survival benefit of adding panitumumab to irinotecan after fluoropyrimidine/oxaliplatin failure

Cet = cetuximab; OS = overall survival; Pan=panitumumab; PFS=progression-free survival; plac=placebo; Pop=population; Pts=patients; RR=response rate

Studies ML18147 and E3200

Study ML18147 evaluated the efficacy and safety of adding bevacizumab (2.5 mg/kg/week dose equivalent) to an irinotecan or oxaliplatin based fluoropyrimidine regimen in patients who had progressed after a first line chemotherapy containing bevacizumab. A 19% reduction in the risk of death was observed in the chemotherapy + bevacizumab arm versus the chemotherapy only arm (HR of 0.81; 95% CI: 0.69, 0.94; unstratified log-rank p = 0.0062).

The median time to death was 1.4 months longer in the chemotherapy + bevacizumab arm (11.2 months) compared with the chemotherapy alone arm (9.8 months). Median PFS was increased of 1.6 months with the addition of bevacizumab compared to chemotherapy alone (4.1 months versus 5.7 months) with a hazard ratio (HR) of 0.68 (95% CI: 0.59, 0.78; unstratified log-rank p <0.0001).

Study E3200 evaluated the efficacy and safety of adding bevacizumab (5 mg/kg/week dose equivalent) to FOLFOX4 in patients who had previously been treated with a fluoropyrimidine or irinotecan containing regimen (but not oxaliplatin or bevacizumab) (refer to Table 8). A 25% reduction in the risk of death was observed in the chemotherapy + bevacizumab arm versus the chemotherapy arm (stratified HR of 0.75; 95% CI: 0.63, 0.89; unstratified log-rank p = 0.0010). The median time to death was 2.2 months longer in the chemotherapy + bevacizumab arm (13.0 months) compared with the chemotherapy alone arm (10.8 months). Median PFS was increased of 3 months with the addition of bevacizumab compared to chemotherapy alone (4.5 months versus 7.5 months) with a HR of 0.53 (95% CI: 0.43, 0.66; unstratified log-rank p< 0.0001).

When assessing the treatment effect on OS in a large Phase III trial such as ML18147, the HR is a more robust measure than the median OS. The HR is a measure of the reduction in risk of death overtime and takes into account all the data/information available, whereas the median is a point estimate at one point in time. The median may be affected by random

variability, and may not always indicate the true benefit observed over time as measured by HR.

Table 8. Comparison of Efficacy of bevacizumab across the Second-Line ML18147 and E3200 mCRC Trials (ITT Population)

	E3200		ML18147	
	FOLFOX4	FOLFOX4 + Bev	Chemo	Chemo + Bev
	N=292	N=293	N=410	N=409
Primary Efficacy Parameter				
Median duration of survival (months) [1]	10.8	13.0	9.8	11.2
Unstratified [1] analysis				
p-value (log-rank test)	0.0010		0.0062	
Hazard ratio (95% CI)	0.75 (0.63, 0.89		0.81 (0.69, 0.94)	
Secondary Efficacy Parameter				
Median PFS after first progression (months) [1]	4.5	7.5	4.1	5.7
Unstratified [2] analysis				
p-value (log-rank test)	< 0.0001		< 0.0001	
Hazard ratio (95% CI)	0.53 (0.43, 0.66)		0.68 (0.59, 0.78)	
Objective Response Rate [3]	8.6%	22.2%	3.9%	5.4%
Difference in response rate (95% CI)	13.6% (7.9, 19.4)		1.5% (–1.5, 4.5)	
p-value (Unstratified)	< 0.0001		0.3113	
Best Overall Response				
Complete response	0.7%	1.7%	0.5%	0.2%
Partial response	7.9%	20.5%	3.4%	5.2%
Stable Disease	NA	NA	50.2%	62.6%

NA = not available.

[1] Estimate from Kaplan-Meier analysis.

[2] The unstratified log-rank test analysis was the basis for comparison between the studies as it was the primary analysis method used in ML18147.

[3] Patients who had best overall response of confirmed CR or PR.

Comparisons between clinical trials have many caveats. For example, selection bias, information bias and confounding bias often make it difficult to compare clinical trials directly. The heterogeneity of the patient population, patient's baseline characteristics and disease history, type and length of chemotherapy and study treatment, standard of care in clinics and follow up could be the main drivers of different findings between clinical trials. Because of these challenges no conclusion should be made based on a comparison of the results of E3200 and ML18147 since the patient populations were different. The numerical differences in results for OS, PFS and Response Rate (RR) in the E3200 study could be due to the fact that patients in E3200 were bevacizumab naïve and therefore potentially more susceptible in particular for the RR observed, to the first introduction of a VEGF targeted drug in second line as supposed to continuation of a VEGF targeted drug through first and second line treatment. Moreover, the dose of bevacizumab was 2.5 mg/kg/week equivalent in ML18147 and 5 mg/kg/week equivalent in E3200. These fundamental and significant differences as well as the differences in chemotherapy backbones make a direct comparison of both studies challenging and may explain in part the differences in results for endpoints for patients in E3200.

Response rates in Study ML18147 were generally low in both the control as well as the experimental arm (5.4% in the chemotherapy + bevacizumab arm versus 3.9% in the chemotherapy arm) as compared with E3200 (22.2% in the chemotherapy + bevacizumab

arm versus 8.6% in the chemotherapy arm). Differences in pretreatment for both studies may account for those differences.

Patients enrolled in ML18147 had already been exposed to more agents in earlier settings as supposed to E3200 and the benefit derived in regards to disease control rate still translated to a significant PFS and OS benefit in second line. Overall disease control rate, that is, stable disease (SD), partial responses (PRs) and complete responses (CRs), is clinically meaningful in the second line setting and was shown to be higher in the chemotherapy + bevacizumab arm in ML18147 (68%) than the chemotherapy only arm (54.1%), with a statistically significant difference ($p < 0.0001$). In cancer drug trials, an improvement in OS is considered the most convincing measure of drug efficacy and clinical benefit, specifically in later lines of therapy. While the results of the two studies were numerically different, both studies consistently demonstrated a statistically significant as well as clinically meaningful treatment benefit and provide a valuable treatment option for patients with mCRC in second line therapy.

The Delegate's Overview states that the benefit seen with bevacizumab also includes the effects of switching chemotherapy regimens between first and second line treatment, from fluoropyrimidine/oxaliplatin to fluoropyrinitdine/irinotecan or vice versa, and that when the impact of chemotherapy is taken into account, the overall survival benefit of bevacizumab is likely to be less than the median increase of 1.4 months. The sponsor disagrees with this conclusion. Study ML18147 was controlled for the effect of the chemotherapy switch.

Therefore, the treatment effect observed in the study is solely based on the treatment effect of the addition of bevacizumab. In addition, this benefit is independent of the sequence of chemotherapy used through first and second line therapy. The stratification applied in the randomisation ensured balance between patients receiving oxaliplatin-based or irinotecan based chemotherapy between the experimental and the control arms, thereby limiting any confounding introduced in the treatment comparison due to the second line chemotherapy administrated. Table 9 shows the frequencies of irinotecan and oxaliplatin in first line and in second line therapy for both arms.

Table 9. Frequencies of irinotecan and oxaliplatin use in 1st and 2nd line chemotherapy in ML18147

	Chemo	Chemo+Bev
1st line chemotherapy		
Irinotecan based	57.7%	58.7%
Oxaliplatin based	42.3%	41.3%
2nd line chemotherapy		
Irinotecan based	43%	42%
Oxaliplatin based	57%	58%

***How plausible are the subgroup results showing that subjects who were more sensitive to** first line therapy that included bevacizumab (progression after > 9 months of first line therapy) are likely to have better overall survival with continuation of bevacizumab in second line therapy?*

Subgroup analyses are an important tool in assessing the robustness and consistency of the overall results of a clinical trial across patient subpopulations. Generally, subgroup analyses are exploratory in nature, are not adjusted for multiple testing and are not powered to detect a statistically significant difference, so caution needs to be taken when interpreting the results. As long as the results in the subgroups point in the same direction as the overall result, there is no statistical rationale to conclude that the subgroup behaves differently from the entire patient population and the most reliable estimate for the treatment effect will always be the one derived from the analysis of all patients. Analyses of efficacy and safety data from the ML18147 study by subgroups did not identify any

subset of patients for which the benefit-risk profile of bevacizumab use as second line therapy in combination with fluoropyrimidine-based chemotherapy following progression on a first line bevacizumab regimen was different than the overall population in Study ML18147.

Subgroup analyses of OS were, in general, consistent with the ITT population, with no major differences in toxicity patterns between subgroups.

Regarding the subgroups of patients with a progression after > 9 months of first line therapy and after ≤ 9 months of first line therapy, the sponsor acknowledges the HR is numerically larger in patients who progress >9 months after first line therapy (see Table 10), nevertheless it still points in the same direction as the overall result (HR < 1) and the confidence intervals for the HR in the two subgroups are largely overlapping, indicating no difference in treatment benefit. Moreover, results of treatment by PFS in first line interaction using the Cox model were not significant (p > 0.05). The median survival for each treatment within the subgroup shows that patients with disease progression after ≤ 9 months in first line still derive a benefit of adding bevacizumab to chemotherapy in second line. In addition, analyses of overall safety by "first line PFS", as shown in Table 11), provide evidence that the overall AE profile reported during second line treatment with bevacizumab in combination with chemotherapy, is comparable for both first line PFS subgroups (≤ 9 months or > 9 months) and similar to the overall safety population. The treatment benefit derived for Study ML18147 in second line mCRC provides a new treatment option for all second line mCRC patients and the evidence demonstrates that regardless of stratification factors, patients derive an OS benefit from the continuation of bevacizumab through second line therapy.

Table 10. Study ML18147 – Subgroup Analysis of Overall Survival

Overall Survival	Subgroup	Fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin based chemotherapy	Fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin based chemotherapy + AVASTIN
Median *mths* Hazard Ratio [95% CI]	progression after ≤ 9 months first-line bevacizumab-fluoropyrimidine chemotherapy	*n=228* *8.5* -	*n=221* *9.5* 0.89 [0.73, 1.09]
Median *mths* Hazard Ratio [95% CI]	progression after > 9 months first-line bevacizumab-fluoropyrimidine chemotherapy	*n=182* *11.4* -	*n=187* *13.4* 0.73 [0.58, 0.92]

Table 11. Summary of Overall Safety by First-Line PFS in Study ML18147 (Safety Population)

	Overall Population		First-Line PFS (≤ 9 months)		First-Line PFS (> 9 months)	
	Chemo	Chemo + Bev	Chemo	Chemo + Bev	Chemo	Chemo + Bev
	n = 409	n = 401	n = 227	n = 216	n = 182	n = 184
Percentage of patients with at least one AE						
Any AE	98.5	98.3	98.2	97.2	98.9	99.5
Serious AE	33.5	32.2	35.2	33.3	31.3	31.0
AE (Grade ≥ 3)	57.5	63.6	55.9	61.1	59.3	66.3
AE leading to death	3.7	3.5	4	2.8	3.3	4.3
AE leading to any study drug discontinuation	8.8	15.7	11	14.4	6.0	17.4
Hypertension (Grade ≥ 3)	1.2	1.7	1.3	0	1.1	3.3
Proteinuria (Grade ≥ 3)	0	< 1	0	1.4	0	0
Bleeding/hemorrhage (Grade ≥ 3)	< 1	2.0	< 1	< 1	0	3.3
GI perforation (any grade)	< 1	2.7	< 1	3.7	< 1	1.6
Abscesses and fistulas (any grade)	0	1.2	0	1.9	0	< 1
Wound-healing complications (Grade ≥ 3)	< 1	< 1	< 1	0	0	< 1
Arterial thromboembolic events (any grade)	1.0	< 1	< 1	< 1	1.6	1.1
Venous thromboembolic events (Grade ≥ 3)	2.9	4.7	4	4.6	1.6	4.9
Congestive heart failure (Grade ≥ 3)	< 1	0	< 1	0	< 1	0
RPLS (any grade)	0	0	0	0	0	0

Benefit-risk balance of bevacizumab in the proposed indication; is the benefit-risk balance improved if continuation of bevacizumab in second line therapy were restricted to subjects who were more sensitive to first line therapy that included bevacizumab (progression after > 9 months of first line therapy)?

Benefit-risk balance on the basis of first line PFS

Based on the above rationale, the sponsor believes a restriction on the basis of first line PFS ≤ 9 months or > 9 months is not scientifically justified. A restriction to one of the subgroups should not be based on subgroup analyses that are exploratory in nature and not powered to detect a statistically significant difference. Additionally, the sponsor questions the ethical considerations for such a restriction.

Benefit-risk balance of 2.5 mg/kg/week and 5 mg/kg/week equivalent bevacizumab doses

The benefit-risk profile of bevacizumab in combination with fluoropyrimidine based chemotherapy for second line bevacizumab pretreated mCRC patients is positive for both the 2.5 mg/kg/week and 5 mg/kg/week equivalent bevacizumab doses. The sponsor considers the proposed dosing recommendation to be justified as it provides physicians with a choice of bevacizumab dose and allows consideration of both beneficial and undesirable effects that may be relevant for an individual patient.

The overall safety profile of bevacizumab in ML18147 was favourable and similar to previous experience in Study E3200. The efficacy outcomes from both these studies have been described above.

In ML18147, the incidence of adverse events (any grade), serious adverse events and Grade 3-5 adverse events were comparable between treatment arms. In addition, patients who died for reasons other than disease progression, and those who died due to an AE (Grade 5) were aslo balanced between the chemotherapy + bevacizumab arm and the chemotherpay only arm. In ML18147, there was a lower incidene with respect to Grade 3-5 AEs, Grade 5 AEs, AEs leading to discontinuation of bevacizumab, and selected AESIs (hypertension, ATEs, abscesses/fistulae/bleeding/hemorrhage) as comapred to the E3200 study. The incidence of Grade3-5 proteinuria, venous thromboembolisms (VTEs), GI perforations and wound healing complications was similar in both studies. Twice as many patients in the E3200 study withdrew from bevacizumab treatment due to an AE when compared to the ML18147 study. This may be expected for a patient population which had been pretreated with, and tolerated, bevacizumab reasonably well in the first line setting, comapred with patients receiving bevacizumab for the first time, as in Study E3200. Moreover, as with the comparison of efficacy between ML18147 and E3200, a relationship

betweeen the apparent lower incidence of AEs reported in ML18147 compared to E3200, to bevacizumab dose cannot be ruled out. However, no clear dose-relationship to toxicity has been observed in the initial dose-finding trial AVF0780g except possibly with respect to hypertension and proteinuria. The safety data from E3200, when comapred to other first line mCRC trials where a dose intensity of 2.5 mg/kg/week equivalent was used, did not show an increased incidence of Grade 3/4 AESI events, with the exception of Grade 3/4 bleeding.

Both E3200 and ML18147 studies confirm the acceptable safety profile of bevacizumab when given with fluoropyrimidine based chemotherapy for second line treatment of mCRC. No new safety signals were noted in either Study E3200 or Study ML18147, and the incidence of AEs associated with bevacizumab treatment was low and treatment was generally well tolerated in both studies. Study ML18147 further demonstrates that administering bevacizumab with switched chemotherapy patients who have already received bevacizumab in the first line setting did not result in any safety concerns.

Comments in response to Delegate's specific requests

As requested by the Delegate, medium overall survival subgroup analaysis was provided.

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 ACPM, taking into account the submitted evidence of safety and efficacy agreed with the Delegate that Avastin concentrated injection containing 100 mg/4 mL and 400 mg/16 mL of bevacizumab has an overall negative benefit-risk profile for the proposed dosage regimen.

In making this recommendation the ACPM noted that despite one high quality study showing a small but statistically significant improvement in the primary endpoint, the toxicity of bevacizumab in the study is as expected and greater than in the control group. Patients nearing the end of their lives were on treatment with its attendant toxicities for more than four months, four weeks longer than controls, to achieve an improvement in survival of less than six weeks. Without formal quality of life measures, the ACPM were of the view it is doubtful that the small increase in survival demonstrated is clinically meaningful.

Outcome

Based on a review of quality, safety and efficacy, the TGA rejected the proposed new low dose option of treatment but approved changes to the approved Product Information (PI) for Avastin bevacizumab injection 100 mg/4 mL and 400 mg/16 mL.

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

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