HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

29 November 2006

TAXOTERE 20 mg, concentrate and solvent for infusion in single-dose vials of 7 ml, individually packed (CIP: 559 517-9)
TAXOTERE 80 mg, concentrate and solvent for infusion in single-dose vials of 15 ml, individually packed (CIP: 559 518-5)

Applicant: SANOFI AVENTIS FRANCE

Docetaxel

List I
Medicinal product restricted to hospital prescription by certain specialists in oncology or haematology or qualified cancer specialists.
Medicinal product requiring specific monitoring during treatment.

Marketing Authorisation (MA) Date (centralised procedure): November 27, 1995 - Amendments: July 17, 1998 – August 28, 2000 - January 9, 2003 – October 20, 2004 - January 5, 2005 – April 27, 2006

Reason for request: Inclusion on the list of pharmaceutical products for use in the hospital sector in the extension of indication “TAXOTERE in combination with cisplatin and 5-fluorouracil is indicated for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease”

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient:

Docetaxel

1.2. Indications

Indication evaluated

TAXOTERE in combination with cisplatin and 5-fluorouracil is indicated for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease.

Other indications already evaluated by the Transparency Committee

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 doxorubicin is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition.

TAXOTERE (docetaxel) monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy including an anthracyclin or an alkylating agent.

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 capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy that included an anthracyclin.

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 unresectable, 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.

1.3. Posology and method of administration

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

The recommended dose of docetaxel is 75 mg/m^2 followed on the same day by a 1 to 3 hour infusion of cisplatin at the dosage of 75 mg/m^2. Immediately upon completion of the cisplatin infusion, starts a 24-hour continuous infusion for 5 consecutive days of 5-fluorouracil at the dosage of 750 mg/m^2/day.

Treatment is repeated every three weeks.

Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration. Prophylactic G-CSF should be used to decrease the risk of haematological toxicity (see also dose adjustments during treatment).

Dosage adjustment in combination with cisplatin and 5-fluorouracil:
If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the docetaxel dose should be reduced from 75 to 60 mg/m^2.

If subsequent episodes of complicated neutropenia occur, the docetaxel dose should be reduced from 60 to 45 mg/m^2.

In case of Grade 4 thrombocytopenia the docetaxel dose should be reduced from 75 to 60 mg/m^2.

Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level > 1,500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3. Treatment should be discontinued if these haematological toxicities persist.

Recommended dose modifications for gastrointestinal toxicities in patients treated with TAXOTERE in combination with cisplatin and 5-fluorouracil (5-FU) are as follows:

Table 1: Recommended dose modifications for gastrointestinal toxicities in patients treated with TAXOTERE in combination with cisplatin and 5-fluorouracil (5-FU)

Toxicity – grade	Dosage adjustments
Diarrhoea – grade 3	First episode: reduce 5-FU dose by 20% Second episode: reduce TAXOTERE dose by 20%
Diarrhoea – grade 4	First episode: reduce TAXOTERE and 5-FU dose by 20% Second episode: discontinue treatment
Stomatitis – grade 3	First episode: reduce 5-FU dose by 20% Second episode: stop 5-FU only, at all subsequent cycles Third episode: reduce TAXOTERE dose by 20%
Stomatitis – grade 4	First episode: stop 5-FU at all subsequent cycles Second episode: reduce TAXOTERE dose by 20%

For cisplatin and 5-fluorouracil dosage adjustments, see manufacturers' summary of product characteristics (SPC).

Based on pharmacokinetic data with docetaxel at 100 mg/m² as single agent, for patients who have both elevations of transaminase (ALT and/or AST) greater than 1.5 times the upper limit of the normal range (ULN) and alkaline phosphatase greater than 2.5 times the ULN, the recommended dose of docetaxel is 75 mg/m^2. For patients with serum bilirubin >ULN and/or ALT and AST >3.5 times the ULN associated with alkaline phosphatase >6 times the ULN, no dose-reduction can be recommended and docetaxel should not be used unless strictly indicated.

In combination with cisplatin and 5-fluorouracil for the treatment of patients with gastric adenocarcinoma, the pivotal clinical trial excluded patients with transaminase levels (ALT and/or AST) > 1.5 × ULN associated with alkaline phosphatase > 2.5 × ULN, and bilirubin> 1 x UNL: consequently, for these patients, no dose-reduction can be recommended and docetaxel should not be used unless strictly indicated.

No data are available in patients with hepatic impairment treated with docetaxel in combination, in the other indications.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC 2006 Classification

L	Antineoplastic and immunomodulator agents
L01	Antineoplastic agents
L01C	Plant alkaloids and other medicinal products of natural origin
L01CD	Taxanes
L01CD02	Docetaxel

2.2. Medicines in the same therapeutic category

Comparator medicines

There is no other taxane with the same indication

2.3. Medicines with a similar therapeutic aim

Cytotoxic agents indicated in the treatment of metastatic gastric adenocarcinoma:
- CISPLATYL (cisplatin) and proprietary drugs containing cisplatin
- ADRIBLASTINE (doxorubicin) and proprietary drugs containing doxorubicin
- FARMORUBICINE (epirubicin)
- FLUOROURACIL ICN (fluorouracil) and proprietary drugs containing fluorouracil
- AMETYCINE 10 and 20 mg (mitomycin C)

3 ANALYSIS OF AVAILABLE DATA

The company submitted the results of 2 studies:

- An open-label, randomised, phase II study (TAX 325) comparing docetaxel + cisplatin combination with docetaxel + cisplatin + 5 fluorouracil combination in 155 chemotherapy-naive patients with locally recurrent or metastatic gastric adenocarcinoma. At the end of this study, results of which will not be described in this opinion, docetaxel + cisplatin + 5 fluorouracil combination was retained for the phase III study.

- An open-label, randomised phase III study (TAX 325A) comparing docetaxel + cisplatin + 5 fluorouracil (TCF) combination with cisplatin + 5 fluorouracil (CF) combination in 457 patients (221 in the TCF arm and 224 in the CF arm) with locally recurrent or metastatic gastric adenocarcinoma and chemotherapy-naive for their metastatic disease.

Baseline patient characteristics

Patient characteristics were similar in the two arms.
The median age of patients in the 2 arms was 55 years. It should be pointed out that only one quarter of patients were older than 65 years (24.4% of the patients in the TCF arm, 24.6% of patients in the CF arm).

The Committee noted that the study population was relatively young compared to that encountered in practice, as the median age of diagnosis is 72 years in men and 77 years in women.[1]

Patients enrolled in the study had a good general health status. The median Karnofsky score (KPS, assessing the patients' physical abilities and score from 0 to 100) was 90 in the 2 arms. 63.8% of the patients had a score >90.

[1] INVS. Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000

All the patients were at a metastatic stage (96.4% of patients in the TCF arm, 96.9% of patients in the CF arm).

The tumoral lesion was located at the gastroesophageal junction in 19% of patients in the TCF arm and 25% of patients in the CF arm.

Dosing regimens:
Patients in the TCF arm received every 3 weeks: docetaxel 75 mg/m^2 on D1 + cisplatin 75 mg/m^2 on D1 + 5FU 750 mg/m^2 administered continuously from D1 to D5.

Patients in the CF arm received every 4 weeks: cisplatin 100 mg/m^2 on D1 + 5FU 1,000 mg/m^2 administered continuously from D1 to D5.

Primary endpoint: time to progression, defined by disease progression or death from all causes.

Statistical analysis for the evaluation of time to progression required 460 patients to detect a 4 to 6 months improvement in the median time to progression, corresponding to a hazard ratio of 1.5 with a statistical power of 95%.

Secondary endpoints: overall survival, response rate, quality of life

3.1. Efficacy results

The analysis was carried out on 445 patients.
The median duration of treatment was 19 weeks in the TCF arm and 16 weeks in the CF arm.

Result for primary endpoint
The median follow-up for this endpoint was 13.6 months.
The median time to progression was 5.6 months (95% CI: 4.86 – 5.91] in the TCF arm *versus* 3.7 months [95% CI: 3.45 – 4.47] in the CF arm (p=0.0004).

Result for the secondary endpoints

- Overall survival:

The median follow-up for this endpoint was 23.4 months.
The median survival was 9.2 months [95% CI: 8.38 – 10.58] in the TCF arm *versus* 8.6 months [95% CI: 7.16 – 9.46] in the CF arm (p=0.0201).
At 1 year, survival was 40.2% in the TCF arm *versus* 31.6% in the CF arm.
At 2 years, survival was 18.4% in the TCF arm *versus* 8.8% in the CF arm.

- Response rate:

An overall response was observed in 36.7% of patients in the TCF arm (81/221) of which 4 had a complete response) *versus* 25.4% of patients in the CF arm (57/224 of which 3 had a complete response), p = 0.0106. The median duration of overall response was not significantly different between the 2 treatment groups (6.1 months in the TCF arm, 5.6 months in the CF arm).

Disease progression was observed in 16.7% of patients in the TCF arm (37/221) *versus* 25.9% of patients (58/224) in the CF arm.

The median time to treatment failure was 4 months in the TCF arm versus 3.4 months in the CF arm (p=0.0335).

- Quality of life:

Quality of life was evaluated by the EORTC QLQ-C30 questionnaire which comprises 15 subscales. Results are only available for 5 subscales. The variables evaluated were physical functioning, social life, nausea, pain and anorexia.

Quality of life was evaluated by the time to definitive deterioration of 5% in overall health status (primary endpoint). This choice was not discussed and this interpretation of the EORTC quality of life scale is unusual. The median time to definitive deterioration of 5% in global health status was 6.5 months for TCF *versus* 4.2 months for CF, p=0.0121.

The median time to definitive worsening of the Karnofsky score was 6.1 months for TCF *versus* 4.8 months for CF (p=0.0088). It should be noted that at baseline, most patients had a good general health status (the median Karnofsky score was 90 in the 2 arms).

The company provided the results for patient subgroups (according to the sex, ethnic origin, age > 65 years) for the following endpoints: time to progression, overall survival. These results did not differ from those observed in the general study population.

3.2. Adverse events

The observed adverse events were as follows:

- Neutropenia: 95.5% for patients in the TCF arm *versus* 83.3% for patients in the CF arm
- Febrile neutropenia: 16.4% for patients in the TCF arm *versus* 4.5% for patients in the CF arm
- Neutropenic infections: 15.9% for patients in the TCF arm *versus* 10.4% for patients in the CF arm
- Anemia: 96.8% for patients in the TCF arm *versus* 93.3% for patients in the CF arm
- Diarrhoea: 77.8% for patients in the TCF arm *versus* 49.6% for patients in the CF arm
- Nausea: 73.3% for patients in the TCF arm *versus* 76.3% for patients in the CF arm
- Vomiting: 66.5% for patients in the TCF arm *versus* 73.2% for patients in the CF arm
- Stomatitis: 59.3% for patients in the TCF arm *versus* 61.2% for patients in the CF arm
- Flu-like symptoms: 62.9% for patients in the TCF arm *versus* 58% for patients in the CF arm
- Fever (in the absence of infection): 35.7% for patients in the TCF arm *versus* 22.8% for patients in the CF arm
- Infections: 29.4% for patients in the TCF arm *versus* 22.8% for patients in the CF arm

Grade 3-4 adverse effects most commonly observed for TCF compared to CF were:

- Neutropenia which concerned 82.3% of patients in the TCF arm (n=220) *versus* 56.8% of patients in the CF arm (n=222).
- Diarrhoea, occurring in 20.4% of patients in the TCF arm and only 8% of patients in the CF arm.
- Infections, observed in 16.3% of the patients in the TCF arm and 10.3% of patients in the CF arm

Doses of treatment administered were reduced because of adverse events for 37.9% of patients in the TCF arm and 36.2% of patients in the CF arm.

Treatment discontinuations due to adverse events were observed in 23.5% of patients in the TCF arm and 21% of patients in the CF arm.

During the study, in the 30 days following the last dose of treatment, 23 deaths occurred in the TCF arm including 6 for adverse events and 19 in the CF arm including 9 for adverse events, mainly infections.

3.3. Conclusion

The efficacy and safety of the TCF combination (docetaxel + cisplatin + 5 fluorouracil) *versus* the CF combination (cisplatin + 5-fluorouracil) were evaluated in a randomised, open-label, phase III study (TAX 325A), conducted in 457 patients (221 in the TCF arm, 224 in the CF arm) with locally recurrent or metastatic gastric adenocarcinoma and chemotherapy-naive for their metastatic disease.

The median time to progression (primary endpoint) was improved by 1.9 months (5.6 months [95% CI: 4.86 – 5.91] in the TCF arm *versus* 3.7 months [95% CI: 3.45 – 4.47] in the CF arm (p=0.0004).

The overall survival benefit was small. Median survival was 8.6 months in the CF arm and 9.2 months in the TCF arm, i.e. a 19-day increase in median survival.

The safety profile of the TCF combination was poor. The main adverse events observed were haematological (neutropenia), gastrointestinal (diarrhoea) and infections.

Patient quality of life was analyzed using the EORTC questionnaire. The endpoint chosen for this analysis was time to a 5% deterioration in health status. This choice was not discussed and this interpretation of the EORTC quality of life scale is unusual.

Assessment of the results of this study shows that the benefit of adding docetaxel to a 5-fluorouracil + cisplatin chemotherapy regimen is low at the expense of a high toxicity.

In addition, no data are available comparing TCF tritherapy (docetaxel + cisplatin + 5-fluorouracil) and ECF tritherapy (epirubicin + cisplatin + 5 fluorouracil) protocol used in practice.

4 CONCLUSIONS OF THE TRANSPARENCY COMMITTEE

4.1. Actual Benefit

Metastatic gastric adenocarcinoma is a serious disorder which is life-threatening in the short term. Median survival does not exceed 1 year.

TAXOTERE is intended for palliative treatment.

Its efficacy/adverse effects ratio is moderate.

This proprietary drug is used for first-line therapy.

There are alternative medications.

Public health benefit:
Metastatic gastric adenocarcinoma represents a considerable public health burden.
Improvement in its management is a public health need falling within the scope of the fight against cancer and the national palliative care development program.
Data from the TAX 325A study do not make it possible to quantify the expected impact of TAXOTERE on the reduction in mortality caused by metastatic gastric adenocarcinoma, as the comparator regimen used (bitherapy) does not reflect current practice (tritherapy). The impact on quality of life is difficult to determine taking into account the unusual interpretation made of the EORTC QLQ-C30 scale in the study.
Extrapolation of the experimental data is difficult as the study population was younger than that likely to receive TAXOTERE in this indication in practice.
Consequently, TAXOTERE is not expected to have an impact on public health in this indication.

The medical benefit is of TAXOTERE substantial

4.2. Improvement in actual benefit

TAXOTERE, in combination with cisplatin and 5-fluorouracil, provides a minor improvement in actual benefit (IAB IV) compared to the cisplatin–5 fluorouracil combination in the management of the metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, in chemotherapy-naïve patients.

4.3. Therapeutic use

Management of metastatic gastric adenocarcinoma

At the advanced stage of gastric cancer, the objective of palliative chemotherapy is to improve patient survival and quality of life in comparison with symptomatic treatment alone.

There is no consensus on the reference treatment of advanced gastric cancer.

Polychemotherapy regimens are more active than single-agent chemotherapy and give better response rates but have a low benefit in terms of survival. The median survival in all phase III studies was low, between 7 and 10 months at best.

The reference chemotherapy regimens are the cisplatin/5-fluorouracil (CF) and epirubicin/cisplatin /5-fluorouracil (ECF) combinations. The choice of chemotherapy depends on age, underlying condition and general health status.

Among the many combinations tested, the ECF combination, reserved for patients in good general health status, seems to be the most widely used in practice.[2]

Role of TAXOTERE in therapeutic strategy

The combination of docetaxel with cisplatin and 5-fluorouracil (TCF combination) provides an alternative treatment for patients with a good general health status with metastatic gastric adenocarcinoma.

4.4. Target population

The target population of TAXOTERE is represented by patients with metastatic gastric adenocarcinoma.

This population comprises two subgroups:

- Patients who already have metastases at the time of diagnosis.
- Patients diagnosed at a localised stage and who progress to a metastatic stage.

This population may be estimated from the following data:

- In France, the incidence of gastric cancer was 7,126 new cases in 2000[3]. Gastric adenocarcinoma represents approximately 95% of gastric cancers[4].
- At the time of the diagnosis, approximately 30% of the patients already have metastases[5] [6].
- Among the remaining 70% patients, diagnosed at a localised stage, 35 to 80% (according to EPAR) will present recurrences including 90% at distant sites (metastases)[7].

On the basis of this data, the target population of TAXOTERE may be estimated to be approximately 3,500 to 5,400 cases per 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.

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[2] Les cancers de l'estomac. Bulletin du cancer. Volume 88. Number 11. 1105-18. November 2001

[3] INVS. Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000.

[4] EPAR

[5] Faycal J, Bessaguet C, Nousbaum JB, Cauvin JM, Cholet F, Bideau K, Robaszkiewic M, Gouérou H. Epidemiology and long term survival of gastric carcinoma in the French district of Finistère between 1984 and 1995

[6] Fédération Nationale des Centres de Lutte Contre le Cancer (http://www.fnclcc.fr)

[7] Incidence and factors associated with recurrence patterns after intended curative surgery for gastric cancer. World J. Surg. 27. 153-158. 2003