Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for bevacizumab

Proprietary Product Name: Avastin

Sponsor: Roche Products Pty Ltd

Date of CER: January 2012

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 Ageing, 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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
VEGF	vascular endothelial growth factor
BV	bevacizumab
EOL	epithelial ovarian cancer
PPC	primary peritoneal cancer
FTC	fallopian tube cancer
RPLS	reversible posterior leucoencephalopathy syndrome
AESI	adverse event of special interest
VTE	venous thromboembolic events

1. Clinical rationale

Bevacizumab is a recombinant humanised monoclonal antibody. It inhibits angiogenesis by neutralising all isoforms of human vascular endothelial growth factor (VEGF) and by combining to VEGF receptors. Bevacizumab has previously been approved for management of patients with metastatic colorectal cancer in combination with chemotherapy and also for metastatic breast cancer in combination with chemotherapy.

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

An application to extend the use of BV in combination with carboplatin and paclitaxel for the front line treatment of patients with epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC) or fallopian tube cancer (FTC) has been submitted. This current application focuses on the use of bevacizumab in the recurrent setting.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

Module 1 contains the relevant application letters, forms, draft Australian PI and CMI as well as FDA approved product label and European summary of product characteristics.

Module 2 contains the appropriate clinical overview, summary of clinical efficacy, summary of clinical safety and references.

Module 5 contains full reports together with tabular summaries of the pivotal study AVF4095G also known as OCEANS which was a multicentre randomised Phase III study of Avastin in combination with carboplatin and gemcitabine chemotherapy for the treatment of patients with recurrent platinum sensitive epithelial ovarian carcinoma, primary peritoneal carcinoma and fallopian carcinoma. Full reports of efficacy and safety in relation to this pivotal trial are provided. Also submitted is data in relation to reviews of studies demonstrating adverse effects seen with the “off-label intraocular” use of bevacizumab for the treatment of macular degeneration. This involves two companies study reports for a total of 240 pages and four published papers for a total of 32 pages to support changes in the Product Information. It should be noted that this area will be dealt with under the heading of *Safety*.

2.2. Paediatric data

Submission does not contain any paediatric data.

2.3. Good clinical practice

All aspects of good clinical practice were observed in the pivotal study.

3. Pharmacokinetics

No new data in relation to pharmacokinetics is presented in this submission.

4. Pharmacodynamics

No new data in relation to pharmacodynamics is presented in this submission.

5. Dosage selection for the pivotal studies

A dose of BV of 15 mg/kg every 21 days is equivalent to a dose of 5 mg/kg per week and is the most commonly used dose of BV that has been shown to be effective in clinical trials across multiple tumour types. In ovarian cancer this dose was also studied in two single arm Phase II studies in ovarian cancer by the Gynaecological Oncology Group demonstrating definite activity of BV as a single agent and was thus the dose chosen for subsequent frontline Phase III trial conducted by the Gynaecological Oncology Group in combination with carboplatin and paclitaxel and has also been chosen by the Gynaecological Oncology Group for the pivotal study in this submission AVF4095G in the recurrent setting.

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

6. Clinical efficacy

6.1. Pivotal study

6.1.1. Study design, objectives, locations and dates

A single study is presented in this submission, being the pivotal Phase III trial AVF4095G which was designed to support an extension of the indication for bevacizumab in combination with carboplatin and gemcitabine for the treatment of patients with recurrent platinum sensitive EOC, FTC and PPC. The study was sponsored and conducted by Genentech Inc. and enrolled 484 patients over 33 months and 96 sites in the United States. The first patient being enrolled in April 2007 and the last enrolled in January 2010 with a clinical cut-off date for efficacy endpoints on the 17th September 2010.

Design of the pivotal study: it was a randomised double blind placebo controlled multicentre Phase III study evaluating the efficacy and safety of carboplatin AUC4 on day 1 every 21 days and gemcitabine 1000mg/m^2 days 1 and 8 every 21 days plus concomitant and extended BV in a dose of 15mg/kg day 1 every three weeks. This was compared to carboplatin and gemcitabine plus concomitant and extended placebo in women with recurrent platinum sensitive EOC, FTC or PPC.

Patients were randomised on a 1:1 basis and stratified by platinum sensitive disease of recurrence 6-12 months from last platinum based treatment vs recurrence >12 months from last platinum based treatment and whether they had undergone cyto-reductive surgery for recurrent disease.

Patients in both arms received carboplatin and gemcitabine for six cycles concurrently with BV or placebo up to 10 cycles of chemotherapy was allowed if the patient was still responding to treatment and had been deemed necessary by the investigator. Patient then continued single agent BV or placebo until disease progression or until unacceptable toxicities. Patients who discontinued one or both chemotherapeutic drugs continued to receive the other drug for a

total of six cycles together with ongoing BV or placebo. Patients who discontinued placebo prior to progressive disease were not allowed to cross over to receive BV. However post-progression therapy was not controlled by the sponsor and BV was not prohibited. At the completion of study when all patients were unblinded, those who had been receiving chemotherapy plus BV were allowed to continue BV until evidence of disease progression.

Eligibility criteria included all patients who were at least 18 years of age with a life expectancy of at least 12 weeks with adequate renal, hepatic, haemalogic, metabolic and coagulation function. Patients who received prior therapy with BV or with other VEGF inhibitors or VEGF receptor target agents were excluded from study.

Patients were required to have histologically documented EOC, FTC or PPC that recurred at least six months after last platinum based chemotherapy. This must have been the first recurrence of disease and they must not have received prior chemotherapy for the malignancy in the recurrent setting. ECOG performance status was 0-1 at baseline was required. All patients were required to have measurable disease according to RECIST criteria.

The primary efficacy endpoint of the study was investigator determined progression free survival (PFS). Secondary efficacy endpoints were overall response rate, duration of objective response determined by the investigator and overall survival.

Exploratory outcome measures of progression free survival, overall response rate and duration of response were as determined by an independent review committee (IRC) using modified RECIST criteria.

Tumour assessments including scans of all disease sites were performed at screening and every nine weeks during treatment according to modified RECIST criteria. Progression of disease was determined using these criteria and an increased in CA-125 levels was not sufficient for a basis of progression with additional signs and symptoms of clinical progression being required.

The primary efficacy analysis was a comparison of investigator determined PFS between the two treatment arms with the use of a two-sided stratified log-rank test. Kaplan-Meier methodology was used to estimate the PFS curves and median times in the treatment arms. A Cox regression model was used to estimate the stratified and unstratified hazard ratio (HR).

PFS was defined as the time from randomisation to disease progression based on an investigator's determination or death due to any cause.

In relation to secondary efficacy analyses for analysis of the duration of overall survival an interim analysis was performed at the time of the final PFS analysis. The final analysis of overall survival is planned when 353 deaths have been observed.

A total of 484 patients have been randomised to the two treatment arms, 242 patients in each treatment arm. Of the patients randomised, four in the chemotherapy plus placebo arm did not receive any placebo treatment and one in the chemotherapy plus BV arm did not receive any BV treatment.

Regarding the disposition of patients and reasons for placebo or bevacizumab discontinuation for all randomised patients, it is noted that more patients on the BV arm of therapy discontinued treatment because of adverse effects.

The mean number of cycles received was 10 with a range 1-36 for the placebo arm and 12 with a range of 1-43 for the BV arm. The same proportion of patients in each arm completed gemcitabine treatment being 78.5% and the proportion of patients completing carboplatin was similar in the two arms being 73.1% and 70.2% for the placebo and BV containing arms.

In relation to baseline demographic data, these were well balanced between the two treatment arms. The median age of patients in the placebo arm was 61 years and 60 years in the BV arm with 35% and 38% of patients being 65 years of age or older. The majority of patients in both arms had a baseline ECOG performance status of 0.

Baseline ovarian cancer history was well balanced between the two treatment arms. The primary type of cancer in the majority of patients was EOC followed by PPC and FTC, with the most prominent histological sub-types being serous adenocarcinoma followed by mucinous clear cell carcinoma. The incidence was comparable in both treatment arms. Cyto-reductive surgery for recurrent disease had been performed in 10 and 12% of patients and time to recurrence when the last frontline platinum therapy was >12 months was 58 and 59% of patients and 6-12 months in 41 and 42% of patients in both arms. All patients had measurable disease at baseline.

All patients had received treatment for ovarian cancer prior to enrolment in study. All had received platinum based chemotherapy as per the protocol inclusion criteria and all but one patient in each arm had received a taxane in the frontline setting. Some 99.6% of patients had undergone primary debulking surgery.

The number of patients who received non-protocol neo-plastic therapy prior to progressive disease while on study was low but similar between the two treatment arms. The proportion of patients who received non-protocol therapy and had not experienced progressive disease was also low although a higher percentage was in the BV arm.

The majority of patients in both treatment arms received some form of anti-neoplastic treatment after PD with a greater proportion of these being in the placebo arm with 73.1% while in the BV arm 55.8%.

6.1.2. Efficacy outcomes

Reviewing efficacy results at the time of data cut-off a total of 338 PFS events had occurred with 187 or 77.3% in the placebo arm, 151 or 62.4% in the BV arm. The primary stratified analysis for PFS was censored for non-protocol therapy and showed that the addition of BV to CG followed by BV until progressive disease led to a statistically significant reduction in the risk of progression or death by 52% compared to the placebo containing arm with an HR 0.484 95%CI 0.388-0.605 and a log rank P value of <0.0001. The median duration of PFS were 8.4 months in the placebo arm and 12.4 months in the BV arm representing an increase of four months. Results of the unstratified analysis of PFS were similar to those of the stratified analysis.

The Kaplan-Meier plot provided showed separation occurred in favour of the BV arm after two months which was maintained essentially over the remainder of the duration of study.

A total of six sensitivity analyses were performed on the PFS endpoint and strongly and consistently support the primary analysis of PFS with stratified HRs ranging from 0.45 to 0.669 associated with log rank P values of at least 0.0001.

Reviewing secondary efficacy endpoints. Analysis of overall response rate as determined by the investigator showed the incidence of patients with a best confirmed overall response of at least CR + PR was statistically significantly higher in the BV arm being 78.5% compared with the placebo arm being 57.4%. The absolute difference in response rate between the two arms was 21.1% stratified and unstratified P<0.0001. The majority of confirmed responses were PRs being 48.3% in the placebo arm vs 61.2% in the BV arm. The proportion of patients with CR as the best confirmed response was higher in the BV arm being 17.4% than the placebo arm being 9.1%.

There was an increase of three months from the investigator determined median duration of overall response in the BV arm being 10.4 months compared with the placebo arm being 7.4 months.

Reviewing overall survival, at the time of data cut-off for the final analysis of progression free survival 29% of patients had died and were included in the interim analysis of overall survival. Accordingly the data was immature. The median duration of survival follow-up was 23.5 months with a range of 0.3 to 38.8 months in the placebo arm and 23.7 months with a range of 1.2 to 40 months in the BV arm. The interim analysis of overall survival showed that there was a

25% reduction in risk of death in the BV arm compared with the placebo arm but this did not reach the pre-specified P value boundary of 0.001 a log interim analysis to declare statistical significance. The stratified HR was 0.75 and log rank P 0.0944. Median duration of overall survival was 29.9 months in the placebo arm and 35.5 months in the BV arm, an increase of 5.6 months in the BV arm.

Among exploratory analyses was an investigator determined vs independent review committee determined concordance analysis. The concordance rate was defined by agreement on investigator and IRC determined progression status (Yes or No) were comparable between the two arms being 73.2% in the placebo arm and 75.2% in the BV arm. The overall concordance rate for the two investigators and IRC determined overall response rates were comparable being 80.6% in the placebo arm vs 78.9% in the BV arm.

The overall exact match of investigator and IRC progression free survival rates were 70.9%. The rate was comparable between the treatment arms being 71.9% in the placebo arm vs 69.8% in the BV arm.

The IRC analysis of overall response rate also showed that the incidence of patients with best overall response rate of CR + PR was significantly higher in the BV arm being 74.8% compared with the placebo arm being 53.7%. The absolute difference in overall response rate between the two arms was 21.1% with a stratified P <0.0001. It is noted the overall rate of CR was higher in the investigator assessment being 9.1% in the placebo arm and 17.4% in the BV arm compared to the IRC assessment being 1.2% in the placebo arm and 0.8% in the BV arm.

Sub-group analyses were undertaken comparing the two arms of therapy in relation to the primary parameter of investigator determined PFS. Sub-groups as prognostic factors for assessing the treatment effect on PFS included the randomisation certification variables, age, race, baseline ECOG performance status, histopathological cell type, size of target lesion at baseline, prior biology therapy, prior hormone therapy and prior myeloablative therapy. The results of all the sub–group analyses showed a marked reduction in the risk of progressive disease or death in the BV arm with a HR rating from 0.41-068 and were consistent with the overall treatment effect.

6.2. Summary and conclusions

These data from a reasonably sized study have clearly shown that the addition of BV to combination chemotherapy of carboplatin and gemcitabine is associated with a statistically significant increase in PFS of four months and also a significantly increased overall response rate. Nevertheless at this time the data is not yet supported by the improvement in overall survival but as the data is relatively immature with only 29% of patients having died at the time of final data cut-off, further follow up would be appropriate. Nevertheless all sensitivity analyses and sub-group evaluations confirm the apparent benefit of the addition of BV to chemotherapy in these patients. Even though the median duration of progression free survival improvement is only of the order of four months in the context of recurrent disease and patients whose survival will be limited this prolongation of progression free survival can be considered clinically meaningful.

7. Clinical safety

7.1. Studies providing evaluable safety data

Safety data for this evaluation comes from the pivotal study AVF4095G. Safety data was recorded up to the 17th September 2010 from a total of 480 safety evaluable patients.

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

All adverse events reported in the study were graded by the investigator for severity according to NCI common toxicity criteria. Patients were evaluated for all adverse events and serious adverse events at each study visit for the duration of their participation in the study and up to 30 days after discontinuation from study treatment. Patients who continued in the open label BV Phase after the study was unblinded were also followed at four weekly intervals until their last dose of BV.

7.2. Patient exposure

Reviewing the overall extent of exposure, the mean number of study drug cycles was greater in the BV arm being 12 cycles compared to the placebo arm being 10 cycles. The median dose intensity was 92.3% for each arm. The overall number of treatment cycles of BV was higher with a range of 1-43 compared to 1-36 for placebo and the median duration of treatment for patients in the BV arm was correspondingly higher at 37.3 weeks compared with 32.1 weeks in the placebo arm.

For carboplatin the median number of cycles was six in both arms. The percentage of patients who received 7-10 cycles was higher in the placebo arm being 40.3% compared to the BV arm of 33.3%. The median dose intensity was comparable between the two treatment arms. The gemcitabine patients received a median number of six cycles in both arms with a slightly higher percentage of patients receiving 7-10 cycles in the placebo arm being 45.5% compared to the BV arm of 41.3%. The median dose intensity was also similar across both treatment arms.

The median duration of follow up in the study population was 8.4 months in the placebo arm and 9.6 months in the BV arm.

7.3. Adverse events

Reviewing the results of adverse events. All patients in both treatment arms experienced one or more adverse events of any grade. For patients receiving BV the most frequently reported adverse events were fatigue in 81.4%, nausea 71.7%, neutropenia 68.8%, thrombocytopenia 57.9%, epistaxis 54.3% and anaemia 52.6%. The majority of these were grade I events with the exception of thrombocytopenia and neutropenia of which the majority were at least grade III.

Reviewing adverse events with at least a 5% or greater incidence in the BV arm. The events which showed the greatest difference in incidence between treatment arms were hypertension in placebo 8.6% vs BV 40.5%, epistaxis placebo 14.2% vs BV 54.3%, headache placebo 30% vs BV 48.6% and proteinuria placebo 3.9% vs BV 16.6%.

Review of adverse events of at least grade III in severity revealed a higher percentage of patients who experienced adverse events at this level in the BV arm compared to the placebo arm being 82.4% vs 89.5%. It is noted that the overall percentage of patients with grade III adverse events was comparable between the two treatment arms with placebo 42.1% vs BV 42.5% with the percentage of patients grade IV adverse events was higher in the BV arm being 46.6% compared to placebo 39.9%. The grade III – V adverse events for which the incidence was at least 2% or higher in the BV arm included thrombocytopenia, nausea, fatigue, headache, proteinuria, dyspnoea, epistaxis and hypertension. Certain events were particularly higher in the BV treated patients including grade III hypertension, placebo 0.4% vs BV 15.4%, grade III proteinuria placebo 0.4% vs BV 7.7% and grade IV thrombocytopenia placebo 18.9% vs BV 28.3%.

7.4. Deaths

Reviewing deaths as of the data cut-off date, 141 or 29.4% of patients had died. The majority of these were due to progressive disease. Fewer patients on the BV arm died than the placebo arm, primarily because of fewer deaths due to progressive disease being 33% for placebo vs 24.3% for BV. Two patients had a treatment emergent fatal adverse event, one on receiving BV who died of an intracranial haemorrhage and one on placebo who died of myocardial infarction. A further patient receiving BV died following an adverse event of sepsis. This death occurred 70 days after the last administration of study drug.

7.5. Serious adverse events

Reviewing serious adverse events, the overall incidence of serious adverse events was higher in the BV arm being 34.8% compared to placebo being 24.9%. There was no single serious adverse event with a 2% or more increased incidence in the BV arm. The most frequently reported serious adverse events were GI disorders for placebo 6.9% vs BV 7.3%, blood and lymphatic system disorders, placebo 6.4% vs BV 5.7%, nervous system disorders, 3% vs 9%, respiratory, thoracic and mediastinal disorders 3.4% vs 4%, infections and infestations 3% vs 4% and vascular disorders 0.9% vs 5.3%. The serious adverse events with the highest incidence in the BV arm were anaemia, placebo 0.4% vs BV 2.4%, hypertension, placebo 0% vs VB 1.6%, epistaxis, placebo 0.4 vs BV 2% and reversible posterior leuko-encephalopathy syndrome(RPLS) 0% vs 1.2%.

7.6. Discontinuations due to adverse events

Reviewing adverse events leading to discontinuation of study drug, there was a high percentage of patients in the BV arm being 19.8% than the placebo arm who experienced adverse event of any grade that led to discontinuation. One factor partly contributed to this was the protocol mandate for discontinuation of study drug in patients who experienced particular events, for example, hypertension and proteinuria.

The most common non-haematologic adverse events leading to drug discontinuation of BV treated patients were hypertension 3.6%, proteinuria 2.4%, RPLS 1.2% and epistaxis 1.2%. Most common haematological events causing BV discontinuation were neutropenia in four patients and thrombocytopenia in four patients.

The majority of study drug discontinuations in both arms occurred during the Phase of chemotherapy concurrent with placebo or BV. 8/11 patients on the placebo arm and 36/49 on the BV arm discontinued study drug between cycles 1 and 10. An additional three patients in the placebo arm and 13 in the BV arm discontinued during the single agent BV or placebo treatment extension Phase.

During the extension Phase of treatment the most common adverse events resulting in treatment discontinuation of BV were grade III hypertension, persistent grade III proteinuria, thrombocytopenia and neutropenia.

7.7. Adverse events of special interest

A number of adverse events of special interest (AESI) were evaluated. Overall a higher proportion of patients in the BV arm reported at least one adverse event of special interest of any grade than the placebo arm experiencing 85% vs BV 94.3%. This difference was due primarily to events classified as non-CNS bleeding affecting 63.2% of patients receiving BV vs 27% for placebo. The majority of which were grade I and II epistaxis, hypertension BV 42.1% vs 8.6% and proteinuria BV 17.4% vs 4.7%.

A higher proportion of patients in the BV arm reported at least one AESI of grade III to IV compared with patients in the placebo arm, placebo 61.8% vs BV 73.7%. The difference in the incidence of grade III to V AESI between treatment groups was primarily due to a higher incidence of hypertension and proteinuria in BV treated patients than in the placebo patients.

The proportion of patients who experienced left ventricular systolic dysfunction, neutropenia and febrile neutropenia were comparable between the two treatment arms. No GI perforations were reported in either treatment arm.

7.7.1. Haemorrhagic events

In relation to arterial thromboembolic events these were more common amongst the BV patients being 2.8% vs 0.9%, the majority were grade III events BV 2% vs placebo 0%.

In relation to bleeding overall three patients experienced bleeding, one on the placebo arm and two on the BV arm, one of which was fatal and the other a grade IV haemorrhagic stroke.

The incidence of non-CNS bleeding events of any grade was higher in the BV arm being 63.2% compared with placebo arm of 27%, the majority of which were grade I and II events, particularly grade I epistaxis being BV 41.3% vs placebo 13.3%.

Grade III non-CNS bleeding was reported in a higher percentage of BV treated patients being 5.7% compared with patients receiving placebo 0.9%. The majority of these were epistaxis being 4.9% for BV vs 0.4%. There were no grade IV or V non-CNS bleeding events reported.

7.7.2. Gastrointestinal events

In relation to gastrointestinal perforation no patient experienced these during the treatment period but two patients in the BV arm experienced perforation more than 30 days after treatment both of which were considered possibly related to therapy.

In relation to fistulas and abscesses these occurred in four patients receiving BV and one in the placebo arm. The BV patients had one grade II and two grade III pelvic abscesses and one grade III rectal abscess.

7.7.3. Hypertension

In relation to hypertension this was more frequent in patients receiving BV 42.1% vs 8.6%. The median time to onset of hypertension was 15.5 months on the BV arm. Grade III hypertension was noted in 17.4% of patients receiving BV vs 0.4% for placebo. Two BV treated patients experienced grade IV hypertension. Overall 9/43 patients with at least grade III hypertension discontinued BV therapy.

7.7.4. Cardiac events

In relation to left ventricular dysfunction/congestive cardiac failure this was noted in six BV treated patients compared to two in the placebo arm. Two of these were grade III in severity and one grade IV involving cardiomyopathy.

7.7.5. Neutropenia

The proportion of patients experiencing neutropenia in the study was similar in both arms being 75.7% for BV vs 76% for placebo with grade III occurring in BV 36.8% vs placebo 33.9% and grade IV in BV 24.6% vs placebo 21.9%. Similarly the proportion of patients experiencing febrile neutropenia was comparable between the treatment groups with four patients in each arm experiencing this of any grade. In the BV arm two of these were grade III and II grade IV whereas in the placebo arm three events were grade III and one grade IV.

7.7.6. Proteinuria and nephritic syndrome

In relation to proteinuria the overall incidence of all grades of proteinuria was 17.4% in the BV arm vs 4.7% in the placebo. The median time to onset of proteinuria was 21.2 months in the BV

arm. In the BV arm 67% of these events resolved during the treatment period. Proteinuria was at least grade III in severity reported in 8.5% of patients on BV vs 0.4 for placebo. The majority of these events were grade III, ie 8.1%. One patient in each treatment arm developed nephrotic syndrome. A total of 6/21 patients with at least grade III proteinuria discontinued BV treatment.

7.7.7. Posterior leukoencephalopathy syndrome

In relation to reversible posterior leukoencephalopathy syndrome (RPLS) three patients in the BV arm experienced this. Two of these were grade III in severity and one grade IV. All resolved over period of several weeks.

7.7.8. Venous thromboembolic events

Venous thromboembolic events (VTE) of at least grade III severity were reported in 4% of BV patients compared to 2.6% on placebo and the majority were grade III. These consisted of deep vein thrombosis in 1.6% of patients on B V while others included jugular vein thrombosis, pulmonary embolism and thrombophlebitis. Five patients experienced grade IV VTEs, three were those on placebo. All were pulmonary embolism. The two BV treated patients experiencing grade IV VTEs were also pulmonary embolism.

7.7.9. Wound healing

A total of two patients experienced wound healing complications including one, a grade III wound dehiscence.

7.8. Laboratory tests and vital signs

Routine clinical laboratory evaluations were not performed in this study for assessment. Similarly no new information regarding vital sign changes during treatment were determined in this study.

7.9. Subgroup analyses

In relation to safety according to age groups it was noted that an increased incidence of hypertension in the BV arm for those patients who were >65 years of age and was at least twice that for patients on placebo. There were no other obvious age related differences. There were no obvious evidence of race related differences and adverse effects associated with BV.

7.10. Post marketing safety data

Initial marketing of BV occurred in 2004. Accordingly there have been subsequently nine safety reports in relation to patients receiving BV, either as part of marketing experience or on clinical trials. More than one million patients have received BV. Summary of the safety data from the Roche Drug Safety Data Base was provided. A total of 42,455 adverse events were reported of which 35,700 were serious and 2,678 cases the outcome was fatal. The most frequently reported serious adverse events for patients treated with BV were GI disorders in 18.9%, respiratory, thoracic and mediastinal disorders 11.2%, general disorders and administration site conditions 10%, vascular disorders in 8.1%.

7.11. Summary and conclusions

The safety profile demonstrated from this pivotal trial was generally in line with that presently recognised for patients receiving BV. Certainly BV is associated with a higher incidence overall and at higher grades of adverse effects that those receiving placebo. The most common of these included arterial thrombotic events, at least grade III hypertension, proteinuria and non-CNS bleeding. It was also noted that a small number of patients who experienced RPLS on BV in this

study which had not been a previously common recognition for this agent. The proportion of patients requiring BV discontinuation given adverse events was also clearly higher on the BV therapy, most often related to hypertension, proteinuria, epistaxis and a small number of occasions of RPLS. Only one patient had experienced death as a direct result of BV therapy.

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

7.12. Safety in relation to intraocular administration of BV

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

In relation to company reports received by Roche from November 2009 – December 2010 a total of 352 cases of patients have received intravitreal BV for an ophthalmologic indication were identified. 291 reports were medically confirmed. 179 possible drug related ocular events were noted, the most frequent of which were inflammatory events including endophalmitis, eye inflammation and uveitis. Also reported were 61 possibly drug related systemic cases, the most frequent being possibly drug related systemic adverse events including cerebrovascular accidents, myocardial infarction and hypertension.

In a publication by Curtis *et al entitled Risks of mortality, myocardial infarction, bleeding and stroke associated with therapies for age related macular degeneration* in Archives of Ophthalmology 2010; 128:1273-1279 a retrospective study of 146,942 Medicare beneficiaries 65 years or older with age related macular degeneration between January 1, 2005 and December 31, 2006 were assessed. Of these patients four groups were identified including one receiving photodynamic therapy, the other groups, patients who received intravitreous pegaptanib, BV or ranibizumab. The main outcome measures assessed included risks of all-cause mortality, incident myocardial infarction, bleeding and incident stroke. It was found that there were no significant differences in the rates of mortality and myocardial infarction by treatment groups. A second analysis performed limiting the study population to the users of intravitreal BV or ranibizumab between July and September 2006 demonstrated that the hazards of mortality and stroke were significantly lower with ranibizumab than with BV. This involved a total assessment of more than 40,000 patients.

A more recently completed Medicare claims data base study performed at John Hopkins University in collaboration with Roche compared adverse event rates following off-label intravitreal BV or ranibizumab in patients treated for age related macular degeneration (AMD). Over 77,000 patients were identified having at least one neo-vascular AMD claim associated with an intravitreal injection. The outcomes of interest were systemic events including myocardial infarction, ischaemic stroke and haemorrhagic stroke, ocular events including endophlamitis, intraocular inflammation, cataract requiring surgery and ocular hypertension as well as all-cause mortality. The primary analysis cohort included 60,147 patients, 54% having received BV and 46% ranibizumab. Results demonstrated that the BV treated population was associated with a 57% increased risk for haemohhragic stroke compared to the ranibizumab population with an incidence rate of 0.41 per 100 patient years vs 0.26 events per 100 patient years for BV and Ranibizumab.

For all-cause mortality BV was associated with an 11% higher risk of death than ranibizumab with unadjusted incidence rates of 6.03 events x 100 years vs 5.5 events x 100 patient years.

Comment

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

8. Clinical questions

The only outstanding question of this reviewer would be to seek further information in relation to mature data on overall survival.

9. Benefit-risk assessment

9.1. Assessment of benefits

The efficacy results from the pivotal study AVF4095G have demonstrated a significant improvement in progression free survival for patients receiving BV in combination with carboplatin and gemcitabine compared to chemotherapy alone with an improvement in median progression free survival of four months. This had statistical significance of P<0.0001. These primary efficacy results were consistent across various patient sub-groups which included ECOG performance status, histologic sub-type, stratification variables and age. Various sensitivity analyses also confirmed the robustness of the data.

Evidence of a significant improvement in overall response rate was also obtained with an overall response rate of 79% for patients receiving BV compared to 57.4% for those receiving placebo with a P value <0.0001. Overall survival data remains immature and does not show a significant difference although at the time of data analysis 32.2% of patients receiving placebo died compared to 26% patients in the BV arm. This study was well conducted involving a reasonably sized patient population. Confirmation of the degree of activity determined by the improvement in progression free survival will await analysis of overall survival on a more mature analysis.

9.2. Assessment of risks

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

The safety data certainly confirmed the adverse event profile of BV previously reported and indicates that this is an agent which needs to be managed with care. This is even more pertinent

in patients with relatively advanced stage 3 of disease who have already failed first line therapy and therefore are facing further therapy with relatively limited survival prospects.

9.3. Assessment of benefit/risk balance

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

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

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

10. Recommendation regarding authorisation

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

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

It is appropriate to comment at this time that it is noted that bevacizumab in combination with carboplatin and paclitaxel has been proposed as a new indication for first line treatment of patients with epithelial ovarian, fallopian tube or primary peritoneal cancer. This is based on data from two studies including the pivotal study GOG0218 and supportive study BO17707. It is noted that both studies demonstrate a significant improvement in progression free survival while this is more clearly demonstrated in the pivotal study GOG0218. It is also noted that the dosage of BV in the former study was 15mg/kg q3 weekly compared to the supportive study BO17707 where dosage of BV was 7.5mg/kg q3 weekly. Data from both of these studies however still does not reveal a significant advantage in terms of overall survival.

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

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