16 February 2012
EMA/CHMP/226681/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Avastin

bevacizumab

Procedure No.: EMEA/H/C/000582/II/0047/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Committee for Medicinal Products for Human Use (CHMP)

CHMP Group of variations assessment report

Invented name Avastin

Procedure No. EMEA/H/C/000582/II/0047/G

Marketing authorisation holder (MAH): Roche Registration Ltd.

1.Background information on the procedure

1.1. Requested Group of variation

Pursuant to Article 7.2(b) of Commission Regulation (EC) No 1234/2008, Roche Registration Ltd. submitted to the European Medicines Agency on 9 September 2011 an application for a group of variations.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Avastin	bevacizumab	See Annex A

The following variations were requested in the group:

Variations requested		**Type**
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

The MAH proposed the update of section 5.1 of the SmPC to:

- Update of section 5.1 of the SmPC to include results from AVANT study in adjuvant colon cell carcinoma.

- Update of section 5.1 of the SmPC with the results from two studies in children aged > 3 years old with relapsed or progressive high-grade glioma.

The requested group of variations proposed amendments to the SmPC.

Rapporteur: Jens Ersbøll

1.2. Steps taken for the assessment

Submission date:	9 September 2011
Start of procedure:	16 October 2011
Rapporteur's preliminary assessment report circulated on:	18 November 2011
Rapporteur's updated assessment report circulated on:	8 December 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	15 December 2011
MAH's responses submitted to the CHMP on:	16 January 2012
Rapporteur's assessment report on the MAH's responses circulated on:	2 February 2012
CHMP opinion:	16 February 2012

2. Scientific discussion

2.1. Introduction

Avastin was approved in the European Union (EU) on 12 January 2005 for the first-line treatment of patients with metastatic cancer of the colon or rectum (mCRC) in combination with fluoropyrimidine-based chemotherapy. Following this, Avastin was approved for the treatment of locally recurrent and metastatic breast cancer in combination with paclitaxel or capecitabine, for Non-Small Cell Lung Cancer (NSCLC) in addition to platinum-based chemotherapy, for the first-line treatment of Renal Cell Cancer (RCC) in combination with interferon alfa-2a, and for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel.

With this variation application the Marketing Authorisation Holder (MAH) proposed to update the following sections of the SmPC:

- Section 5.1 of the SmPC to include results from AVANT study in adjuvant colon cell carcinoma.

- Section 5.1 of the SmPC with the results from two studies in children aged > 3 years old with relapsed or progressive high-grade glioma. In addition, section 4.2 of the SmPC has been updated to include a statement that avastin should not be used in children aged 3 years to less than 18 years with recurrent or progressive high-grade glioma in order to reflect the results from the paediatric studies.

Regarding the paediatric studies, in July 2010 an application for a Paediatric Investigation Plan (PIP) for bevacizumab in view of new indications being developed was submitted to the European Medicines Agency. During the procedure, the Paediatric Committee (PDCO) concluded that no paediatric trial should be required for the paediatric development of bevacizumab in children over the age of 3 years with relapsed high-grade glioma, since 2 studies published in 2010 indicated to the PDCO a lack of activity of bevacizumab in children with refractory/recurrent or relapsed high-grade glioma / glioblastoma. However the applicant was advised to submit the data for assessment and for any update of the product information as appropriate, in accordance with Article 46 of Regulation (EC) No 1906/2006

- In a single-arm phase II study conducted by the Paediatric Brain Tumour Consortium (study PBTC-022), paediatric patients with recurrent malignant glioma and intrinsic brainstem glioma were treated with bevacizumab and irinotecan.
- In a publication from Narayana et al. (Neuro oncol 2010), a retrospective analysis from clinical records of a single institution has been performed on 12 children with a relapsed or progressive high-grade glioma treated with bevacizumab and irinotecan.

During the evaluation of the PIP the PDCO requested an update to the SmPC, according to Article 46 of the Paediatric Regulation, to reflect the results observed in the two studies mentioned above. In response to the PDCO's request, the MAH submitted this variation to update section 5.1 of the SmPC to describe the lack of efficacy of bevacizumab observed in children aged 3 years or older with recurrent or progressive high-grade glioma.

2.2. Clinical Efficacy aspects

2.2.1 Methods – analysis of data submitted

- ***AVANT (BO17920) study***

The AVANT (BO17920) study was an open-label Phase III, multicenter, multinational, randomized, 3-arm study, which investigated bevacizumab (q3w or q2w), in combination with either intermittent capecitabine plus oxaliplatin (XELOX) every three weeks, or fluorouracil/leucovorin with oxaliplatin (FOLFOX4) every two weeks, versus FOLFOX4 regimen alone, as adjuvant chemotherapy in colon carcinoma (aCC).

The treatment phase consisted of two parts of 24 weeks for a total of 48 weeks:

- The first part (weeks 1 to 24) with either FOLFOX4, FOLFOX4 + bevacizumab (Bv), or XELOX+Bv.
- The second part (weeks 25 to 48) with Bv as single-agent (3-week cycle for a total of 8 cycles) for patients randomized to either Bv-containing arm, or an observation period for patients assigned to the FOLFOX4-alone arm.

The primary objectives were

- To demonstrate that the combination of Bv+FOLFOX4 is superior to FOLFOX4 alone in terms of disease-free survival (DFS) in chemotherapy-naïve patients who underwent surgery with curative intent for colon carcinoma (aCC patients).
- To demonstrate that the combination of Bv+XELOX is superior to FOLFOX4 alone in terms of DFS in aCC patients.

The secondary objectives were

- To demonstrate that the combination of Bv+FOLFOX4 is superior to FOLFOX4 alone in terms of overall survival (OS) in aCC patients.
- To demonstrate that the combination of Bv+XELOX is superior to FOLFOX4 alone in terms of OS in aCC patients.
- In case both primary objectives are achieved, to further investigate if the combination of Bv+XELOX is at least as efficacious as the combination of Bv+FOLFOX4 in terms of DFS and OS.
- To evaluate and compare the safety profiles of the treatment groups.
- To evaluate the immunogenicity of Bv measured as induction of human anti-humanized antibody (HAHA).

- **Paediatric studies**

Study PBTC-022

A phase II study of bevacizumab plus irinotecan (CPT-11) was conducted in children with recurrent malignant glioma (MG) and intrinsic brainstem glioma (BSG).

Eligible patients received two doses of Bv intravenously (10 mg/kg) two weeks apart and then Bv plus CPT-11 (125-350 mg/m²) once every two weeks until progressive disease, unacceptable toxicity, or a maximum of two years of therapy. Correlative studies included diffusion weighted and T1 dynamic contrast–enhanced permeability imaging, Bv pharmacokinetics, and estimation of vascular endothelial growth factor receptor 2 (VEGFR-2) phosphorylation in peripheral blood mononuclear cells (PBMC) after single-agent Bv.

The primary objective of the study was to estimate the rate of sustained (≥8 weeks) objective response to Bv plus CPT-11 in children with recurrent malignant glioma (stratum A) or diffuse infiltrating pontine glioma (stratum B) over four courses of therapy.

Narayana et al (Neuro Oncol 2010)

In a retrospective single institution series, 12 consecutive (2005 to 2008) paediatric patients with relapsed or progressive high-grade glioma (3 with WHO grade IV, 9 with grade III) were treated with bevacizumab (10 mg/kg) and irinotecan (125 mg/m²) every 2 weeks.

Magnetic resonance imaging (MRI) was performed prior to therapy and every 8 weeks subsequently. Radiological responses were defined according to MacDonald's criteria.

Progression free survival (PFS), OS and toxicities were analyzed.

2.2.2 Results

- ***AVANT (BO17920) study***

3451 high-risk stage II, or stage III colon cancer patients were randomized to the three study arms on a 1:1:1 basis, stratified according to geographic region and disease stage:

- 1151 patients to FOLFOX4 alone
- 1155 to FOLFOX4+Bv
- 1145 patients to XELOX+Bv

Of these, 2867 out of 3451 patients (83%) had stage III disease and formed the primary population for the efficacy analyses.

The AVANT study did not meet its primary endpoint: The p-value of the global hypothesis was 0.2024 indicating that there was no difference in the distribution of DFS between the three treatment arms in patients with stage III disease (n=2867). Therefore, all other efficacy analyses performed were considered as exploratory only.

The results favoured the control arm (FOLFOX4) with more relapses in both bevacizumab arms. The hazard ratios for DFS in patients with stage III disease were 1.17 (95% confidence interval [CI]: 0.98-1.39) for the FOLFOX4+Bv arm and 1.07 (95% CI: 0.90-1.28) for the XELOX+Bv arm.

In the first year, the risk of a DFS event in the Bv-containing arms was lower than in the control arm. The hazard ratios of DFS versus the FOLFOX4 arm were 0.63 (95% CI: 0.45-0.89) and 0.61 (95% CI: 0.43-0.86) for FOLFOX4+Bv and XELOX+Bv arms, respectively. After one year, the risk of a DFS event in the Bv-containing arms became higher than in the control arm.

The estimated hazard ratios for DFS in most subgroups were consistent with the overall estimate for all patients.

The OS data were immature. There were more deaths in the Bv-containing arms than in the control arm. The hazard ratios versus the FOLFOX4 arm were 1.31 (95% CI: 1.03-1.67) for the FOLFOX4+Bv arm and 1.27 (95% CI: 0.99-1.62) for the XELOX+Bv arm in patients with stage III disease. The results were consistent between most subgroups for OS, except for the group of patients with high-risk stage II disease. In this subgroup, the unstratified hazard ratios were 0.95 (95%CI: 0.49-1.84) and 0.62 (95%CI: 0.29-1.30) for the FOLFOX4+Bv arm and XELOX+Bv arm, respectively.

Overall, the safety profile was similar and consistent to the previous experience observed with Bv in combination with FOLFOX4 or XELOX, or as a monotherapy.

The proportion of patients with adverse events (AEs) of all grades was similar across the treatment arms. Nausea/vomiting (all treatment arms) and neutropenia (FOLFOX4 arms) were the most common AEs (≥ 50% of patients). The proportion of patients with grade 3 to 5 AEs was greater in the FOLFOX4 arms (approximately 75% vs. 65% in the XELOX arm), mainly accounted for by neutropenia. The proportion of patients with SAEs was greater in the Bv arms (FOLFOX4+Bv 26% and XELOX+Bv 25% vs. FOLFOX4 20%), mainly accounted for by gastrointestinal disorders.

The major cause of death was disease progression. The same proportion of patients in each arm (2%) died due to causes other than disease progression. Deaths from causes other than colon cancer had no clear pattern and affected a range of body systems.

- **Paediatric studies**

PBTC-022

There were 31 evaluable patients in the study, of whom 18 had non-pontine high-grade glioma (HGG) including 8 with glioblastoma (WHO grade IV), 9 patients with anaplastic astrocytoma (grade III) and 1 with anaplastic oligodendroglioma (grade III). These patients received a median of two courses of Bv plus CPT-11 (range, 1 to 19). No sustained responses were observed in either stratum. Median time to progression was 127 days for MG and 71 days for BSG. Progression-free survival rates at 6 months were 41.8% and 9.7% for MG and BSG, respectively. Toxicities related to Bv included grade 1 to 3 fatigue in seven patients, grade 1 to 2 hypertension in seven patients, grade 1 CNS haemorrhage in four patients and grade 4 CNS ischemia in two patients. The mean diffusion ratio decreased after two doses of Bv in patients with MG only.

Vascular permeability parameters did not change significantly after therapy in either stratum. Inhibition of VEGFR-2 phosphorylation in PBMC was detected in eight of 11 patients after Bv exposure.

Narayana et al (Neuro Oncol 2010)

Ten patients had supratentorial HGG; two had Diffuse Intrinsic Pontine Glioma (DIPG). Ten (83.3%) patients tolerated bevacizumab without serious toxicity. Therapy was discontinued in 1 patient because of anaphylaxis. Another patient developed grade III delayed wound healing and deep vein thrombosis. Two patients (16.7%) experienced a partial response after the first MRI. No complete radiographic responses were seen. Stable disease was noted in 4 (33.3%) patients. The median PFS and OS were 2.25 and 6.25 months, respectively. A diffuse invasive recurrence pattern was noted in 5 (45.5%) patients.

2.2.3 Discussion

- ***AVANT (BO17920) study***

Based on the results in this study, the benefit/risk balance for the treatment of aCC patients with bevacizumab is considered not to be favourable. The MAH proposed to update the section 5.1 of the SmPC to reflect the findings from this study.

However the CHMP considered that section 5.1 of the SmPC should mention information which is relevant to the prescriber and to other health-care professionals, taking into account the approved therapeutic indications and the potential adverse drug reactions. Since Avastin is not indicated for the adjuvant treatment of colorectal cancer the proposed information from the AVANT study is not considered appropriate to be included in the SmPC.

- **Paediatric studies**

Based on the results of the paediatric studies the MAH suggested to update section 5.1 with the statement that anti-tumour activity was not observed in two studies among a total of eleven children aged > 3 years old with relapsed glioblastoma when treated with bevacizumab and irinotecan and that there is insufficient information to determine the safety and efficacy of Avastin in children with glioblastoma. However the CHMP concluded that there is sufficient information in the relapsed/recurrent setting > 3 years, therefore the above statements should be revised under section 5.1 and section 4.2 of the SmPC should be updated as well to include a statement that avastin should not be used in children aged 3 years to less than 18 years with recurrent or progressive high-grade glioma in order to reflect the results from the paediatric studies.

Furthermore the CHMP requested the MAH to describe the results from the two paediatric studies with more details under section 5.1 in order to be in line with the SmPC guideline. Information should include the results of the main endpoints, the main characteristics of the population studied (including age and numbers of patients), the doses used and any information on safety.

In reply to CHMP 's request the MAH updated both sections 4.2 and 5.1 of the SmPC.

2.2.4 Changes to the Product Information

During the procedure, the CHMP requested further amendments to the PI (new wording in bold and underlined) as discussed in detail above:

- **4.2 Posology and method of administration**

Paediatric population

[…]

Avastin should not be used in children aged 3 years to less than 18 years with recurrent or progressive high-grade glioma because of efficacy concerns (see 5.1 for results of paediatric trials).

[…]

- **5.1 Pharmacodynamic properties**

[…]

Paediatric population

[…]

Anti-tumour activity was not observed in two studies among a total of 30 children aged > 3 years old with relapsed or progressive high-grade glioma when treated with bevacizumab and irinotecan. There is insufficient information to determine the safety and efficacy of bevacizumab in children with newly-diagnosed high-grade glioma.

In a single-arm study (PBTC-022), 18 children with recurrent or progressive non-pontine high-grade glioma (including 8 with glioblastoma [WHO grade IV], 9 with anaplastic astrocytoma [grade III] and 1 with anaplastic oligodendroglioma [grade III]) were treated with bevacizumab (10 mg/kg) two weeks apart and then with bevacizumab in combination with CPT-11 (125-350 mg/m²) once every two weeks until progression. There were no objective (partial or complete) radiological responses (MacDonald criteria). Toxicity and adverse events included arterial hypertension and fatigue as well as CNS ischaemia with acute neurological deficit.

In a retrospective single institution series, 12 consecutive (2005 to 2008) children with relapsed or progressive high-grade glioma (3 with WHO grade IV, 9 with grade III) were treated with bevacizumab (10 mg/kg) and irinotecan (125 mg/m²) every 2 weeks. There were no complete responses and 2 partial responses (MacDonald criteria).

3. Overall conclusion and impact on the benefit/risk balance

The CHMP concluded that the update of section 5.1 of the SmPC regarding the AVANT study is not acceptable.

In addition, the CHMP agreed with the inclusion of the results of the two paediatric studies under section 5.1 of the SmPC and the inclusion of the statement under section 4.2 in order to reflect the results from the paediatric studies.

The CHMP considers that the benefit/risk balance of Avastin remains positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Update of section 5.1 of the SmPC with the results from two studies in children aged > 3 years old with relapsed or progressive high-grade glioma. In addition, section 4.2 of the SmPC has been updated to include a statement that Avastin should not be used in children aged 3 years to less than 18 years with recurrent or progressive high-grade glioma.

The requested variation proposed amendments to the SmPC.

In addition, the CHMP considers the following variation not acceptable and therefore does not recommend the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation rejected		**Type**
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Update of section 5.1 of the SmPC to include results from AVANT study in adjuvant colon cell carcinoma.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Update of section 5.1 of the SmPC with the results from two studies in children aged > 3 years old with relapsed or progressive high-grade glioma. In addition, section 4.2 of the SmPC has been updated to include a statement that Avastin should not be used in children aged 3 years to less than 18 years with recurrent or progressive high-grade glioma.

Summary

Based on the results from two paediatric studies, anti-tumour activity was not observed among a total of 30 children aged > 3 years old with relapsed or progressive high-grade glioma when treated with bevacizumab and irinotecan. There is insufficient information to determine the safety and efficacy of bevacizumab in children with newly-diagnosed high-grade glioma.

More specifically, in a single-arm study (PBTC-022) there were no objective (partial or complete) radiological responses reported from 18 children with recurrent or progressive non-pontine high-grade glioma who were treated with bevacizumab (10 mg/kg) in combination with CPT-11 (125-350 mg/m²). Toxicity and adverse events included arterial hypertension and fatigue as well as CNS ischaemia with acute neurological deficit.

In addition, in a retrospective single institution series, no complete responses and two partial responses have been reported from 12 children with relapsed or progressive high-grade glioma who were treated with bevacizumab and irinotecan.

The section 5.1 of the SmPC has been updated to include the above results and section 4.2 has been updated as well to include a statement that Avastin should not be used in children aged 3 years to less than 18 years with recurrent or progressive high-grade glioma.