HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

15 February 2006

Taxotere 20 mg, concentrate and solvent for solution for infusion
B/1 vial of Taxotere and 1 vial of solvent (CIP code: 559 517-9)

Taxotere 80 mg, concentrate and solvent for solution for infusion
B/1 vial of Taxotere and 1 vial of solvent (CIP code: 559 518-5)

Applicant: **Aventis**

docetaxel

List I

Reserved for hospital use

European Marketing Authorisation: 27 November 1995 - Amendments: 17 July 1998, 28 Aug-2000, 09 January 2003, 20 October 2004 and 05 January 2005

Reason for application: inclusion on the list of medicinal products reimbursed by hospitals with 2 extensions of indication
"Taxotere (docetaxel) in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer."
"Taxotere (docetaxel) in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumours overexpress HER2 and who have not previously received chemotherapy for metastatic disease."

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

docetaxel

1.2. Indications

Breast cancer

Taxotere (docetaxel) in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

Taxotere (docetaxel) in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumours overexpress HER2 and who have not previously received chemotherapy for metastatic disease.

Taxotere (docetaxel) in combination with doxorubicin is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic chemotherapy for this condition.
Taxotere (docetaxel) monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous chemotherapy should have included an anthracycline or an alkylating agent.
Taxotere (docetaxel) in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.

Non-small cell lung cancer

Taxotere (docetaxel) is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.
Taxotere (docetaxel) in combination with cisplatin is indicated for the treatment of patients with non-resectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition.

Prostate cancer

Taxotere (docetaxel) in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer.

The use of docetaxel should be confined to units specialised in the administration of cytotoxic chemotherapy and docetaxel should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy.

1.3. Dosage

In the adjuvant treatment of operable node-positive breast cancer, the recommended dose of docetaxel is 75 mg/m^2 administered after doxorubicin 50 mg/m2 and cyclophosphamide 500 mg /m2 every 3 weeks for 6 cycles.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

L	Antineoplastic and immunomodulating agents
01	Antineoplastic agents
C	Plant alkaloids and other natural products
D	Taxanes
02	docetaxel

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

paclitaxel (Taxol)

2.3. Medicines with a similar therapeutic aim

Cytotoxics used for the treatment of breast cancer, as monotherapy or in combination:

Anthracyclines:
- doxorubicin (Adriblastine; doxorubicin, Asta; doxorubicin, Dakota Pharm; doxorubicin, Teva)
- epirubicin (Farmorubicin)

Other intercalating agents:
- mitoxantrone (Novantrone)

Alkylating agents:
- cyclophosphamide (Endoxin, Asta)
- mitomycin C (Ametycine)

Antimetabolites:
- fluorouracil (fluorouracil, ICN; fluorouracil, Dakota Pharm; fluorouracil, Roche; fluorouracil, Teva)
- methotrexate (Ledertrexate; methotrexate, Bellon; methotrexate, Teva)

plant alkaloids:
- vinblastine (Velbe)
- vinorelbine (Navelbine)

Pyrimidine analogues:
Gemcitabine (Gemzar)
capecitabine (Xeloda)

Hormone therapy used for adjuvant treatment of breast cancer or treatment of metastatic disease:
- tamoxifen (Nolvadex) and its generic products
- anastrozole (Arimidex)
- letrozole (Femara)
- exemestane (Aromasine)

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy and safety assessment concerns the indication “adjuvant therapy for breast cancer”, with a reminder of the results for taxotere in combination with trastuzumab (Herceptin) in metastatic breast cancer, already assessed by the Committee on 20 July 2005.

A/ Reminder of results for the combination of Herceptin + Taxotere in metastatic breast cancer (see Opinion on Herceptin issued by the Committee on 20 July 2005).

Trial M77001:

Randomised, open phase II trial comparing Herceptin + Taxotere versus Taxotere alone in patients with metastatic breast cancer whose tumours overexpress HER2 (classed as IHC 3+) who had not previously received chemotherapy for metastatic disease.
Trial duration was 3 years.

Primary endpoint: level of response (complete and partial)
Secondary endpoints: median duration of response, median time to disease progression, overall survival.

Results:

Median age of patients was 53 or 55 years, depending on group.
The trial recruited 186 female patients, 92 in the Herceptin + Taxotere group and 94 in the docetaxel alone group.
Global response level was 61% (56/92) in the Herceptin + Taxotere group compared with 34% (32/94) in the Taxotere alone group (p=0.0002). A complete response was observed in 6 patients in the Herceptin + Taxotere group compared with 2 patients in the Taxotere alone group.
Median duration of response was 11.4 months in the Herceptin + Taxotere group compared with 5.1 months in the Taxotere alone group (p=0.0011).
Median time to tumour progression was 10.6 months in the Herceptin + Taxotere group compared with 5.7 months (p=0.0001).
Median survival was higher in the Herceptin + Taxotere group (30.5 months) than in the Taxotere alone group (22.1 months; p=0.0062).
No data are available on quality of life.

Side effects:

The most common side effects included:
- neutropenia (grade 3-4): 32% under Herceptin + Taxotere compared with 22% under Taxotere alone.
- febrile neutropenia : 23% under Herceptin + Taxotere compared with 17% under Taxotere alone.
- infection: 53% under Herceptin + Taxotere compared with 40% under Taxotere alone.
- skin rash: 24% under Herceptin + Taxotere compared with 12% under Taxotere alone.

There were more grade 3 (67% versus 55%) and grade 4 (34% versus 23%) events in the Herceptin + Taxotere group than in the Taxotere alone group.

Treatment withdrawals related to side effects were 12% in the Herceptin + Taxotere group compared with 24% in the Taxotere alone group.
Reduced left ventricular ejection fraction (≥15%) was observed in 17% of patients in the Herceptin + Taxotere group compared with 8% of patients in the Taxotere alone group.
There were 2.2% cases of symptomatic heart failure in the Herceptin + Taxotere group compared with 0% in the Taxotere alone group.

B/ As adjuvant therapy in breast cancer

The dossier contained one phase III open randomised pivotal trial (TAX 316) in 1,491 female patients with node-positive breast cancer. The trial compared adjuvant therapy with Taxotere combined with doxorubicin and cyclophosphamide (TAC regimen), with fluorouracil combined with doxorubicin and cyclophosphamide (FAC regimens).

Trial regimens:
- TAC: Taxotere 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m2 and cyclophosphamide 500 mg/m2
- FAC: doxorubicin 50 mg/m2 followed by fluorouracil 500 mg/m2 and cyclophosphamide 500 mg/m2

Both regimens were administered on day 1 of the cycle every 3 weeks for 6 cycles.

Primary endpoint: disease-free survival

Disease-free survival was defined as time from randomisation to date of onset of local recurrence or regional or metastatic spread, or onset of a second cancer or death from any cause.
The final analysis of the trial was planned for onset of 590 events concerning the primary endpoint.

Secondary endpoints: overall survival, quality of life measured by questionnaire QLQ-C30.

Results:
The results presented are from an interim analysis performed after 399 events concerning the primary endpoint, corresponding to a median follow-up of 55 months.

Median age of patients in the trial was 49 years.
Approximately one third of patients in each group were postmenopausal. Sixty-two percent (62%) of patients had 1–3 positive lymph nodes, and 37.9% had 4 or more.
In both groups, after the last cycle of chemotherapy, patients with oestrogen- and/or progesterone-positive receptors received tamoxifen 20 mg daily for 5 years. Adjuvant radiation therapy was prescribed in 69% of patients in the TAC group and 72% of patients in the FAC group.

Disease-free survival (primary endpoint) measured at 5 years was 75% in the TAC group and 68% in the FAC group, i.e. a 7% reduction in absolute risk of relapse (p=0.001).
Overall survival measured at 5 years was 87% in the TAC group and 81% in the FAC group, i.e. a 6% reduction in absolute risk of death (p=0.008).

In a subgroup analysis, disease-free survival measured at 5 years in patients with 1–3 positive nodes was 82% under TAC compared with 74% under FAC (p=0.0009). There was no significant difference between the two treatment regimens in patients with 4 or more positive nodes.
There was no difference in quality of life between the two groups.

The Committee notes that the reference treatment (FAC 50) used as a comparator in this trial conducted according to an American design is not the standard treatment given in France, which would rather be FEC 100 (epirubicin 100 mg/m^2 followed by fluorouracil 500 mg/m^2 and cyclophosphamide 500 mg/m^2).

3.2. Undesirable effects

Treatment withdrawals because of undesirable effects were 6% in the TAC group compared with1.1% in the FAC group.
There were more cases of grade 3 or 4 neutropenia under TAC than under FAC. The level of febrile neutropenia reported in the TAC group was high, namely 22.4% compared with 1.1% in the FAC group.
Cardiotoxicity was more common in the TAC group than the FAC group, particularly onset of congestive heart failure: 12 versus 3 cases.
There were no deaths from side effects.

Other data:

PACS 01 trial, unpublished, carried out under the aegis of the French *Fédération Nationale des Centres de Lutte Contre le Cancer* (27th Annual San Antonio Breast Cancer Symposium, December 8 - 11, 2004, San Antonio, Texas)

Between June 1997 and March 2000, in 85 centres in France and Belgium, nearly 2000 pre- and postmenopausal women with node-positive breast cancer without remote metastases, were treated after surgery with chemotherapy consisting of an equivalent number of 6 cycles every 3 weeks:

- either a sequential regimen of 3 cycles of FEC 100 (fluorouracil, epirubicin, Endoxan (cyclophosphamide)) followed by 3 cycles of Taxotere (100 mg/m2).

- or 6 cycles of FEC 100.

Patients in both groups received radiation therapy during the 4-week period following the end of their chemotherapy. Women with hormone receptor-positive tumours were given tamoxifen daily for 5 years. Median age of patients was 50 years.

The primary endpoint of the trial was disease-free survival. Secondary endpoints compared overall survival, safety and side-effects, and quality of life.

The trial showed a significant increase in disease-free survival in patients who had received the sequential regimen of 3 FEC followed by 3 Taxotere compared with the 6 FEC 100 group (78.3% and 73.2%, p= 0.014). Subgroup analysis showed benefit in the subgroup of patients over 50 and the subgroup of patients with 1-3 positive nodes.
After 60 months' follow-up, overall survival was 90.7% in the group treated with 3 FEC followed by 3 Taxotere compared with 86.7% in the comparator arm (p= 0.050).

There were more cases of grade 3 or 4 neutropenia in the FEC 100 group than in the comparator group from the 3rd cycle onwards, i.e. 20.2% compared with 10.9%.
Patients in the group given 3 FEC followed by 3 Taxotere had higher rates of febrile neutropenia (4.6% versus 1%) and of moderate to severe nail dystrophy (10.3% versus 1%) compared with the FEC 100 arm alone.
Cardiotoxicity was higher in the FEC 100 group than in the 3 FEC followed by 3 Taxotere group: 4 cases of clinical heart failure compared with none in the comparator arm.

3.3. Conclusion

In an open, randomised phase III trial (TAX 316) in 1,491 female patients with axillary lymph node-positive breast cancer, after median follow-up of 55 months, disease-free survival (primary endpoint) measured at 5 years was 75% in the TAC group and 68% in the FAC group, i.e. a 7% reduction in absolute risk of relapse (p=0.001).
In a subgroup analysis, disease-free survival measured at 5 years in patients with 1–3 positive nodes was 82% under TAC compared with 74% under FAC (p=0.0009). There was no significant difference in this rate between the two treatment regimens in patients with 4 or more positive nodes.

Overall survival measured at 5 years was 87% in the TAC group compared with 81% in the FAC group, i.e. a 6% reduction in absolute risk of death (p=0.008).
There was no difference in quality of life between the two groups.
The safety profile was better in the FAC group than in the TAC group, with in particular, less haematological toxicity (febrile neutropenia: 2% compared with 22.4%) and cardiotoxicity (4 cases of congestive heart failure compared with 2).

The Committee notes that the reference treatment (FAC 50) used as a comparator in this trial conducted according to an American design was not the standard treatment in France, which would rather be FEC 100 (epirubicin 100 mg/m2 followed by fluorouracil 500 mg/m2 and cyclophosphamide 500 mg/m2). In addition, since the publication of the results of trial PACS 01 in 2004, some French prescribers give Taxotere as adjuvant therapy for breast cancer using a different regimen from that in the experimental arm of trial TAX 316, i.e. the so-called sequential regimen of 3 x FEC 100 followed by 3 Taxotere. Data from the PACS 01 trial have shown that this regimen was similar in efficacy, with lower haematological toxicity.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

1/ In adjuvant therapy for breast cancer:

Breast cancer is a life-threatening disease.
This medicinal product is used as curative therapy.

Anticipated public health impact:

Breast cancer is a major public health burden. In the subpopulation of patients likely to benefit from Taxotere in this indication (as adjuvant therapy in patients with operable node-positive breast cancer), the burden is substantial.
The therapeutic requirement corresponding to this indication is insufficiently covered.
In view of data from the TAX 316 trial, a moderate theoretical impact may be anticipated with docetaxel used in combination with doxorubicin and cyclophosphamide, compared with the comparator arm of the trial. In real conditions of use in France, this impact would probably be lower in view of the results obtained with the sequential regimen of the PACS 01 trial (3 cycles of FEC 100 followed by 3 cycles of Taxotere).
Consequently, in the current state of knowledge, it is anticipated that the medicinal product Taxotere will have public health benefit in this indication. This benefit is moderate.

The efficacy/undesirable effects ratio for this medicinal product is high in this indication.

This medicinal product is a first-line drug (in combination with doxorubicin and cyclophosphamide).
Alternative drug therapies are available.

The actual benefit of this medicinal product is substantial.

2/ In the treatment of metastatic breast cancer with overexpression of HER2:
Metastatic breast cancer is a life-threatening disease.
This medicinal product is used as curative therapy.
The efficacy/undesirable effects ratio is high.
The medicinal product is a first-line drug (in combination with Herceptin).
Alternative drug therapies are available.

Anticipated public health impact:

Metastatic breast cancer is a substantial public health burden. In the subpopulation of patients likely to benefit from Taxotere in this indication (metastatic breast cancer with tumour overexpression of HER2), the burden is moderate.
The therapeutic requirement corresponding to this indication is insufficiently covered.
Data from the M 7701 trial have already been analysed in the Opinion issued by the Transparency Committee on trastuzumab on 20 July 2005. In view of the drug combinations used to date, docetaxel used in combination with trastuzumab still has a moderate impact in terms of morbidity and mortality and quality of life.
It is not certain that trial results will be translated into normal practice.
Consequently, in the current state of knowledge, it is anticipated that the medicinal product Taxotere used in combination with trastuzumab in this indication will have public health benefit. This benefit is minor.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit:

Taxotere combined with anthracycline chemotherapy substantially improves actual benefit (level II) in terms of morbidity and mortality compared with anthracycline chemotherapy alone.

After reviewing the data already assessed on 20 July 2005, the Committee maintains the level II IAB allocated to the combination of Taxotere and Herceptin in the indication of metastatic breast cancer with overexpression of HER2.

4.3. Therapeutic use

Treatment of localised node-positive breast cancer is based on resection surgery followed by so-called adjuvant chemotherapy to prevent recurrence.
Historical data in this population suggest that the 5-year survival rate without adjuvant chemotherapy is 60%, and with adjuvant chemotherapy, 70%[1], [2].
Since the end of the 1990s, anthracycline chemotherapy regimens have been recognised as more effective in adjuvant therapy than chemotherapy not including anthracyclines.[3]

[1] Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 352; 930-942, 1998.
[2] Data from the American College of Surgeons

The FEC 100 protocol (fluorouracil, epirubicin, cyclophosphamide) usually used in Europe is preferred to FAC 50 (fluorouracil, adriamycin, cyclophosphamide) because it has lower cardiotoxicity.
In the opinion of a large majority of experts, the taxanes (docetaxel and paclitaxel) represent an advance in treatment similar to that of anthracyclines 20 years earlier, with an absolute benefit in survival of about 5%.
With regard to paclitaxel, two trials have been published to date comparing a sequential regimen with reference adjuvant therapy in the United States (4 cycles of 'AC). The CALGB trial showed a significant improvement in survival, unlike the NSABP trial, but both showed a significant improvement in recurrence-free survival with globally satisfactory safety and side-effects in the experimental arm (AC followed by paclitaxel). However, there have been no direct comparisons between the two taxanes in an adjuvant setting.
In some French centres, since publication of comparison results of the PACS 01 trial which demonstrated the superiority of the regimen 3 x FEC 100 followed by 3 cycles of Taxotere over administration of 6 cycles of FEC in terms of progression-free survival (78.3% and 73.2%, p= 0.014) and in overall survival at 5 years (90.7% compared with 86.7%, p= 0.050), Taxotere has been prescribed according to this sequential regimen.

4.4. Target population

1/ Adjuvant therapy for breast cancer:
In 2000, the incidence of breast cancer was about 42,000 female patients.[4]
Between 5%[5] and 15%[6] of these cases were metastatic on diagnosis, i.e. approximately 2,100–6,300. Locoregional therapy including surgery may be indicated in a further 35,700–39,900 patients.
One third of cases were node-positive.[7]

The estimated target population for Taxotere in this indication is 11,900–13,300 cases a year.

2/ Treatment of metastatic breast cancer with overexpression of HER2:
The target population for Taxotere consists of patients with metastatic breast cancer overexpressing HER2, which can be divided into two subpopulations:

- metastatic disease at diagnosis
- localised disease which will progress to the metastatic stage.

These two subpopulations were estimated from the following data:

- In France, the estimated incidence of breast cancer was approximately 42,000 cases in 2000
- 5% to 15% of these cases are metastatic at diagnosis
- 28% of cases will develop from local disease to become metastatic[8]
- 85%[9] of patients are likely to receive chemotherapy.

On the basis of these data, the estimated number of patients with metastatic breast cancer at diagnosis is 5,300. The estimated number of patients with localised breast cancer

[3] Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 352; 930-942, 1998.
[4] Change in incidence and mortality from cancer in France between 1978 and 2000 (INVS 2003)
[5] FRANCIM
[6] FLNCC survey
[7] Sant M; Eurocare Working Group. Differences in stage and therapy for breast cancer across Europe. Int J Cancer. 2001 Sep;93(6):894-901
[8] Louis Harris survey, 2003
[9] Louis Harris survey, 2003

progressing to metastatic disease is 10,000. The total number of patients at a metastatic stage is 15,300.
30% of cancers overexpress the HER2 gene.[10]

The estimated number of incident cases treated with Herceptin is approximately 4,600 patients a year.

The total target population for Taxotere in these two extensions of indication is likely to be approximately 16,500–18,000 cases a year.

4.5. Transparency Committee recommendations

The committee recommends inclusion on the list of medicinal products approved for use by hospitals and various public services in these two extensions of indication.

[10] US Department of Health and Human Services "New monoclonal antibody approved for advanced breast cancer" (25 September 1998)