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Evaluation of Medicines for Human Use

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ASSESSMENT REPORT
FOR
AVASTIN

International non-proprietary name/Common name:
bevacizumab
Procedure No. EMEA/H/C/582/II/0025

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1.1. Introduction

Bevacizumab is a recombinant humanized monoclonal antibody. It inhibits angiogenesis by neutralizing all isoforms of human vascular endothelial growth factor-A (VEGF), and blocking their binding to VEGF receptors.

Avastin was approved in the European Union (EU) on January 12, 2005 for the first-line treatment of patients with metastatic cancer of the colon or rectum (mCRC), in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan. Following this, Avastin was approved for the treatment of locally recurrent and metastatic breast cancer, for Non- Small Cell Lung Cancer for Renal Cell Cancer and for use in combination with platinum containing regimen for mCRC in 2007.

The scope of this variation is to update the SmPC, as follows:

- Update to Section 4.3 "Contraindications" to remove the contraindication in patients with untreated CNS metastases. As a consequence, the relevant information under heading "*Haemorrhage"* in Sections 4.4 "Special Warnings and Precautions for Use" and 4.8 "Undesirable effects" has also been updated, to reflect the data derived through the safety review, supporting the removal of the contraindication.

- Updates to Section 5.1 "Pharmacodynamic Properties":
    - to include the results of the final overall survival analysis from BO17704 study, thus also fulfilling a post-approval commitment made at the time of the extension of the indication for first-line treatment of unresectable advanced, metastatic or recurrent non-small cell lung cancer, other than predominantly squamous cell histology, in combination with platinum-containing chemotherapy (procedure number EMEA/H/C/582/II/009, Commission Decision dated 21 August 2007);
    - to include the results of the retrospective independent radiological review of tumour assessments from BO17705 study, thus also fulfilling a post-approval commitment made at the time of extension of the indication for Avastin to register new indication for first-line treatment of advanced and/or metastatic renal cell cancer in combination with interferon-alfa-2a (procedure number EMEA/H/C/582/II/015, Commission Decision dated 14 December 2007).

The Annex III (Package Insert) has also been updated, where appropriate.

1.2 Clinical aspects

- Removal of the contraindication in patients with untreated CNS metastases

Avastin (bevacizumab) is currently contraindicated in patients with untreated central nervous system (CNS) metastases. The contraindication in this patient population was introduced during the original MAA review in 2004, based on a single case of fatal intracranial bleeding in a patient with metastatic hepatocellular carcinoma, enrolled in a Phase I study of bevacizumab. Of note, the CNS metastases from hepatocellular carcinoma tend to have an inherently high tendency of bleeding – with 87.5% bleeding rate reported in literature. At the time of the original MAA review for Avastin, in the absence of further safety data from patients with untreated CNS metastases exposed to bevacizumab, it was a prudent step to introduce a contraindication in the prescribing information for Avastin, and to exclude such patients from the clinical trials of bevacizumab.

Since then, with greater experience of bevacizumab use, gathered through the extensive clinical development program, as well as the use of the product in clinical practice, Roche decided to re-evaluate the need to continue maintaining the contraindication for bevacizumab use in patients with CNS metastases. To this end, a retrospective review of safety data in patients with CNS metastases, with specific focus on the risk of intracranial bleeding in patients with CNS metastases, was carried out. The safety data included in this review came from controlled and single-arm clinical trials conducted by Roche, Genentech and ECOG, as well as data from Roche's Global Safety Database

ADVENT, and from a Postmarketing Safety Report of treated CNS Metastases in patients enrolled in 2 bevacizumab studies, prepared by Genentech to meet a post-approval commitment made to the FDA. Since brain metastases was an exclusion criterion in most of the clinical trials with bevacizumab, the safety data from clinical trials, used in this review, came either from patients who had undiagnosed brain metastases at study entry or from patients who developed brain metastases during the trials. The same also applies to patients who had been treated with bevacizumab in clinical practice in the Roche territories– either their treatment was initiated despite presence of CNS metastases or they had developed such metastases during the treatment. Of note, the use of bevacizumab in patients with CNS metastases is not and has not been contraindicated in the USA, therefore, post-marketing data derived from the Roche's Global Safety Database ADVENT includes data from patients treated with bevacizumab in the USA with diagnosed brain metastases, who had been treated according to the USPI for bevacizumab since February 2004 (approval date of Avastin in the USA).

In addition to the Roche's review of safety data in patients with untreated CNS metastases, Genentech had conducted a review of data from two post-marketing studies conducted in patients with treated CNS metastases, as part of post-approval commitment made to the FDA at the time of the original approval for Avastin in the USA, as mentioned above.

Below is the summary of the key findings from this report:

- In randomized, controlled clinical trials including over 8400 subjects in various indications, 3 patients (all of NCI/CTC grade 4) out of 91 (3.30%) with brain metastases experienced a CNS bleeding when treated with bevacizumab, compared to 1 (NCI/CTC grade 5) out of 96 (1.04%) that were not exposed to bevacizumab.
- Exploratory OS analysis does not appear to show a detrimental effect on survival for bevacizumab-exposed patients with brain metastases, compared to patients with brain metastases, who had not received bevacizumab.
- In 2 ongoing, post-approval, open-label, single-arm studies, including over 3200 patients, 68 patients developed brain metastases during study treatment; no case of CNS bleeding was observed, as of cut-off date used for the safety review.
- In a postmarketing safety report prepared by Genentech, one subject out of 83 (1.2%) developed a grade 2 CNS hemorrhage in a population of NSCLC patients with treated brain metastases.
- Individual case analysis of reports retrieved from Roche's safety database ADVENT revealed 4 reports of patients with brain metastases and suspected tumor associated hemorrhage for which at least a contributing role of bevacizumab could not formally be ruled out on the basis of a possible temporal relationship.
- The review of published literature does not contain information referring to bleeding of CNS metastases in relation to treatment with bevacizumab.
- Epidemiological data report a background rate of 5% to 87.5% of CNS bleeding from brain metastases, depending on the origin of the primary tumor.

Based on the results of this safety review, a contraindication for bevacizumab use in patients with brain metastases is no longer justified. The presented data show no increased CNS bleeding risk compared to the reported background rates. The rates and severity of CNS bleeding, with or without bevacizumab therapy, as observed in the controlled clinical studies, were within the expected background range for studied tumor types. Whilst there appears to be a numerically higher incidence of intracranial bleeding in patients with CNS metastases, when exposed to bevacizumab, based on the numbers derived from clinical studies of bevacizumab, this increase is not of such magnitude as to represent a prohibitively high risk, justifying continued withholding of a potentially beneficial treatment from these patients. Therefore, it is proposed to remove the contraindication in patients with untreated brain metastases from the Avastin SmPC, thus allowing access to bevacizumab treatment for this patient population. The treatment decisions should be driven by risk/benefit assessment carried out by the treating physicians for individual patients. To aid the physicians in making treatment decisions in these situations, Roche also proposes to update the relevant parts of the "Special Warnings and Precautions for Use" and "Undesirable Effects" sections of the SmPC with information derived

through the safety review, underpinning the application for contraindication removal, as follows (deleted text in strikethrough, new text – underlined):

Section 4.3 "Contraindications":

Proposed text:

- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to Chinese hamster ovary (CHO) cell products or other recombinant human or humanised antibodies.
- Pregnancy (see section 4.6).
- ~~Avastin is contraindicated in patients with untreated CNS metastases (see sections 4.4 and 4.8).~~

Section 4.4 "Special warnings and precautions for use":

Proposed text:

Haemorrhage

~~The risk of CNS haemorrhage in patients with CNS metastases receiving Avastin could not be fully evaluated, as these patients were excluded from clinical trials. Thus, Avastin should not be used in these patients (see sections 4.3 and 4.8).~~

Patients treated with Avastin have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Avastin should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during Avastin therapy (see section 4.8).

Patients with untreated CNS metastases were routinely excluded from clinical trials with Avastin, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patients has not been prospectively evaluated in randomised clinical studies (see section 4.8). Patients should be monitored for signs and symptoms of CNS bleeding, and Avastin treatment discontinued in case of intracranial bleeding.

There is no information on the safety profile of Avastin in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting Avastin treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of grade 3 or above bleeding when treated with a full dose of warfarin and Avastin concomitantly.

Section 4.8 "Undesirable effects"

Proposed text:

Haemorrhage

Tumour-associated haemorrhage (see section 4.4).

Major or massive pulmonary haemorrhage/haemoptysis has been observed primarily in studies in patients with non-small cell lung cancer (NSCLC). Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, Avastin therapy, previous medical history of atherosclerosis, central tumour location and cavitation of tumours prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were Avastin therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent phase III studies, while patients with unknown tumour histology were included.

In patients with NSCLC excluding predominant squamous histology, all grade events were seen with a frequency of up to 9% when treated with Avastin plus chemotherapy compared

with 5% in the patients treated with chemotherapy alone. Grade 3-5 events have been observed in up to 2.3% of patients treated with Avastin plus chemotherapy as compared with < 1% with chemotherapy alone. Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome.
Gastrointestinal haemorrhages, including rectal bleeding and melaena have been reported in colorectal cancer patients, and have been assessed as tumour-associated haemorrhages.

Tumour-associated haemorrhage was also seen rarely in other tumour types and locations, including ~~a~~ cases of central nervous system (CNS) bleeding in ~~a~~ patients with ~~hepatoma with occult~~ CNS metastases (see section 4.4~~3~~) ~~and another patient who developed continuous oozing of blood from a thigh sarcoma with necrosis~~.

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomised clinical studies. In an exploratory retrospective analysis of data from 13 completed randomised trials in patients with various tumour types, 3 patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all Grade 4) when treated with bevacizumab, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to bevacizumab. In two ongoing studies in patients with treated brain metastases, one case of Grade 2 CNS haemorrhage was reported in 83 subjects treated with bevacizumab (1.2%) at the time of interim safety analysis.

Across all clinical trials, ***mucocutaneous haemorrhage*** has been seen in 20% - 40% of Avastin-treated patients. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in the Avastin treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epistaxis) may be dose-dependent.

There have also been less common events of minor mucocutaneous haemorrhage in other locations, such as gingival bleeding or vaginal bleeding.

Please note that the historical information on the case of continuous blood oozing from a thigh sarcoma has been deleted, since the rest of the text pertaining to tumour-associated haemorrhage provides an all-encompassing information on such occurrences with bevacizumab use, and does not necessitate specific descriptions of individual observations.

Changes, associated with the removal of contraindication in patients with untreated CNS metastases, have also been made to the Patient Information Leaflet (Annex III).

With the provision of the Drug Safety Report, reviewing the risk of intracranial bleeding in patients with CNS metastases, Roche considers that the following post-approval commitment (made at the time of the original MAA approval) is also addressed; **FUM026:** To explore the question of bleeding in patients with CNS metastases.

Discussion

The available data provides adequate reassurance that the risk of CNS bleeding in patients with brain metastases is not unduly increased with the use of bevacizumab and, thus, supports the proposed revisions to the SmPC- the downgrading of the contraindication for patients with untreated CNS metastases to the proposed new Warnings and Precautions statement, as well as describing the available safety data in the Section 4.8, Undesirable Effects.
It is also noted that currently the assessment of the extension of indication to include the treatment of malignant gliomas. High grade malignant gliomas are highly vascularised, therefore any potential propensity of bevacizumab to cause CNS bleeding would have been particularly evident in these patients.

There is no biological or pharmacological rationale to suspect that the incremental benefit derived from bevacizumab would be any different in patients with brain metastases, than those without. And whilst it is acknowledged that the prognosis and performance status of patients with CNS metastases could be inherently worse than that of patients without brain metastases, this does not preclude an incremental benefit to these patients from bevacizumab-treatment.

Bevacizumab has not been contraindicated in the USA for use in patients with CNS metastases. It has been on the US market since February 2004, and, with extended use in a large number of patients, there have been no indications that patients with brain metastases are unduly exposed to a risk of CNS bleeding. The spontaneous safety reports on MAH's safety database also include all the reports from the USA, and do not provide any indication of disproportionately increased risk.

There is a non-comparative, non-randomized, open-label Phase II trial, being conducted by Roche in France (ML 21823), assessing the efficacy and safety of bevacizumab combined with first-line paclitaxel/carboplatin or second-line erlotinib in non-squamous NSCLC patients with asymptomatic brain metastasis. The study aims to recruit 66 patients to the first-line carboplatin/paclitaxel + bevacizumab arm, and 49 patients to the second-line erlontinib + bevacizumab arm. The first results from this study are expected in 2012 (subject to recruitment rate).

The MAH commits to provide the results of this study, when available, to the CHMP as a post-approval commitment. However, in the MAH's opinion, the currently available data already provide sufficient rationale to justify replacing the current contraindication with the proposed Warnings and Precautions statement and, thus, making bevacizumab available to this patient population.

These changes are acceptable in view of the now extensive experience with Avastin in patients with brain metastases. The risk of bleeding in patients with brain metastases does not seem to be increased to an extent which warrants a contraindication.

Update of section 5.1 " Pharmacodynamic Properties"

The MAH proposes to make the following changes to Section 5.1:

- to include the results of the final overall survival analysis from BO17704 study
- to include the results of the retrospective independent radiological review of tumour assessments from BO17705 study

Update To Description Of Efficacy Results From Study BO17704

BO17704 study was submitted as part of a Type II Variation application to register new indication for first-line treatment of unresectable advanced, metastatic or recurrent non-small cell lung cancer, other than predominantly squamous cell histology, in combination with platinum-containing chemotherapy (procedure number EMEA/H/C/582/II/009, Commission Decision dated 21 August 2007). At the time of the approval the following commitment was made by Roche:

> ***Provision of Overall Survival Data from Study BO17704***
> *The MAH commits to provide a survival update report for study BO17704, and if appropriate, submit a Type II variation to update the SmPC to reflect the overall survival analysis by 15 November 2008.*

To fulfil this post-approval commitment, Roche provides a Clinical Study Report Addendum for BO17704 study and also proposes to include the following information in section 5.1 of the SmPC, describing the overall survival analysis results from BO17704 (deleted text in strikethrough, new text – underlined):

Study BO17704 was a randomised, double-blind phase III study of Avastin in addition to cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with locally advanced (stage IIIb with supraclavicular lymph node metastases or with malignant pleural or pericardial effusion), metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy. The primary endpoint was progression free survival ~~(PFS)~~, secondary endpoints for the study included the duration of overall survival.

Patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m2 i.v. infusion on day 1 and gemcitabine 1250 mg/m2 i.v. infusion on days 1 and 8 of every 3-week cycle for up to 6 cycles (CG) with placebo or CG with Avastin at a dose of 7.5 or 15 mg/kg IV infusion day 1 of every 3-week cycle. In the Avastin-containing arms, patients could receive Avastin as a single-agent every 3 weeks until disease progression or unacceptable toxicity. Study results show that 94% (277 / 296) of eligible patients went on to receive single agent bevacizumab at cycle 7. A high proportion of patients (approximately 62%) went on to receive a variety of non-protocol specified anti-cancer therapies, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 10 of the SPC.

Table 10 Efficacy results for study BO17704

	Cisplatin/Gemcitabine + placebo	**Cisplatin/Gemcitabine + Avastin 7.5 mg/kg q 3 weeks**	**Cisplatin/Gemcitabine + Avastin 15 mg/kg q 3 weeks**
Number of Patients	347	345	351
Progression-Free Survival Median (months) Hazard ratio	6.1	6.7 (p = 0.0026) 0.75 [0.62;0.91]	6.5 (p = 0.0301) 0.82 [0.68;0.98]
Best Overall Response Rate [a]	20.1%	34.1% (p< 0.0001)	30.4% (p=0.0023)
Overall Survival			
Median (months) Hazard ratio	13.1	13.6 (p = 0.4203) 0.93 [0.78; 1.11]	13.4 (p = 0.7613) 1.03 [0.86, 1.23]

a patients with measurable disease at baseline

With the provision of the BO17704 CSR addendum and the inclusion of information on overall survival results from this study in the SmPC, the relevant post-approval commitment should be considered fulfilled.

Discussion
It is correct to include the results of the analysis of overall survival in this pivotal trial. There is no significant difference in overall survival between patients who did and patients who did not receive Avastin. This may partly be due to other treatments once a relapse had occurred.

Update to description of efficacy results from study BO17705
BO17705 study was submitted as part of a Type II Variation application to register new indication for first-line treatment of advanced and/or metastatic renal cell cancer in combination with interferon-alfa-2a (procedure number EMEA/H/C/582/II/015). At the time of the approval the following commitment was made by Roche:

Clinical 2: Perform an independent retrospective review of the tumour assessments done in study BO17705 with the objective to collect all images from all patients enrolled in the study:

To fulfil this post-approval commitment, Roche submitted a Clinical Study Report Addendum for BO17705 study, with the results of the independent radiological review of tumour assessments, to the CHMP on 3 October 2008. The same CSR addendum is included in this application, to support the proposed revisions to the SmPC.

A retrospective tumor assessments performed by an independent review committee (IRC) support the investigator-assessed PFS data (see table below):

- The median PFS in both treatment arms (10.4 months in the Avastin + IFN arm vs. 5.5 months in the Placebo+ IFN arm) is consistent with the investigator-assessed results (10.2 months in the Avastin + IFN arm vs. 5.4 months in the Placebo+ IFN arm).
- The concordance between the IRC and investigator assessment in PFS event status was 74.4% in the Pl + IFN arm and 72.6% in the Avastin + IFN arm.
- The increase in the duration of PFS in the Avastin + IFN arm, as assessed by IRC, is significant (stratified HR 0.571, p value < 0.0001), confirming the analysis of investigator assessed data (unstratified HR 0.63, p value <0.0001).

	Investigator assessment		**PFS Assessed by IRC (IRC Population)**	
	IFN + Placebo	IFN + Bevacizumab	IFN + Placebo	IFN + Bevacizumab
Number of Patients	322	327	281	288
Progression-Free Survival				
Median (months)	5.4	10.2	5.5	10.4
Hazard ratio	0.63[a] (p-value < 0.0001)		0.571[b] (p-value < 0.0001)	
Objective Response Rate (%) in Patients with Measurable Disease				
Number of Patients	289	306	220	226
Response rate	12.8 %	31.4 %	12.3%	31.4%
	(p-value < 0.0001)		(p-value < 0.0001)	

a - unstratified analysis
b - stratified analysis

Accordingly, Roche proposes to include the following information in section 5.1 of the SmPC, describing efficacy results from BO17705 (deleted text in strikethrough, new text – underlined):

Avastin in Combination with Interferon alfa-2a for the First-Line Treatment of Advance and/ or Metastatic Renal Cell Cancer (BO17705)

……

At the data cut-off, 505 progression events had occurred, 111 patients remained on treatment, 287 had discontinued (discontinuations of trial treatment due to AEs were 12% with IFN alfa-2a vs. 28% with IFN alfa-2a +Avastin), and 251 died. Ninety seven (97) patients in the IFN alfa-2a arm and 131 patients in the Avastin arm reduced the dose of IFN alfa-2a from 9 MIU to either 6 or 3 MIU three times a week as pre-specified in the protocol. Dose-reduction of IFN alfa-2a did not appear to affect the efficacy of the combination of Avastin and IFN alfa-2a based on PFS event free rates over time, as shown by a sub-group analysis. The 131 patients in the Avastin + IFN alfa-2a arm who reduced and maintained the IFN alfa-2a dose at 6 or 3 MIU during the study, exhibited at 6, 12 and 18 months PFS event free rates of 73, 52 and 21% respectively, as compared to 61, 43 and 17% in the total population of patients receiving Avastin + IFN alfa-2a. The addition of Avastin to IFN alfa-2a significantly increased PFS and objective tumour response rate ~~(see Table 11)~~. Investigator-assessed median PFS was 10.2 months for Avastin plus IFN-alfa-2a, and 5.4 months for placebo plus IFN-alfa-2a (see Table 11). An independent review of progression and response assessments confirmed the investigator-

assessed PFS and ORR results. The overall survival (OS) data were not mature at the time of the ~~interim~~ final PFS analysis.

With the provision of the BO17705 CSR addendum and the inclusion of information on independent review of efficacy outcomes in this study in the SmPC, Roche considers the related post-approval commitment fulfilled.

Discussion
The assessment of FUM045 was circulated 16 December for an opinion at the January 09 CHMP. The commitment was considered fulfilled. As for the introduced changes to the SPC there are no further comments.

Changes To Package Leaflet
In line with the proposed removal of contraindication in patients with untreated CNS metastases, the relevant section of the Package Insert has also been updated, as follows (deleted text in strikethrough):

Proposed text:

2. BEFORE YOU USE AVASTIN

Do not use Avastin if:
- you are allergic (hypersensitive) to bevacizumab or to any of the other ingredients of Avastin.
- you are allergic (hypersensitive) to Chinese hamster ovary (CHO) cell products or to other recombinant human or humanised antibodies.
- ~~you have cancer in your brain which has not been treated.~~
- you are pregnant.

2. CONCLUSION

On 19 February 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.