HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

5 December 2007

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

Applicant : ROCHE

Bevacizumab
List I
Restricted to hospital use
L01XC07

Date of Marketing Authorisation: January 12, 2005 (centralised Marketing Authorisation)
Revision of Marketing Authorisation: March 27, 2007 extension of indication

Reason for request: Inclusion on the list of medicines approved for hospital use in the extension of indication “First-line therapy in patients with metastatic breast cancer, in combination with paclitaxel”.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

bevacizumab

1.2. Indication

AVASTIN (bevacizumab) is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum, in combination with intravenous 5-fluorouracil/folinic acid chemotherapy with or without irinotecan

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

1.3. Dosage

General:
AVASTIN must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.
It is recommended to continued the treatment until progression of the underlying disease.
The initial dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.
The initial dose must be administered following chemotherapy, all subsequent doses may be administered prior to or following chemotherapy.

Do not administer as an intravenous push or bolus.
AVASTIN infusions must not be administered, or mixed with glucose solutions.

Metastatic breast cancer:
The recommended dose of AVASTIN is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

L	Antineoplastics 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

Medicines indicated in the treatment of metastatic breast cancer: hormone therapy, cytotoxic agents and the monoclonal antibody trastuzumab (HERCEPTIN: only for HER2 positive tumours).

3 ANALYSIS OF AVAILABLE DATA

In the extension of the indication "first-line treatment of patients with metastatic breast cancer, in combination with paclitaxel", the laboratory has submitted the pivotal Marketing Authorisation study (study E2100).

Objectives:
To evaluate the efficacy of the bevacizumab/paclitaxel combination compared to paclitaxel alone, as first-line treatment, in patients with locally recurrent or metastatic breast cancer.

Methodology:
This was a randomised, open-label, parallel-group study. Patients were treated until progression of the disease.
Randomisation was stratified according to the following factors: recurrence-free intervals (< or ≥ 24 months), number of metastatic sites (< or ≥ 3), previous adjuvant chemotherapy treatment (yes or no), and status of oestrogen receptors (positive, negative, or unknown).

Endpoints:
The primary endpoint for efficacy was median progression-free survival, defined as the time between randomisation and progression of the disease or death, regardless of cause.
Secondary endpoints were overall survival (defined as the time between randomisation and death), objective response rate, objective response duration, quality of life, and treatment toxicity.

Inclusion criteria:

- Histology or cytology confirmed breast carcinoma, in locally recurrent or metastatic stage;
- Patients ≥ 18 years;
- Patients not previously treated with chemotherapy for locally recurrent or metastatic breast cancer;
- ECOG[1] performance status 0 or 1.

Exclusion criteria:

- Patients with HER2-overexpression tumours unless previously treated with Herceptin (trastuzumab). If the HER2 status was unknown, patients were not included unless Herceptin was contraindicated or inappropriate.

Results:

A total of 722 patients were included:

- 368 patients in the bevacizumab/paclitaxel group (PAC/BEV group).
  Treatment cycles had a duration of 4 weeks. Dosing schedule was as follows: 90 mg/m^2 of paclitaxel as 1-hour IV infusion every week for 3 weeks followed by one off-week, combined with IV infusion of 10 mg/kg of bevacizumab administered at week 1 and week 3.
- 354 patients in the paclitaxel alone group (PAC group). The dosing and administration schedule for paclitaxel were identical to those of the PAC/BEV group.

The median duration of treatment was 9.6 months for the PAC/BEV group compared to 5.8 months for the PAC group.

Among the randomised patients, 65% had previously been treated with adjuvant chemotherapy for a localised tumour, 19% of which with taxanes and 49% with anthracyclines.

Table 1: Characteristics of patients included in study E2100

	PAC/BEV	**PAC**
N (ITT)	368	354
Median age (years - ET)	55.5 ± 11.7 [27 – 85]	
Local recurrence	9/366 (2.5 %)	4/353 (1.1 %)
Metastatic cancer	357/366 (97.5 %)	349/353 (98.9 %)
HER 2 Overexpression		
- Positive	10/368 (2.7 %)	6/354 (1.7 %)
- Negative	331/368 (89.9 %)	316/354 (89.3 %)
- Unknown	27/368 (7.3 %)	32/354 (9.0 %)

[1] ECOG (Eastern Cooperative Oncology Group) Scale: 4 grades are defined: Grade 0 = Fully active – the patient undertakes normal activity without restriction; Grade 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature without significant discomfort; Grade 2 = Ambulatory and capable of all self-care but unable to carry out any work activities for more than 50% of waking hours; Grade 3 = Capable of only limited care, confined to bed or chair for more than 50% of waking hours ; Grade 4 = Completely disabled, totally confined to bed or chair, unable to undertake self-care .

The protocol provided for two interim analyses:

1. A first interim analysis was conducted on 395 observed events*. An event was defined as progression of the disease or death.
   - 188 events were observed in the PAC/BEV group: 153 progression of disease and 35 deaths;
   - 207 events were observed in the PAC group: 183 progression of disease and 24 deaths;

Median progression-free survival was 13.3 months in patients treated with the bevacizumab/paclitaxel combination compared to 6.7 months in patients treated with paclitaxel alone, i.e., a 52% decrease in the relative risk (HR = 0.48; 95% CI [0.39; 0.59]; p<0.0001).
An increase in median progression-free survival was also observed in each stratum of patients (defined in the methodology paragraph).

Among those patients whose tumour was evaluable at baseline (246 patients of the PAC/BEV group and 268 patients of the PAC group), the objective response rate (secondary efficacy endpoint) was 36.2 % (89/246) in the PAC/BEV group compared to 16.4 % (44/248) in the PAC group, i.e., a 19.8% difference between the two groups (95% CI [12.3 %; 27.2 %], p < 0.0001).

2. A second interim analysis was conducted on 337 events**. An event was defined as a death.
   - 169 deaths were observed in the PAC/BEV group;
   - 168 deaths were observed in the PAC group;

Median overall survival (secondary efficacy endpoint) was 25.7 months, 95% CI [24.18; 29.44] in the PAC/BEV group compared to 23.8 months, IC 95% [21.22; 27.66] in the PAC group, i.e., a non-significant reduction in the relative risk between the two groups (HR = 0.82, 95% CI [0.66;1.03], NS).
Overall survival at 1 year of treatment, an analysis not planned in the study protocol, was found to be more significant in the paclitaxel/bevacizumab group than in the paclitaxel group: 82.3 % compared to 73.8% (p = 0.007). Patient quality of life was not analysed for the totality of questionnaires (various data was found to be missing) and, as this was an open-label study, the results of this analysis can therefore not be taken into consideration in this opinion.

* 546 events were required for the final analysis.
**481 events were required for the final analysis.

Adverse events:

- 67.1% of patients of the PAC/BEV group compared to 46.2% of patients of the PAC group experienced at least one grade 3 to 5 non-haematological adverse event or a grade 4 or 5 haematological adverse event.
- The grade 3 and 4 adverse events observed at a frequency greater than 2% in the PAC/BEV group compared to the PAC group were the following: sensory neuropathies (23.2% compared to 16.5%), hypertension (15.5% compared to 1.4%), fatigue (8.6% compared to 4.9%), diarrhoea (3.6% compared to 1.4%), dehydration (2.5% compared to 0.3%), muscle fatigue (4.4% compared to 2.3%) and proteinuria (3.0% compared to 0%).
- 5 patients of the PAC/BEV group experienced congestive heart failure compared to 0 in the PAC group. These five patients have previously received anthracycline treatments.

Conclusion:

The first interim analysis of study E2100 results demonstrated that patients with metastatic breast cancer under first-line therapy of paclitaxel/bevacizumab combination had a greater median progression-free survival rate than those treated with paclitaxel alone: 13.3 months compared to 6.7 months. The efficacy of this first-line metastatic breast cancer treatment has only been evaluated in patients with negative HER2 tumours.

A second interim analysis on overall survival, conducted approximately 8 months later, did not reveal any difference between the two treatment groups: 25.7 months in the PAC/BEV group compared to 23.8 months in the PAC group (HR = 0.82, 95% CI [0.66;1.03], NS).

The Transparency Committee emphasises that paclitaxel in weekly monotherapy is not usually employed in France as first-line metastatic breast cancer treatment. The selection of this comparator medicine and its dosing regimen (90 mg/m^2 every week instead of 175 to 220 mg/m^2 every 3 weeks) has not been justified.

This study does not allow for the quantification of the therapeutic benefit of the bevacizumab/paclitaxel combination with regards to the usually employed combinations for first-line therapy in France, in particular capecitabine/docetaxel.

The grade 3 and 4 adverse events were more frequently observed in the group of patients treated with the paclitaxel/bevacizumab combination than in the group of patients treated with paclitaxel alone: 67.1% compared to 46.2%.

The main adverse events whose frequency was greater in the paclitaxel/bevacizumab group than in the paclitaxel group were sensory neuropathies, hypertension and proteinuria. In the paclitaxel/bevacizumab group, 5 cases of congestive heart failure were observed.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Breast cancer is a life-threatening disease.
This medicinal product is intended as a curative treatment.
The efficacy/adverse effect ratio is high.
There are treatment alternatives.
This medicinal product is intended as a first-line treatment.

In terms of public health, the burden due to breast cancer is very high. The burden on the sub-population of patients suffering from metastatic breast cancer and likely to benefit from AVASTIN treatment is high.
The availability of novel therapeutic methods in treating metastatic breast cancer, particularly when the tumour is HER2 negative, is an identified public health priority.
The impact of AVASTIN in combination with paclitaxel on morbidity-mortality and quality of life related to metastatic breast cancer, compared to the current care management, cannot be estimated from the available data. Extrapolation of experimental data is not guaranteed, particularly due to the fact that the comparator product selected does not correspond to customary practice in France.
In light of the current state of knowledge, the exact response provided by AVASTIN to the identified public health requirement cannot be assessed.
Therefore, it is not expected that AVASTIN will have any public health benefit.

The actual benefit of AVASTIN is substantial.

4.2. Improvement in actual benefit

AVASTIN provides a moderate improvement in actual benefit (IAB III) in the care management of patients with metastatic breast cancer, of HER 2 negative status, or those not eligible for Herceptin treatment.

4.3. Therapeutic use

First-line treatment of metastatic breast cancer depends on:

- The time elapsed between adjuvant treatment and metastatic first-line therapy (< 6 months, between 6 months and 1 year, > 1 year),
- The presence or absence of hormone receptors and/or HER2 overexpression,
- The type of metastases: number of sites, size or localisation (in particular visceral),
- The patient's general condition,
- The type of adjuvant therapy.

1/ In the absence of low prognosis factors and presence of hormone receptors, the first-line treatment is hormone therapy.

2/ In the presence of low prognosis factors, the first-line treatment is chemotherapy. If low prognosis factor associated with the presence of hormone receptors, chemotherapy and hormone therapy may be undertaken in a sequential manner.

- Positive HER2 tumour: The recommended first-line treatment is trastuzumab, combined with paclitaxel or docetaxel.

- Negative HER2 tumour: Polychemotherapies, based on anthracyclines and taxanes, are employed. If the patient was previously treated with anthracyclines, taxanes are combined with capecitabine. In case of failure, vinorelbine (alone or in combination with fluorouracil), and gemcitabine are then employed.

Paclitaxel in monotherapy is not recommended as a first-line treatment of metastatic breast cancer.

AVASTIN in combination with paclitaxel is a new first-line therapeutic modality in the treatment of metastatic breast cancer in patients with negative HER2 status: its importance in therapeutic use is yet to be determined.

4.4. Target population

The target population of AVASTIN comprises patients with metastatic breast cancer. This population is composed of two sub-populations:
- Immediately diagnosed metastatic stage;
- Localised stage that progress into metastatic stage;

In France, these two sub-populations may be estimated from the following data:
- In 2000, the incidence of breast cancer was 42,000 cases. As the mean annual rate of change in the incidence of breast cancer is 2.4% per year[2], the number of cases of breast cancer in 2007 can be estimated at 48,000.
- Immediately diagnosed metastatic stage cancer represents 5%[3] to 15%[4] of cases, i.e., between 2,400 and 7,200 patients.
- Metastatic stage following local progression represents 28%[5] of cases, i.e., approximately 13,500 patients.
- 85%[5] of patients are likely to undergo chemotherapy.

The efficacy of the bevacizumab/paclitaxel combination as first-line treatment of metastatic breast cancer has only been shown in patients with negative HER2 tumour.
The HER2 gene is present in 20% to 30% of cases[6].

Based on this information, the target population of AVASTIN is estimated between 9,400 and 14,000 patients.

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 the extension of indication.

[2] Trétarre et al. Cancer du sein chez la femme : incidence et mortalité, France 2000. BEH n°4/2004 du 26 octobre 2004.
[3] FRANCIM [Association of French Cancer Registries]
[4] FLNCC [National Federation of Centres in the Fight against Cancer] survey
[5] Louis Harris 2003 Survey
[6] Herceptin Opinion (4 October 2006)