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TRANSPARENCY COMMITTEE

OPINION

27 January 2010

ABRAXANE 5 mg/ml, powder for suspension for infusion
B/1 100 mg vial (CIP: 384 418-7)

Applicant: ABRAXIS BIOSCIENCE SAS

Paclitaxel

ATC code: L01CD01

List I
Medicine for hospital prescription only. Prescription restricted to oncology and haematology specialists or doctors with cancer training. Medicine requiring special monitoring during treatment.

Date of Marketing Authorisation (centralised): 11 January 2008

Reason for request: Inclusion on the list of medicines approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1   CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1.   Active ingredient
paclitaxel

1.2.   Background
ABRAXANE contains nanoparticles of paclitaxel bound to human serum albumin, the paclitaxel being in an amorphous state. Albumin is known to mediate endothelial transcytosis of plasma constituents and *in vitro* studies have demonstrated that the presence of albumin enhances paclitaxel transport across endothelial cells.

1.3.   Indication
"ABRAXANE monotherapy is indicated for the treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated."

1.4.   Dosage
"The recommended dose of ABRAXANE is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks."

2   SIMILAR MEDICINAL PRODUCTS

2.1.   ATC Classification (2009)
L   Antineoplastic and immunomodulating agents
L01   Antineoplastic agents
L01C   Plant alkaloids and other natural products
L01CD   Taxanes
L01CD01   Paclitaxel

2.2.   Medicines in the same therapeutic category
    2.2.1. Comparator medicines

- TAXOL (paclitaxel) and its generics
- TAXOTERE (docetaxel)

2.3.   Medicines with a similar therapeutic aim
Cytotoxic agents used in the treatment of breast cancer alone or in combination:

Anthracyclines:
- ADRIBLASTINE (doxorubicin) and its generics
- FARMORUBICINE (epirubicin)

Other intracalating agents:
- NOVANTRONE (mitoxantrone)

Alkylating agents:
- ENDOXAN ASTA (cyclophosphamide)
- AMETYCINE (mitomycin C)

Antimetabolites:
- FLUORO-URACILE ICN (fluorouracil)
- METHOTREXATE BELLON (methotrexate)

Antimitotic agents:
- VELBE (vinblastine)
- NAVELBINE (vinorelbine)

Pyrimidine analogues:
- GEMZAR (gemcitabine)
- XELODA (capecitabine)

Monoclonal antibodies:
- AVASTIN (bevacizumab)
- HERCEPTIN (trastuzumab)

- Hormone therapy: anti-aromatases, anti-œstrogens and progestogens.

3 ANALYSIS OF AVAILABLE DATA

ABRAXANE is composed of paclitaxel bound to human serum albumin. It differs from the standard paclitaxel formulation already available in hospitals in that the solvent is replaced with albumin.

The dossier submitted for the application for inclusion on the list of medicines approved for hospital use as monotherapy in the treatment of metastatic breast cancer in the second-line plus setting comprises:
- One Phase II study (CA 201)
- One Phase III study (CA 012)
- One comparative Phase II study (CA024) versus docetaxel in the first-line treatment of metastatic breast cancer. This study does not relate to the indication to be evaluated (second-line plus) and will not therefore be analysed
- One comparison of the safety results from the pivotal study of ABRAXANE versus historical safety data for docetaxel[1]. The lack of a precise methodology for comparing the percentages of adverse events observed in each of the two studies makes it impossible to draw any conclusions from these data.

3.1. Efficacy
Study CA 201
Open-label, randomised Phase II study, conducted in China, which compared the efficacy and safety of ABRAXANE versus paclitaxel in the first- or second-line treatment of metastatic breast cancer.

Inclusion criteria:
- Patients aged between 18 and 70, not pregnant or breast feeding, with measurable metastatic breast cancer which was histologically and cytologically confirmed and who had a life expectancy of more than 12 weeks
- No previous chemotherapy for metastatic breast cancer or following failure of chemotherapy for metastatic breast cancer
- No other malignant tumour apart from non-melanoma skin cancers or in situ cervical cancer
- Acceptable laboratory test results at study entry
- ECOG performance status <1
- No symptoms of heart failure or serious ECG abnormality

The treatments:
- ABRAXANE 260 mg/m^2 administered intravenously over 30 minutes once every 3 weeks, without standard premedication
- Paclitaxel 175 mg//m^2, administered intravenously over 3 hours once every 3 weeks, with standard premedication with dexamethasone and antihistamines

The primary efficacy endpoint was the percentage of patients who achieved a (complete[2] or partial[3]) overall response.
Secondary endpoints: Time to disease progression, progression-free survival and overall survival.

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1 Harvey V, Mouridsen H, Semiglazov V, Jakobsen E, Voznyi E, Robinson BA, Groult V, Murawsky M, and Cold S. Phase III trial comparing Three Doses of Docetaxel for Second-Line Treatment of Advanced Breast Cancer. Journal of Clinical Oncology, 2006, 24:4963-4970

2 corresponds to disappearance of all the target lesions and maintenance of this response for 4

3 corresponds to a reduction of $\geq$ 30% in the longest diameter of the target lesions compared with the status on inclusion and maintenance of this response for 4 weeks

Results:

In total, 212 patients were included. The efficacy data for 210 are presented (no details are available regarding the reasons for the two other patients being excluded from the analysis). The average age of the patients was 49.2. First-line patients represented 60% and second-line patients 40% of the cases.

The overall response rate was 54% in the ABRAXANE group and 29% in the paclitaxel group (p<0.001). The results for the first-line treatment subgroup were in favour of ABRAXANE in respect of the primary endpoint. In the second-line subgroup (corresponding to the population covered by the Marketing Authorisation), however, no difference was observed in terms of the overall response rate between the two paclitaxel formulations.
No difference was observed between the two treatments in terms of the time to disease progression, progression-free survival and overall survival.

Study CA012
Open-label, randomised Phase III study which compared the efficacy and safety of ABRAXANE versus paclitaxel in the first- and second-line plus treatment of metastatic breast cancer.

Inclusion criteria:
- Patients aged 18 and above with measurable metastatic breast cancer which was histologically and cytologically confirmed
- A life expectancy of more than 12 weeks
- Candidates for monotherapy with paclitaxel
- No previous treatment with paclitaxel or docetaxel for metastatic carcinoma
- No recurrence of a metastatic tumour following adjuvant treatment with paclitaxel or docetaxel in the last year
- No history of another malignant tumour during the last 5 years (apart from non-melanoma skin cancers, cervical intraepithelial neoplasia or in situ cervical cancer)

Primary efficacy endpoint: Percentage of patients with a confirmed complete or partial target lesion response.
The target lesions correspond to tumour sites (initial tumour, metastatic sites) selected on inclusion for evaluation of the tumour response.

Secondary endpoints:
- Percentage of patients with a complete or partial response for all lesions and all cycles
- Time to disease progression, defined as the time between randomisation and tumour progression
- Progression-free survival, defined as the time between randomisation and tumour progression or death
- Overall survival
- Quality of life

The statistical analysis comprised 3 steps:
- Establish the non-inferiority of ABRAXANE versus paclitaxel in the ITT population. Non-inferiority was established if the lower limit of the 95% confidence interval for the ratio of the response rates between the two treatments (ABRAXANE/paclitaxel) was greater than 0.75
- Carry out a superiority test of ABRAXANE versus paclitaxel in the ITT population in the event of demonstration of non-inferiority
- Carry out a superiority test of ABRAXANE versus paclitaxel in the subgroup of first-line patients

The treatments:
- ABRAXANE 260 mg/m^2 administered intravenously over 30 minutes once every 3 weeks, without standard premedication
- Paclitaxel 175 mg//m^2, administered intravenously over 3 hours once every 3 weeks, with standard premedication with dexamethasone and antihistamines
Six cycles of treatment were planned in each of the groups.

Three efficacy assessments were carried out: the first one by the investigator (inv: investigator), the second by independent radiologists under blinded conditions (irl: independent radiology laboratory) and the third being an algorithm derived from the two previous assessments (rec: reconciliated).

Results:

In total, 460 patients were included. The ITT analysis related to 454 patients, 229 in the ABRAXANE group and 225 in the paclitaxel group.
The average age of the patients was 53.2. Postmenopausal patients represented 83% of the cases and 79% had visceral metastases.
The patients were receiving first-line treatment in 41% and second-line plus treatment in 59% of the cases (42% second-line and 13% third-line).

The confirmed target lesion response rate was 31.4% in the ABRAXANE group compared with 16.4% in the paclitaxel group, $p<0.001$. The ratio between the two treatments was 1.876 (1.322 – 2.661).
The lower limit of the 95% confidence interval for the ratio of the response rates between the two treatments was 1.322 and hence higher than the 0.75 limit specified in the protocol to establish non-inferiority.

Table 1: Efficacy results from study CA-012 – Superiority test for all patients and for the patients receiving first-line treatment with the investigational product

	ABRAXANE	Paclitaxel	Ratio	p
invTLRR				
All patients	72/229 31.4% (25.43 – 37.45)	37/225 16.4% (11.60 – 21.29)	1.876 (1.329 – 2.649)	<0.001
Patients receiving first-line treatment with the product	38/97 39.2% (29.46 – 48.89)	23/89 25.8% (16.75 – 34.94)	1.516 (0.986-2.332)	0.053
irl TLRR				
All patients	37/176 21.0% (15.00 – 27.04)	13/171 7.6% (3.63 – 11.57)	2.650 (1.472 – 4.769)	0.001
Patients receiving first-line treatment with the product	23/74 31.1% (20.54 – 41.63)	8/64 12.5% (4.40 – 20.60)	2.486 (1.196 – 5.168)	0.009
recTLRR				
All patients	55/229 24.0% (18.48 – 29.55)	25/225 11.1% (7.00 – 15.22)	2.110 (1.376 – 3.236)	<0.001
Patients receiving first-line treatment with the product	33/97 34.0% (24.59 – 43.45)	16/89 18.0% (10.00 – 25.96)	1.892 (1.121 – 3.193)	0.013

TLRR: overall target lesion response rate

Results for secondary endpoints:

1/ In the overall population:
The overall response rate for all the lesions was 24.0% compared with 11.1%, p < 0.001.
The median time to disease progression was 23.0 weeks in the ABRAXANE group compared with 16.6 weeks in the paclitaxel group, p = 0.002.
The median progression-free survival time was 22.7 weeks in the ABRAXANE group compared with 16.6 weeks in the paclitaxel group, p=0.003. No difference was observed between the groups in terms of quality of life.
There was no difference between the groups in terms of median overall survival (65.0 weeks compared with 55.3, p = 0.322).

2/ In the second-line plus subgroup (population covered by the Marketing Authorisation):
In view of the chosen methodology (two superiority tests, one in the overall population and the other in the first-line subgroup), the results available in the second-line plus setting apply only to the secondary endpoints for the study.
The overall response rate for all the lesions was 26.5% in the ABRAXANE group and 13.2% in the paclitaxel group, p = 0.006.
The median time to disease progression was 20.9 weeks in the ABRAXANE group compared with 16.1 weeks in the paclitaxel group, p = 0.001.
The median progression-free survival time was 20.6 weeks in the ABRAXANE group compared with 16.1 weeks in the paclitaxel group, p = 0.01.
Median overall survival was 56.4 weeks in the ABRAXANE group and 46.7 weeks in the comparator group, p = 0.020.

3.2. Adverse effects

Discontinuations of treatment linked to adverse effects were observed in 7% of patients in the ABRAXANE group compared with 4% in the paclitaxel group. The observed difference was related mainly to neurotoxicity.

The incidence of grade 3 sensory neuropathies related to treatment was higher in the ABRAXANE group than in the paclitaxel group: 10% compared with 2%.

Neurotoxicity under paclitaxel is a known adverse effect, the sensory effects of which generally regress or disappear a few months after the end of treatment. The course of peripheral neuropathy after more than 6 cycles of ABRAXANE (return to baseline or sequelae) has not been evaluated and remains unknown.

Grade 3-4 neutropenia was observed in 30% of the patients in the ABRAXANE group compared with 46% of the patients in the paclitaxel group. Febrile neutropenia was observed in 4 patients in the ABRAXANE group compared with 1 patient in the paclitaxel group.

3.3. Conclusion

The efficacy and safety of ABRAXANE (paclitaxel bound to albumin) were evaluated in an open-label, randomised study versus paclitaxel, in 454 patients with metastatic breast cancer.

First-line patients represented 41% and second-line plus patients 59% of the cases (42% second-line and 13% third-line).

In the overall study population, the confirmed target lesion response rate (primary efficacy endpoint) was higher with ABRAXANE than with paclitaxel (31.4% compared with 16.4%, $p < 0.001$), i.e. a ratio of 1.876 (1.322 – 2.661) between the two treatments. The lower limit of the 95% confidence interval for the ratio of the response rates between the two treatments (1.322) was higher than the 0.75 limit specified in the protocol for the establishment of non-inferiority. The overall response rate for all the lesions was higher with ABRAXANE than with paclitaxel (24% compared with 11%, $p < 0.001$). The median time to disease progression was longer with ABRAXANE than with paclitaxel (22.7 weeks compared with 16.6 weeks, $p = 0.002$), as was the median progression-free survival time (23 weeks compared with 17 weeks, $p = 0.003$). There was no difference between the two treatments in terms of median overall survival.

In the second-line plus subgroup (population covered by the Marketing Authorisation), in view of the chosen methodology (following the non-inferiority outcome, two superiority tests were conducted, one in the overall population and the other in the first-line subgroup), the results available in this population apply only to the secondary endpoints for the study. The overall response rate for all the lesions was higher with ABRAXANE than with paclitaxel (26.5% compared with 13.2%, $p = 0.006$). The median time to disease progression was around a month longer with ABRAXANE than with paclitaxel (20.9 weeks compared with 16.1 weeks, $p = 0.001$). The median progression-free survival time was around a month longer with ABRAXANE than with paclitaxel (20.6 weeks compared with 16.1 weeks, $p = 0.01$). Median overall survival was 56.4 weeks in the ABRAXANE group and 46.7 weeks in the comparator group, $p = 0.020$.

Discontinuations of treatment linked to adverse effects were more frequent with ABRAXANE than with paclitaxel (7% compared with 4%), the observed difference being related mainly to neurotoxicity. The frequency of grade 3 sensory neuropathies related to treatment was higher with ABRAXANE than with paclitaxel (10% compared with 2%). The course of peripheral neuropathy after more than 6 cycles of ABRAXANE (return to baseline or sequelae) has not been evaluated and remains unknown. However, the sensory manifestations observed with paclitaxel generally regress or disappear a few months after the end of treatment.

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4   TRANSPARENCY COMMITTEE CONCLUSIONS

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4.1.   Actual benefit

Breast cancer is life-threatening.

This medicinal product is intended as curative therapy.

The efficacy/adverse effects ratio is high.

This is a second-line plus therapy.

Alternative medicinal products exist.

Public health benefit:

In France, breast cancer remains the most frequent type of cancer in women (around 50,000 new cases in 2005). In terms of mortality, it is the number one cause of death by cancer in women[4]. The public health burden posed by breast cancer is therefore high. The burden relating to the subgroup of patients with metastatic breast cancer likely to benefit from second-line plus treatment with ABRAXANE is moderate.

Improving the management of patients with cancer and their quality of life constitutes a public health need which comes within the scope of the established priorities (Public Health Law 2004, Cancer Plan, Plan for improving the quality of life of patients with chronic diseases).

In view of the data available from a subgroup analysis of the pivotal study versus paclitaxel, no additional impact is expected in terms of morbidity and mortality in patients treated with ABRAXANE compared with paclitaxel.

Furthermore, no improvement in quality of life was demonstrated in the pivotal study, and an increase in neurotoxicity (grade 3 neuropathies), liable to result in premature discontinuations of treatment, was observed in this same study.

The medicinal product ABRAXANE does not provide any additional cover of the identified public health need compared with paclitaxel.

Consequently, it is not expected that ABRAXANE will benefit public health.

The actual benefit of this medicinal product is substantial.

4.2.   Improvement in actual benefit (IAB)

ABRAXANE provides a minor improvement in actual benefit (level IV) compared with TAXOL.

4.3.   Therapeutic use

In the absence of poor prognostic factors, notably visceral involvement and in the presence of hormone receptors, the first-line treatment of metastatic breast cancer is hormone therapy.

In the presence of poor prognostic factors, the first-line treatment is chemotherapy. If hormone receptors are present, chemotherapy and hormone therapy may also be used sequentially. In cases of tumoral HER2 overexpression, the recommended first-line treatment is trastuzumab in combination with paclitaxel or docetaxel regardless of hormonal status[5] [6]. In the absence of HER2 overexpression, the reference treatment is a combination of anthracycline and taxane.

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4 Belot A *et al*. Cancer incidence and mortality in France over the period 1980-2005. Rev Epidemiol Sante Publique. 2008 Jun;56(3): 159-75. Epub 2008 Jun 10
http://www.invs.sante.fr/surveillance/cancers/estimations_cancers/default.htm [Access 02 11 2009]
5 Recommandations pour la pratique clinique: Saint Paul de Vence 2007 « cancers du sein »
6 National Cancer Institute recommandations. Breast Cancer Treatment (WWW.cancer.gov/ updated: 02/01/2008)

In patients who have received high cumulative doses of anthracyclines during adjuvant/neoadjuvant therapy, contraindicating their reintroduction in the metastatic phase because of their cardiotoxicity, treatment with taxane alone or in combination with other medicinal products (docetaxel/capecitabine, gemcitabine/paclitaxel, bevacizumab/ paclitaxel) may be used. Two trials compared docetaxel with paclitaxel and showed docetaxel to be superior to paclitaxel as monotherapy in the second-line treatment of metastatic breast cancer[7] [8]. Furthermore, weekly paclitaxel seems to have greater efficacy than paclitaxel administered every 3 weeks[9].

In the absence of comparison with an optimal regimen of paclitaxel use (weekly) or with docetaxel, the place of ABRAXANE monotherapy in the treatment strategy remains to be specified.

4.4.   Target population

In 2005, the incidence of breast cancer in France was 49,814[10].

The target population for ABRAXANE is represented by patients with metastatic breast cancer following failure of first-line treatment. The population of patients with metastatic breast cancer combines two subpopulations:
   -    metastatic disease at presentation (5 %[11] to15%[12] of cases at diagnosis)
   -    localized disease which will progress to metastatic disease (28%[13] of cases)

85%[13] of patients with metastatic disease are likely to receive chemotherapy as a first-line treatment, i.e. 13,970 to 18,200 patients.

In view of the low rate of maintenance of sustained remission following first-line treatment, the mortality rate at this stage and the associated comorbidities, experts estimate that around three quarters of patients would be candidates for second-line therapy, i.e. 10,400-13,600 patients.

The WHO data indicate taxane use as follows:
- in 56% of cases as a first-line treatment (not concerned by the indication)
- in 32% of cases as a second-line treatment (i.e. 3,330 to 4,350 patients)
- in 19% of cases as a third-line treatment (and after) (i.e. 1,970 to 2,580 patients)

The number of patients with metastatic breast cancer in a second-line plus setting likely to be treated with a taxane is thus estimated at 5,500 to 7,000 per year.

The committee stresses that this is a maximalist estimate because it is based on a rate of taxane use both as monotherapy and in combinations. Consequently, the ABRAXANE population in the indication covered by the Marketing Authorisation (monotherapy) is probably lower.

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 indication and at the dosage in the Marketing Authorisation.

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7 Jones S E, Erban J, Overmoyer B, et al: Randomized Phase III Study of Docetaxel Compared With Paclitaxel in Metastatic Breast Cancer. J Clin Oncol 2005; 23: 5542-5551

8 Vu T, Ellard S, Speers C H., et al: A. Survival outcome and cost-effectiveness with docetaxel and paclitaxel in patients with metastatic breast cancer: a population-based evaluation. Ann Oncol, 2008; 19: 461-464

9 Seidman A D, Berry D, Cirrincione C, et al: Randomized Phase III Trial of Weekly Compared With Every-3-Weeks Paclitaxel for Metastatic Breast Cancer, With Trastuzumab for all HER-2 Overexpressors and Random Assignment to Trastuzumab or Not in HER-2 Nonoverexpressors: Final Results of Cancer and Leukemia Group B Protocol 9840. J Clin Oncol 2008; 26:1642-1649

10 InVS, HCL, Francim, INCa: Présentation des dernières données d'incidence et de mortalité par cancer en France et des tendances des 25 dernières années (1980-2005) – Press conference of 21 February 2008

11 FRANCIM

12 FLNCC survey

13 Louis Harris survey 2003