HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

4 March 2009

AVASTIN 25 mg/ml concentrate for solution for infusion
Box of 1 x 4 ml vial (CIP: 566 200-7)
Box of 1 x 16 ml vial (CIP: 566 201-3)

Applicant: ROCHE

Bevacizumab
ATC code: L01XC07

List I
For hospital use only

Date of centralised marketing authorisation: 12 January 2005
Corrections to the MA: 27 March 2007 (breast cancer) - 21 August 2007 (lung cancer) - 14 December 2007 (renal cell cancer) - 25 January 2008 (indication to be assessed)

Reason for request: inclusion on the list of medicines approved for use by hospitals in the extension of indication (second-line treatment of metastatic cancer of the colon or rectum) and analysis of updated information for the first-line indication.

The former indication wording for treatment of cancer of the colon or rectum was limited to first-line treatment: “AVASTIN is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with 5-fluororacil/folinic intravenous chemotherapy with or without irinotecan.” It has been extended to second-line treatment: “AVASTIN (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.”

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1 Active ingredient

bevacizumab

1.2 Indications

"AVASTIN (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.

AVASTIN in combination with paclitaxel is indicated for first-line treatment of patients with metastatic breast cancer.

AVASTIN, in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.

AVASTIN in combination with interferon alfa-2a is indicated for first-line treatment of patients with advanced and/or metastatic renal cell cancer."

1.3 Dosage

"Metastatic carcinoma of the colon or rectum:

The recommended dose of AVASTIN, administered as an intravenous infusion, is either 5 mg/kg or 10 mg/kg once every 2 weeks or 7.5 mg/kg or 15 mg/kg once every 3 weeks."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01X	Other antineoplastic agents
L01XC	Monoclonal antibodies
L01XC07	bevacizumab

2.2. Medicines in the same therapeutic category

None.

2.3. Medicines with a similar therapeutic aim

Cytotoxic agents indicated in the treatment of carcinoma of the colon or rectum:
- FLUOROURACIL ICN (fluorouracil) solution for infusion and proprietary drugs containing fluorouracil
- ELVORINE (folinic acid) and proprietary drugs based on folinic acid indicated in combination with fluoruracil.
- XELODA (capecitabine)
- UFT (tegafur)
- ELOXATINE (oxaliplatin)
- CAMPTO (irinotecan)
- TOMUDEX (raltitrexed)
- AMETYCINE (mitomycin C)

Monoclonal antibodies for use in “targeted therapy" indicated in the treatment of cancer of the colon or rectum:
- ERBITUX (cetuximab)
- VECTIBIX (panitumumab)

3 ANALYSIS OF AVAILABLE DATA

AVASTIN has been indicated for first-line treatment of metastatic carcinoma of the colon or rectum since January 2005. This indication was assessed by the Transparency committee on 8 June 2005.
On 25 January 2008, this indication was extended to second-line treatment of carcinoma of the colon or rectum on the basis of a pivotal study (E3200) which will be analysed below.
The pharmaceutical company also submitted updated data for the first-line indication. These data will be summarised in section B.

A/ Second-line indication for carcinoma of the colon or rectum
The efficacy and safety of AVASTIN as second-line treatment for metastatic carcinoma of the colon or rectum, following failure of 5-FU and irinotecan based chemotherapy were assessed in an open-label randomised pivotal phase III study (E3200) comparing AVASTIN in combination with the FOLFOX 4 regimen (5-FU, folinic acid and oxaliplatin) with FOLFOX 4 alone with AVASTIN as monotherapy.

The primary efficacy endpoint was overall survival, defined as the interval between randomisation and death due to any cause.

The secondary endpoints were:
- progression-free survival, defined as the interval between randomisation and progression of the disease within a period of 60 days, or death due to any cause occurring within 30 days after the end of treatment.
- the percentage and duration of objective responses (complete or partial, confirmed according to RECIST criteria)[1]
- the length of objective response, defined as the time from first assessment of the tumour and progression of the disease or death due to any cause within 30 days after the end of treatment.
- tolerance.

The AVASTIN dose was 10 mg/kg on day 1 of each cycle, prior to administration of chemotherapy (for patients in the AVASTIN + FOLFOX-4 group) once every two weeks.
The FOLFOX-4 chemotherapy regimen was administered every two weeks and comprised:
- oxaliplatin: 85 mg/m² IV on day 1
- folinic acid: 200 mg/m² IV on days 1 and 2
- 5-FU: 400 mg/m² followed by 600 mg/m² IV on days 1 and 2.
Treatments were administered until the disease progressed or until unacceptable toxicity was observed.

[1] Corresponding to the criteria used to assess response in solid tumours, and summarised as follows:
Complete response: disappearance of all tumour lesions
Partial response: 30% reduction in the largest lesion diameter
Disease progression: 20% increase in the largest lesion diameter
Stable disease: changes to tumour size that do not meet the aforementioned conditions.

Results
The median age of the 829 patients randomised (293 with AVASTIN + FOLFOX-4, 292 with FOLFOX-4 alone and 244 with AVASTIN as a monotherapy) was 61. More than 90% of patients were in good general condition (ECOG score 0 to 1). Approximately 97% of patients had failed after a 5-FU based chemotherapy in first-line .
Approximately 80% of patients had received adjuvant chemotherapy and 26% had previously undergone radiotherapy.

N.B.: patients taking part in the study had failed first-line chemotherapy (5-FU based) given as a monotherapy. AVASTIN is known as a standard first-line treatment in combination with 5-FU based chemotherapy since 2005.

Because of the results of an intermediate analysis showing overall survival inferior to that of the groups which had received chemotherapy-based treatment, the AVASTIN monotherapy group was stopped.

The results presented are those of a final analysis on 585 patients in the AVASTIN + FOLFOX and FOLFOX monotherapy groups after 525 patients died.
In the AVASTIN + FOLFOX-4 group compared to the FOLFOX-4 monotherapy group:
- overall survival was 2.2 months longer (13 months vs. 10.8 months, p=0.0012), ie a gain of 2.2 months.
- median progression-free survival was better (7.5 months vs. 4.5 months, p<0.0001).
- the objective response rate, mainly partial responses, was better (22.2% vs. 8.6%, p<0.0001).
- the median duration of the objective response was not different (6.2 months vs. 6 months).

This study did not provide any quality-of-life data.

3.1. Adverse effects
The proportion of patients discontinuing treatment because of adverse events was 23.6% in the FOLFOX-4 monotherapy group and 22.5% in the AVASTIN + FOLFOX-4 group.
The frequency of serious adverse events was 43% in the AVASTIN + FOLFOX-4 group compared to 38% in the FOLFOX-4 monotherapy group.
The grade 3 to 5 adverse events reported more often in the AVASTIN + FOLFOX-4 than in the FOLFOX-4 monotherapy group comprised mainly: proteinuria (0.7% vs. 0%), arterial hypertension (6.3% vs. 1.8%), haemorrhage (4.9% vs. 0.7%) and gastrointestinal perforations (2.1% vs. 0%).

3.2. Conclusion
The efficacy and safety of AVASTIN in combination with the FOLFOX-4 regimen as second-line treatment for metastatic carcinoma of the colon and rectum were assessed in a comparative, randomised phase III study versus FOLFOX 4 alone. 829 patients took part in the study.
Overall survival (primary efficacy endpoint) was 13 months in the AVASTIN + FOLFOX-4 group vs. 10.8 months in the FOLFOX-4 monotherapy group (p=0.0012), ie a gain of 2.2 months.
The median progression-free survival time was 7.5 months in the AVASTIN + FOLFOX-4 group versus 4.5 months in the FOLFOX-4 monotherapy group (p<0.0001).
The objective response rate, mainly partial responses, was 22.2% in the AVASTIN + FOLFOX-4 group versus 8.6% in the FOLFOX-4 monotherapy group (p<0.0001).
The median length of response did not differ between the two groups: 6.2 months in the AVASTIN + FOLFOX-4 group versus 6 months in the FOLFOX-4 monotherapy group.
This study did not provide any quality-of-life data.

The grade 3 to 5 adverse events reported more often in the AVASTIN + FOLFOX-4 than in the FOLFOX-4 monotherapy group comprised mainly: proteinuria (0.7% vs. 0%), arterial hypertension (6.3% vs. 1.8%), haemorrhage (4.9% vs. 0.7%) and gastrointestinal perforations (2.1% vs. 0%).

B/ Update of first-line data.

The dossier reports on a randomised phase III study (NO16966[2]) conducted on patients receiving first-line treatment for carcinoma of the colon or rectum, with two objectives:

- to demonstrate that the combination of XELOX with or without AVASTIN was not inferior to the combination of FOLFOX-4 with or without AVASTIN in terms of progression-free survival (this objective is not linked to the medicinal product under investigation)
- to demonstrate that AVASTIN in combination with chemotherapy (XELOX[3] or FOLFOX-4) was superior to chemotherapy alone in terms of progression-free survival

Progression-free survival (the primary efficacy endpoint) was 1.4 months better when AVASTIN was administered in combination with chemotherapy compared to chemotherapy alone (9.4 months vs. 8 months, p=0.0023).

The median overall survival time was not different between the two treatments (21.3 vs. 19.9 months, p=0.0769).

Unlike the registration study (study AVF 2107g[4]) analysed in 2005, this study did not confirm the survival gain (of 5 months) observed when AVASTIN was added to chemotherapy for patients undergoing first-line treatment for carcinoma of the colon and rectum.

The Committee takes note of these data and will reassess AVASTIN when reviewing proprietary medicinal products indicated for the treatment of metastatic carcinoma of the colon and rectum.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Carcinoma of the colon or rectum is a serious and potentially life-threatening condition;
These proprietary products are intended for curative treatment:
It is a second-line treatment;
There are alternative drugs available;
The efficacy/adverse effects ratio is high;

Public health benefit:

Carcinoma of the colon or rectum is a frequent and serious clinical condition which constitutes a major public health burden. Metastatic carcinoma of the colon or rectum represents a significant burden. The burden represented by the (small) population of patients likely to benefit from this drug (in second-line treatment after the failure of fluoropyrimidine based chemotherapy regimens and who did not receive AVASTIN as first-line treatment) can be considered as small.

Improving the management of this condition is a public health need which is an identified priority (GTNDO [5]: management of cancer).

Considering the data available (2 months improvement in overall survival during an open-label trial), a low impact on patients morbidity and mortality can be expected for AVASTIN

[2] Saltz LB et al. Bevacizumab in Combination With Oxaliplatin-Based Chemotherapy As First-Line Therapy in Metastatic Colorectal Cancer: A Randomized Phase III Study. J Clin Oncol 2008 ;26:2013-2019

[3] Combination of Xeloda + oxaliplatin

[4] AVASTIN in combination with IFL Saltz chemotherapy (irinotecan + 5FU+FA) vs. this particular chemotherapy alone

[5] Groupe Technique National de Définition des Objectifs [National Technical Objective Definition Group] (2003)

However, there is no guarantee that the results of the trial can be transposed into actual practice. Patients taking part in the trial could have been eligible for first-line treatment with AVASTIN, which could not be the case under real conditions of use (patients who did not receive AVASTIN as first-line treatment because of a contraindication). Therefore, it is impossible to know whether AVASTIN, in this indication, will meet the identified public health need.
The proprietary drug AVASTIN should therefore not be able to meet the identified public health need.
Consequently, in the current state of knowledge, the proprietary drug AVASTIN is not expected to benefit public health in this extension of indication.

The actual benefit of AVASTIN is substantial.

4.2. Improvement in actual benefit (IAB)

AVASTIN in combination with a FOLFOX-4 regimen offers a minor improvement in actual benefit (level IV) in terms of efficacy compared to the FOLFOX-4 regimen alone.

4.3. Therapeutic use

Major progress has been made in recent years in the treatment of metastatic carcinoma of the colon and rectum. Firstly, overall survival has improved significantly thanks to the routine use of irinotecan and oxaliplatin, combined with 5-fluorouracil (5FU) and folinic acid (FA) in the form of LV5FU2, combinations called Folfiri and Folfox respectively. One study showed that Folfiri – Folfox and Folfox – Folfiri sequences were equally effective in first- and second-line treatment[6].
Since targeted therapies were first introduced, the benefit of combining chemotherapy and targeted therapy in first-line and second-line care appears to be generally accepted[7].
The anti-VEGF antibody bevacizumab (AVASTIN) and the anti-EGFR antibody cetuximab have been assessed in first-line treatment. The progression-free survival gain for combination with Folfiri is 47% with bevacizumab and only 11% with cetuximab[8].
Consequently, bevacizumab remains the best option for first-line combination treatment with chemotherapy. No predictive factor for response to bevacizumab has yet been identified.
In case of progression under treatment with irinotecan plus bevacizumab in second-line treatment, , the options are either to modify the chemotherapy by replacing irinotecan with oxaliplatin or to change the targeted therapy by introducing cetuximab, an anti-EGFR antibody. Practitioners are no longer advised to test patients' EGFR status by an immunohistochemistry test because the method is not reliable and not predictive of patient's response. A better option is to test for absence of mutation of the KRAS gene (wild type) within the tumour.
The expert consensus is that bevacizumab (AVASTIN) should be reserved for patients who failed first-line chemotherapy that did not involve AVASTIN because of a haemorrhagic risk, in particular the presence of a peritoneal carcinosis or of a tumour in site.

[6] Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A.J Clin Oncol. 2004 ;22:229-37
[7] Thésaurus de cancérologie digestive SNFGE, 2007
[8] Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. N Engl J Med 2005 ; 352 : 476-87.

4.4. Target population

The target population of AVASTIN is made up of patients who have failed first-line chemotherapy which did not involve AVASTIN.

According to experts, first-line chemotherapy without AVASTIN should be offered to patients at risk of haemorrhage, mainly because of a related peritoneal carcinosis or a tumour in site. This sub-population accounts for about 20% of cases.

The incidence of carcinoma of the colon or rectum was approximately 36,000 cases in 2000.[9] Almost half of all cases involve metastatic stages.[10]

Assuming that all patients who undergo first-line treatment will relapse and will subsequently receive second-line treatment, the target population of AVASTIN in this extension of indication would be 3,600 patients a year.

The committee notes that this estimate might be excessively high because of the recent introduction of first-line targeted therapy involving cetuximab (MA awarded in July 2008), which would (according to an unpublished survey supplied by the pharmaceutical firm) reduce this population estimate by 8%. This would make the target population for AVASTIN 3,300 patients a year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in this extension of indication.

[9] Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000 (INVS 2003)
[10] EPAR Erbitux 2004