PUBLIC SUMMARY DOCUMENT
Product: Docetaxel, injection set containing 1 single use vial concentrate for I.V. infusion 20 mg (anhydrous) in 0.5 mL and 1 single use vial solvent 1.5 mL, injection set containing 1 single use vial concentrate for I.V. infusion 80 mg (anhydrous) in 2 mL and 1 single use vial solvent 6 mL, Taxotere®
Sponsor: Sanofi-Aventis Australia Pty Ltd
Date of PBAC Consideration: July 2008

1. Purpose of Application
The submission sought an extension to the current authority required listing for docetaxel to include induction treatment of locally advanced squamous cell carcinoma of the head and neck (SCCHN) in combination with cisplatin and 5-fluorouracil (PF).

2. Background
Docetaxel had not previously been considered by the PBAC for squamous cell carcinoma of the head and neck.

3. Registration Status
Docetaxel was registered by the TGA on 2 August 2007 for the new indication as follows:
Docetaxel in combination with cisplatin and 5-fluorouracil, is indicated for the induction treatment of patients with inoperable, locally advanced squamous cell carcinoma of the head and neck.

Docetaxel is also registered for the following indications:
Breast cancer:

- Locally advanced or metastatic breast cancer in whom previous chemotherapy has failed;
- In combination with capecitabine for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy;
- In combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with node positive breast cancer.
- In combination with trastuzumab for the treatment of patients with metastatic breast cancer whose tumours overexpress HER2 and who previously have not received chemotherapy for metastatic disease.

Non-small cell lung cancer:
Locally advanced or metastatic non-small cell lung cancer, including those who have failed platinum based chemotherapy.

Ovarian cancer:
Metastatic carcinoma of the ovary after failure of first line or subsequent chemotherapy.

Prostate cancer:
Androgen independent (hormone refractory) prostate cancer.

4. Listing Requested and PBAC's View
Authority required

Induction treatment of locally advanced, squamous cell carcinoma of the head and neck in combination with cisplatin and fluorouracil.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Most head and neck cancers are squamous cell carcinomas originating in the upper aerodigestive tract, including the oral cavity, pharynx and larynx. Head and neck cancers are treated primarily with chemoradiotherapy and less commonly with radiotherapy, followed by surgery depending on the stage and location of disease. Induction chemotherapy is administered to patients prior to chemoradiotherapy or radiotherapy with the aim of down staging the disease and improving the efficacy of chemoradiotherapy.

Currently patients are treated with combination cisplatin and fluorouracil as induction therapy followed by chemoradiotherapy or radiotherapy. The addition of docetaxel to the current combination of cisplatin and fluorouracil will provide an alternative induction regimen for the treatment of squamous cell carcinoma of the head and neck (SCCHN).

6. Comparator

The submission nominated the standard induction therapy regimen of cisplatin and fluorouracil (PF) as the main comparator. The PBAC considered this was appropriate.

7. Clinical Trials

The submission presented one pivotal randomised trial TAX 324 and one supportive trial RCT TAX 323, comparing TPF (docetaxel + cisplatin and 5 fluorouracil (PF)) with PF in patients with locally advanced squamous cell carcinoma of the head and neck. In TAX 324, TPF was administered every three weeks for three cycles followed by chemoradiotherapy, while in TAX 323, chemotherapy induction of four cycles of either TPF or PF was followed by radiotherapy alone.

The trials published at the time of submission are as follows:

Trial/First author	Protocol title/ Publication title	Publication citation
TAX 324		
Posner MR et al	Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer.	NEJM 2007; 357: 21-31
Parthan A et al	Economic evaluation of the TAX 324 trial comparing docetaxel plus cisplatin and 5-fluorouracil (TPF) versus standard treatment with cisplatin and 5-fluorouracil (PF) as induction chemotherapy followed by concurrent chemoradiation therapy in locally advanced squamous cell carcinoma of the head and neck (SCCHN).	J Clin Oncol 2007; 25 (18S): Abs: 6079.
TAX 323		
Vermorken JB et al.	Cisplatin, fluorouracil and docetaxel in unresectable head and neck cancer.	NEJM 2007; 357 (17):11-20
Bernier J et al.	Impact on quality of life (QoL) of the addition of docetaxel (T) to neoadjuvant cisplatin plus 5-fluorouracil treatment in patients with locally advanced unresectable squamous cell carcinoma of the head and neck (SCCHN): EORTC study 24971. [Abstract]	J Clin Oncol 2006; 24 (Suppl 18): A-5522,285s

Jansen J et al.	Cost-effectiveness analysis of the EORTC 24971 (TAX 323) trial comparing docetaxel plus cisplatin and 5-fluorouracil versus standard treatment (cisplatin and 5-fluorouracil) as induction chemotherapy followed by radiation therapy in locally advanced unresectable squamous cell carcinoma of the head and neck (SCCHN). [Abstract]	J Clin Oncol 2007; 25 (Suppl 18): A-6090,321s
Remenar E et al.	A randomized phase III multicenter trial of neoadjuvant docetaxel plus cisplatin and 5-fluorouracil (TPF) versus neoadjuvant PF in patients with locally advanced unresectable squamous cell carcinoma of the head and neck (SCCHN). Final analysis of EORTC 24971. [Abstract]	J Clin Oncol 2006; 24 (Suppl 18): A-5516
Vermorken JB et al.	Standard cisplatin/infusional 5-fluorouracil (PF) vs. docetaxel (T) plus PF (TPF) as neoadjuvant chemotherapy for nonresectable locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN): a phase III trial of the EORTC Head and Neck Cancer Group (EORTC #24971). [Abstract]	J Clin Oncol 2004; 22 (Suppl 14): A-5508, 490s

8. Results of Trials

In both TAX 324 and TAX 323, the TPF group demonstrated statistically significant survival benefits compared to the PF group. However, in cancers of the hypopharynx and oral cavity, after adjusting for the potential effect of the prognostic factors on survival, there were no statistically significant survival benefits of TPF over PF. Based on pre-specified subgroup analyses by tumour site, while there were no statistically significant differences, there was a consistent trend toward improved survival regardless of the primary site and disease inoperability. Patients with carcinomas of the hypopharynx (17%) and oral cavity (13%) represented a minority of cases, which contributed to the wide confidence intervals and the difficulty demonstrating significance. The point estimates for survival consistently favoured TPF over PF (e.g. median overall survival 32 months vs 20 months for hypopharynx, 37 months vs 14 months for oral cavity).

Both trials were conducted on patients with relatively good performance status (WHO PS score of 0 or 1), a subgroup of patients inclined to show better treatment efficacy compared to patients with poorer performance status.

Treatment efficacy of TPF and PF was not demonstrated in patients with tumours of the nasopharynx, nasal and paranasal cavities, as those patients were excluded from both trials.

TPF and PF demonstrated different toxicity profiles. However, haematological toxicity (higher rates of grade 3/4 neutropenia and leukopenia) associated with TPF may be a safety concern.

For PBAC's comments on these results, see Recommendations and Reasons.

9. Clinical Claim

The submission claimed that compared to PF, TPF is superior in terms of comparative effectiveness and non-inferior in terms of comparative safety. Based on the supporting data, the PBAC considered this claim was reasonable.

For PBAC's views, see Recommendations and Reasons.

10. Economic Analysis

The submission presented a stepped economic evaluation. The economic model was a cost-effectiveness model with two health states: alive and dead. Benefit was assessed as survival (time in the alive state), which is estimated using the Kaplan-Meier curve until the time of median follow-up in the pivotal trial TAX 324 with an assumed mean survival extrapolated to 5 years after that time. A cost per life year gain was presented as the base-case. Costs for the model were based on resource use recorded in the pivotal trial during the induction chemotherapy period only.

The incremental cost effectiveness ratio was estimated to be less than $10,000 per extra life year gained.

The model was most sensitive to the estimated survival and changes in costs for supportive treatment and treatment of adverse events.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be less than 10,000 patients in Year 5. The PBAC considered the submission's estimate might be underestimated due to the exclusion of patients with salivary gland tumour.

The financial cost per year to the PBS was estimated to be less than $ 10 million in Year 5. The PBAC considered the submission's estimate might be underestimated due to the underestimation of the number of patients.

12. Recommendation and Reasons

The PBAC recommended the listing of docetaxel on the PBS for the neoadjuvant treatment of squamous cell carcinoma on the basis of acceptable cost-effectiveness compared with standard induction therapy regimen of cisplatin and fluorouracil (PF). The PBAC noted the current Risk Sharing Arrangement for docetaxel and recommended that the deed be updated to include this extension.

The PBAC considered that the restriction should not specify "head and neck" because the trials excluded nasopharynx, nasal and paranasal cavities and these patients are treated differently. The WHO score of 1 or less should be included as this is consistent with the trial and patients in this group had greater efficacy benefit. The PBAC considered that staging should also be included to be consistent with national and international guidelines and noted that "advanced" is too ambiguous.

The PBAC noted that severe toxicity is the dominant factor in the utility study but as the treatment is curative and not palliative, it is unlikely that docetaxel used in neoadjuvant setting would contribute much to chronic toxicity, at least between the arms of the study.

The PBAC noted that the proposed TGA registration wording includes the word "inoperable" but of the two trials included in the submission, one trial (Trial 324) allowed the inclusion of patients with "inoperable" cancer due to patient preference for organ preservation, and the other (Trial 323) excluded those who chose organ preservation. The PBAC noted that there was no evidence of different outcomes in the trials and that inoperability did not seem to be a treatment effect modifier in terms of cost-effectiveness. Thus the Committee considered it appropriate that the restriction allow use in patients with tumours that were either technically inoperable or because of a desire for organ preservation.

The PBAC noted that both trials showed a statistically significant survival benefit compared with the PF group with a hazard ratio of 0.7 (TAX 324) and 0.72 (TAX 323). However, the PBAC noted that there were a larger proportion of oropharangeal cancers in the studies than would be expected in an Australian population and that these patients tend to do better. The Committee considered the ICER would remain acceptable even if the distribution of cancers was different.

Recommendation

DOCETAXEL, injection set containing 1 single use vial concentrate for I.V. infusion 20 mg (anhydrous) in 0.5 mL and 1 single use vial solvent 1.5 mL, injection set containing 1 single use vial concentrate for I.V. infusion 80 mg (anhydrous) in 2 mL and 1 single use vial solvent 6 mL

Restriction:	Authority required Neoadjuvant treatment of a patient with a WHO performance status of 1 or less, with inoperable Stage III, IVa or IVb squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx in combination with cisplatin and fluorouracil. NOTE: The carcinoma can be considered inoperable for technical or organ preservation reasons.
Maximum quantity:	1 (both strengths)
Repeats:	Nil

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Sanofi-aventis welcomes the PBAC's decision to recommend PBS listing of docetaxel for use as induction chemotherapy treatment of patients with locally advanced squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx in combination with cisplatin and fluorouracil.