HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 March 2008

TAXOTERE 20 mg concentrate and solvent for solution for infusion
Pack of 1 vial of Taxotere and 1 vial of solvent (CIP: 559 517-9)

TAXOTERE 80 mg concentrate and solvent for solution for infusion
Pack of 1 vial of Taxotere and 1 vial of solvent (CIP: 559 518-5)

Applicant: SANOFI AVENTIS FRANCE

docetaxel

ATC Code: L01CD02

List I

Medicinal product prescription reserved for certain hospital specialists in oncology or hematology or oncology physicians competent.

Medicinal product requiring specific monitoring during treatment.

Date of initial marketing authorisation: 27 November 1995
Date of extension of indication for assessment (centralised procedure): 23 November 2007

Reason for request: inclusion on the list of medicines approved for use by hospitals for the extension of indication: **"TAXOTERE (docetaxel) in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck".**

Medical, Economic and Public Health 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 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 previously have not 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. 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 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.

Gastric adenocarcinoma

TAXOTERE (docetaxel) 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.

New indication applied for:

TAXOTERE (docetaxel) in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck."

1.3. Dosage for the indication "Head and neck cancer":

"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.

For head and neck cancers, premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg daily (e.g. 8 mg BID) for 3 days starting 1 day before to infusion docetaxel, unless contraindicated, can be used. Patients must receive premedication with antiemetics and appropriate hydration (prior to and after administration of cisplatin). Prophylactic G-CSF can be used to mitigate the risk of haematological toxicities. All patients on the docetaxel arm of the TAX 323 and TAX 324 studies received prophylactic antibiotics.

In the induction treatment of patients with locally advanced (technically unresectable, low probability of surgical curability or organ preservation) squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel is 75 mg/m^2 by intravenous infusion of 1 hour on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3 hour infusion, followed by 5-fluorouracil 1000 mg/m^2/day as a continuous infusion from day 1 to day 4.
This regimen is administered every 3 weeks for 3 cycles. Following chemotherapy, the patients should receive chemoradiotherapy."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2007)

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01C	Plant alkaloids and other natural products
L01CD	Taxanes
L01CD02	docetaxel

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

Cytotoxic drugs indicated for the treatment of head and neck cancers:

- Alkylating agents – Platinum derivatives

- CISPLATYL (cisplatin) and cisplatin-based products indicated for ear, nose and throat (ENT) cancers. Squamous cell carcinoma
- PARAPLATIN (carboplatin) and carboplatin-based products indicated for squamous cell carcinoma of the head and neck.

- Topoisomerase inhibitors – Anti-topoisomerase II – Anthracyclines and similar products

- FARMORUBICIN (epirubicin) and epirubicin-based products indicated for squamous cell carcinoma of the ear, nose and throat.

- Antimetabolites – Anti-pyrimidines

- FLUORO-URACILE ICN (fluorouracil) and fluorouracil-based products indicated for squamous cell carcinoma of the head, neck and oesophagus.

- Antimetabolites – Folic acid antagonists

- METHOTREXATE BELLON (methotrexate) and methotrexate-based products indicated for head and neck cancer.

- Antimetabolites – Other cytotoxic agents

- BLEOMYCINE BELLON (bleomycin) indicated for squamous cell carcinoma.

- Monoclonal antibodies

- ERBITUX (cetuximab) in combination with radiotherapy, indicated for the treatment of patients with locally advanced squamous cell carcinoma of the head and neck.

3 ANALYSIS OF AVAILABLE DATA

The company has submitted the results of a phase III study, TAX 324[1]. Its objective was to evaluate the efficacy and safety of TPF (docetaxel combined with cisplatin and 5-fluorouracil (5FU)) induction chemotherapy followed by chemoradiotherapy in 501 patients with locally advanced squamous cell carcinoma of the head and neck (SCHN).

3.1. Efficacy results

Methodology:

An open label, randomised, phase III study comparing TPF (docetaxel + cisplatin + 5FU) with PF (cisplatin + 5FU), in each case followed by chemoradiotherapy, in 501 patients (255 in the TPF arm and 246 in the PF arm).

Inclusion criteria:

- SCHN (buccal cavity, oropharynx, hypopharynx or larynx), confirmed histologically and cytologically
- tumor measurable in at least 1 or 2 dimensions
- non-metastatic stage III or IV[2]
- tumor regarded as inoperable: i.e. technically unresectable, low probability of surgical curability (all stages T3-T4, all stages N2-N3 except T1N2), and patients aiming at organ preservation
- ECOG[3] score = 0 or 1.

Exclusion criteria:

- tumors of the nasopharynx, and nasal and paranasal cavities
- any prior chemotherapy or radiotherapy for any reason or surgery for head and neck cancer.

Dosing regimen:

Patients were randomised to receive:

- 3 cycles of induction chemotherapy at 3-week intervals:
    - either TPF: docetaxel 75 mg/m², followed by cisplatin 100 mg/m² on day 1, followed by a continuous infusion of 5-fluorouracil 1,000 mg/m²/day for 4 days
    - or PF: cisplatin 100 mg/m² on day 1, followed by a continuous infusion of 5-fluorouracil 1,000 mg/m²/day for 5 days

- then chemoradiotherapy (carboplatin IV infusion for 1 hour once a week, with a maximum of 7 doses during radiotherapy, delivered at a dose of 2 Gy per day, 5 days a week) starting 3 to 8 weeks after the induction chemotherapy and lasting for 7 weeks. Surgical treatment was authorised after the chemoradiotherapy.

Premedication with an antiemetic and a granulocyte stimulating factor (G-CSF) was administered to each treatment group for secondary prophylaxis, starting in the 2nd chemotherapy cycle.

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[1] Posner MR, Hershock DM, Blajman CR et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. NEJM, 2007, 357 : 1705-15

[2] Stage III : T3N0M0 or T1-3N1M0 ; Stage IV : T4N0-1M0 or T1-4N2-3M0

[3] The ECOG (Eastern Cooperative Oncology Group) performance scale is a scale to assess the patient's general condition and a prognosis factor. This scale ranges from 0 to 4:
0: Fully active; no performance restrictions
1: Strenuous physical activity restricted; fully ambulatory and able to carry out light work
2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about >50 percent of waking hours
3: Capable of only limited selfcare; confined to bed or chair >50 percent of waking hours
4: Completely disabled; cannot carry out any selfcare; totally confined to bed or chair

Patients in the TPF arm received prophylactic antibiotic treatment and corticosteroid premedication.
Treatment continued until disease progression, appearance of adverse effects or patient refusal of treatment.

Primary endpoint: overall survival[4]

Secondary endpoints:
- median progression-free survival
- median time to treatment failure
- objective response rate (percentage of patients with a full or partial response) after induction chemotherapy, after chemoradiotherapy, and after induction chemotherapy + chemoradiotherapy
- median duration of response
- patient quality of life assessed on the FACT HN (Head and Neck Quality of life) scale
- clinical benefit (local symptoms) assessed on the PSS-HN scale[5]

Results (ITT population):
Median duration of treatment (induction chemotherapy + chemoradiotherapy) was 19 weeks in both groups.
Median duration of induction chemotherapy was 9 weeks in the TPF arm and 10 weeks in the PF arm.

Main patient characteristics:

	TPF arm (n = 255) n (%)	PF arm (n=246) n (%)
Age (years)		
35-50	53 (20.8)	61 (24.8)
50-65	168 (65.9)	147 (59.8)
65-75	29 (11.4)	30 (12.2)
median	55	56
WHO score		
0	142 (55.7)	126 (51.2)
1	113 (44.3)	117 (47.6)
Tumour location		
Hypopharynx	42 (16.5)	34 (13.8)
Larynx	48 (18.8)	42 (17.1)
Buccal cavity	33 (12.9)	38 (15.4)
Oropharynx	132 (51.8)	131 (53.3)
Reason disease is inoperable		
Technically unresectable	92 (36.1)	84 (34.1)
Low probability of surgical curability	78 (30.6)	75 (30.5)
Organ preservation	85 (33.3)	87 (35.4)
Tumour classification		
T1	13 (5.1)	9 (3.7)
T2	43 (16.9)	56 (22.8)
T3	74 (29.0)	88 (35.8)
T4	125 (49.0)	92 (37.4)
Lymph node classification		
N0	42 (16.5)	35 (14.2)
N1	53 (20.8)	49 (19.9)
N2	128 (50.2)	123 (50.0)
N3	32 (12.5)	38 (15.4)
Clinical stage		
III	41 (16.1)	46 (18.7)
IV	214 (83.9)	199 (80.9)

[4] Defined as the time from randomisation to death from any cause.
[5] Performance Status Scale for Head and Neck cancer patients, measuring intelligibility of speech, the ability to eat in public and to eat normally, intensity of pain on the VAS scale and deterioration in the WHO scale.

Baseline patient characteristics were comparable in the two treatment arms. Disease of the oropharynx was predominant (approximately 50%). All patients were in good general condition (WHO score of 0 or 1).

Results for primary endpoint: (ITT analysis)
Median overall survival was 70.6 months [49.0; not attained] in the TPF arm versus 30.1 months [20.9; 51.5] in the PF arm (HR = 0.70; 95%CI: [0.54 - 0.90]; p < 0.0058).
Survival rate was:
- at 1 year, 80.0% [75.0; 84.9] in the TPF arm against 69.9% [64.1; 75.7] in the PF arm
- at 2 years, 67.3% [61.5; 73.2] in the TPF arm against 54.5% [48.2; 60.8] in the PF arm
- at 3 years, 62.1% [55.9; 68.2] in the TPF arm against 48.1% [41.7; 54.5] in the PF arm[6].

Results for secondary endpoints:
- median progression-free survival:
Median progression-free survival was 35.5 months in the TPF arm versus 13.1 months in the PF arm (HR = 0.71, 95% CI [0.56; 0.90], p = 0.004).

- median time to treatment failure: it was 20.5 months in the TPF arm versus 10.8 months in the PF arm (HR = 0.74, 95% CI [0.59; 0.93], p = 0.0102).

- objective response rate: no statistically significant difference was observed between the two treatment arms in terms of objective response assessed after induction chemotherapy, at the end of chemoradiotherapy, and after induction chemotherapy followed by chemoradiotherapy.

- median duration of response:
The median duration of response was not attained in the TPF arm. It was 41.9 months in the PF arm (HR = 0.67, 95% CI [0.48; 0.93], p = 0.018).

- quality of life/clinical benefit:
No difference was observed between the two treatment arms on these criteria.

No data is available to evaluate the success of organ preservation in one third of patients included in each treatment arm.

3.2. Adverse effects (during induction chemotherapy)

The main adverse events of all grades associated with the treatment that were more frequently observed in the TPF arm (n=251) than in the PF arm (n=243) were as follows: nausea (75.7% versus 78.2%), alopecia (67.7% versus 43.2%), stomatitis (64.5% versus 67.1%), fatigue (58.6% versus 51%), vomiting (56.2% versus 60.9%), diarrhoea (42.2% versus 37.4%), anorexia (37.8% versus 30.9%), non-infection pyrexia (26.3% versus 17.3%).

The most commonly observed grades 3-4 adverse effects were: nausea (13.9% of patients in the TPF arm versus 13.6% of patients in the PF arm), stomatitis (20.7% versus 27.2%), anorexia (12.0% versus 11.1%) and oesophagitis/dysphagia/odynophagia (12.0% versus 7.4%).

Grades 3-4 anaemia occurred in 12.4% of TPF patients versus 9.5% of PF patients.
Grades 3-4 leucopenia were more common in the TPF arm (54.2%) than in the PF arm (23.5%), most cases being of grade 3.

[6] Given the large number of patients leaving the study after 2 years, the 3-year survival rates should be interpreted with caution (See EPAR page 21).

Neutropenia was more common in the TPF arm (94.8% of patients) than in the PF arm (84.2% of patients), grades 3-4 being the most common (83.5% of TPF patients versus 56.0% of PF patients), irrespective of G-CSF use. N.B.: Only 7.5% of cycles in the TPF arm (15.5% of patients) versus 6.4% of cycles in the PF arm (11.9% of patients) had G-CSF administered as secondary prophylaxis.
More cases of febrile neutropenia (12.1% versus 6.6%) and infections associated with neutropenia (11.7% versus 8.3%) were observed in the TPF arm than in the PF arm.
There has been one death associated with neutropenic infections in each treatment arm.

Treatment discontinuations due to adverse effects involved 19/255 patients in the TPF arm and 19/246 patients in the PF arm.

3.3. Conclusion

The efficacy and safety of TPF (docetaxel + cisplatin + 5 fluorouracil) as neoadjuvant treatment to chemoradiotherapy were compared with PF (cisplatin + 5 fluorouracil) in a randomised, open-label, phase III study (TAX 324) conducted in 501 patients with locally advanced squamous cell carcinoma of the head and neck. The study included patients in good general condition whose tumors were technically unresectable, patients with a low probability of surgical curability or organ preservation.
In the TPF arm compared with the PF arm:
- median overall survival (primary endpoint) was improved by 40.5 months (70.6 versus 30.1 months, HR = 0.70; 95% CI: [0.54; 0.90], p=0.0058), or a 30% relative reduction in mortality risk.
- median progression-free survival was improved by 22.4 months (35.5 months in the TPF arm versus 13.1 months in the PF arm; HR = 0.71, 95% CI [0.56; 0.90], p = 0.004).
No significant difference between the two treatment arms was observed in terms of:
- - objective response rate
- - quality of life/clinical benefit.

The safety profile of the TPF combination was marked by haematological toxicity (principally grades 3-4 neutropenia). This toxicity did not have a significant impact on treatment discontinuations or patients' quality of life.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Squamous cell carcinoma of the head and neck (SCCHN) is a life-threatening disease. The risk factors are smoking and chronic alcoholism. Dysphagia, dysphonia and dyspnoea are the most common clinical signs.
These medicinal products are intended for curative treatment.
The efficacy/safety ratio is high.
They are used for first-line therapy.
At this stage of the disease, there are few alternative treatments.

Public health benefit:
Cancers of the head and neck represent a considerable public health burden. In the population of patients with locally advanced squamous cell carcinoma, the burden is moderate because of the smaller number of patients concerned compared to the total population of SCCHN patients in France.
The prevention and improved management of cancer of the head and neck is a public health need.
In light of the results of the TAX 324 study, particularly the median overall survival, docetaxel combined with cisplatin and 5-fluorouracil (TPF) is expected to have a considerable impact in reducing morbidity and mortality associated with locally advanced squamous cell carcinoma of the head and neck, compared with the combination of cisplatin and 5 fluorouracil (PF).
TAXOTERE, in combination with cisplatin and 5 fluorouracil, therefore seems able to provide some response to the public health need.
Accordingly, TAXOTERE, in combination with cisplatin and 5 fluorouracil, is expected to benefit public health in this indication. This benefit is moderate.

The actual benefit of these medicinal products is substantial.

4.2. Improvement in actual benefit

Taking into account the benefit observed in terms of median survival, the Transparency Committee considers that TAXOTERE, in combination with cisplatin and 5 fluorouracil, provides a substantial improvement in actual benefit (IAB level II) compared with the combination of cisplatin + 5 fluorouracil in the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck.

4.3. Therapeutic use

The previous standard therapeutic management for locally advanced tumors of the head and neck was basically surgery (if technically feasible) or radiotherapy. Because of its mutilating nature (radical surgery to excise the larynx, affecting phonation and/or swallowing with its social and occupational consequences), surgery may be associated with severe functional effects.
In France, the usual treatment for ENT tumors currently consists of a concomitant combination of radiotherapy and chemotherapy based on platinum salts with or without 5-fluorouracil. The superiority of this protocol over conventional radiotherapy alone, which has been demonstrated in several randomised studies, is shown by the locoregional control rate and overall survival[7,8,9]. Use of this combination has increased the overall 3-year survival rate

[7] Brizel and Esclamado. Concurrent Chemoradiotherapy for Locally Advanced, Non metastatic, Squamous Carcinoma. J Clin Oncol.2006; 24: 2612-2617

from 15-20% to 30-50%[10]. This benefit, however, is achieved at the cost of an increase in both immediate and delayed toxicity, radioepithelitis in particular.
There is no consensus on the use of induction chemotherapy (neoadjuvant treatment prior to chemoradiotherapy). Induction chemotherapy (the standard combination being cisplatin + 5 fluorouracil) followed by chemoradiotherapy is, however, an alternative to radical surgery, especially in potentially operable patients who are candidates for an organ preservation programme.

TAXOTERE (docetaxel) in combination with cisplatin and 5-fluorouracil (TPF) administered as a neoadjuvant treatment prior to chemoradiotherapy represents a new first-line therapeutic option for the management of patients with locally advanced squamous cell carcinoma of the head and neck who are technically inoperable, have a low probability of surgical curability, or are candidates for a larynx preservation programme.

4.4. Target population

The target population for TAXOTERE consists of patients with locally advanced squamous cell carcinoma of the head and neck who are technically inoperable, have a low probability of surgical curability, or are candidates for a larynx preservation programme.
This population may be estimated from the following data:
- the incidence of cancers of the head and neck was estimated at approximately 20,000[11] new cases in 2000. These cancers are squamous cell carcinomas in more than 95% of cases.
- the locally advanced stage accounts for approximately 60% of cases, or around 12,000 cases a year.
- 60% of patients[12] at this stage are considered to have an unresectable tumor (i.e. 7,200 patients) and 40% a resectable tumor (i.e. 4,800 patients).
- according to the experts, out of these 4,800 patients with a resectable tumor:
    - roughly 50% will be candidates for organ preservation, i.e. 2,640 patients
    - roughly 10% have a low probability of surgical curability, i.e. 480 patients.

Overall, the target population for TAXOTERE may be estimated at approximately 10,000 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 the extension of indication and at the dosage given in the marketing authorisation.

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[8] Denis F, Garaud P, Bardet E, et al: Final results of the 94-01 GORTEC randomized trial comparing radiotherapy alone to concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 22:69-76, 2004
[9] Wendt T, Grabenbauer G, Rodel C, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: A randomized multicenter study. J Clin Oncol 16:1318-1324, 1998
[10] Posner MR, and Wirth L. Cetuximab and Radiotherapy for Head and Neck Cancer . N Engl J Med 2006; 354:634-636
[11] Rapport de la Commission d'orientation sur le cancer, INVS 2003
Remontet L, Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000. INVS 2003
[12] C. Monnerat et al. End points for new agents in induction chemotherapy for locally advanced head and neck cancers. Annals of oncology 13 : 995 – 1006, 2002