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 and 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: November 2006

1. Purpose of Application

The resubmission requested an extension to the authority required PBS listing for docetaxel to include the treatment of hormone refractory prostate cancer.

2. Background

At the July 2005 meeting, the PBAC rejected a submission to extend the authority required listing to include the treatment of androgen independent (hormone refractory) prostate cancer because of uncertain and unacceptable cost-effectiveness.

The PBAC did not accept that docetaxel in the treatment of prostate cancer met the PBAC's definition of "rule of rescue" because there are other therapies available to treat the condition.

3. Registration Status

Docetaxel is registered by the TGA for the following indications:
Breast cancer:

- Treatment of patients with locally advanced or metastatic breast cancer in whom previous chemotherapy has failed.
- Taxotere in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy.
- The adjuvant treatment of patients with operable node-positive breast cancer, in combination with doxorubicin and cyclophosphamide.

Non-small cell lung cancer: Treatment of patients with locally advanced or metastatic non-small cell lung cancer, including those who have failed platinum based chemotherapy.
Ovarian cancer: Treatment of metastatic carcinoma of the ovary after failure of first line or subsequent chemotherapy.
Prostate cancer: Treatment of patients with androgen independent (hormone refractory) prostate cancer.

4. Listing Requested and PBAC's View

Authority required
Treatment of androgen independent (hormone refractory) prostate cancer.

See Recommendation and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy

Prostate cancer is the most common cancer in Australian men and the second leading cause of male cancer deaths. Long-term disease-free intervals are commonly associated with

surgical or radiotherapeutic treatment in more than 60% of subjects with localised cancer. Such outcomes are not common for subjects with locally spreading or distant metastatic prostate cancer. Although hormonal manipulations, such as luteinising hormone-releasing hormone (LHRH) agonists/antagonists or castration, are initially effective for 90% of prostate cancer patients, all of them eventually progress after a median of 18 to 24 months of treatment to become "androgen independent"(hormone refractory).

Upon progression, secondary hormonal manipulations are often employed. However, these treatments are generally less effective, and any activity against the cancer is usually short-lived. Docetaxel can be used in the treatment of patients with androgen independent (hormone refractory) prostate cancer (AIPC), and has shown a survival benefit in this group of patients.

6. Comparator

The submission nominated mitozantrone as the comparator, which was considered by the PBAC to be appropriate.

7. Clinical Trials

As in the July 2005 submission, evidence was presented from one key randomised controlled clinical trial (TAX327) and one supportive study (SWOG9916). No new data were presented. TAX 327 was a randomised controlled trial that compared docetaxel plus prednisone versus mitozantrone plus prednisone with a median follow-up of approximately 20 months. This study was published at the time of submission, as follows:

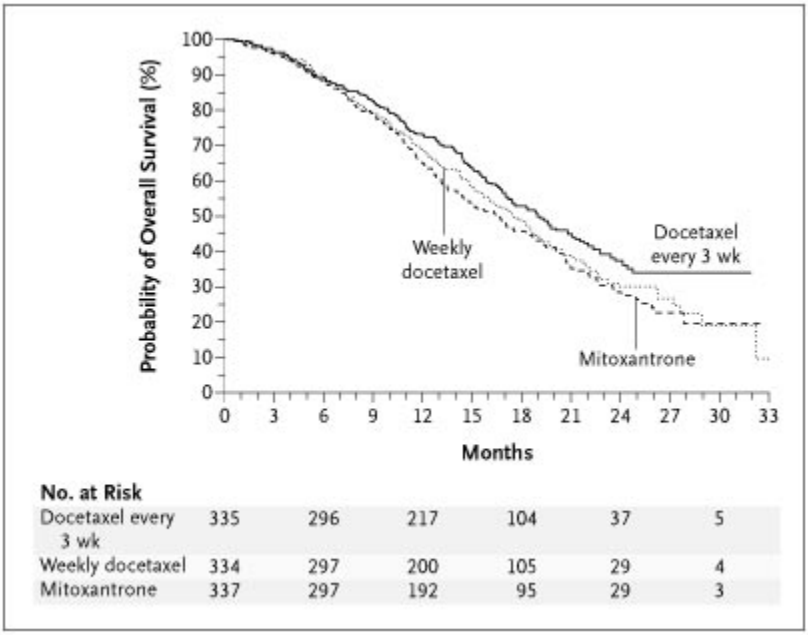
Trial/First author	Protocol title	Publication citation
TAX327 /Tannock	A multicentre Phase III randomised trial comparing TAXOTERE® administered either weekly or every three weeks in combination with prednisone versus mitozantrone in combination with prednisone for metastatic hormone-refractory prostate cancer.	New England Journal of Medicine 2004; 351: 1502-12.

8. Results of Trials

An additional analysis of the key trial TAX327 excluding crossover patients was presented, based on the assumption that crossovers would tend to bias the results unfavourably to docetaxel given that docetaxel is more beneficial than mitozantrone.

In the key trial TAX 327, analysis showed that docetaxel plus prednisone achieved an overall median survival benefit of 2.43 months, equivalent to a statistically significant 24% reduction in the risk of mortality (hazard ratio = 0.76; 95% CIS: 0.62, 0.94), compared with mitozantrone plus prednisone when crossover patients were included (ITT), and a median survival benefit of 3.78 months when crossover patients were excluded.

The Kaplan-Meier curve for overall survival in TAX 327 is shown in the figure below:



No. at Risk						
Docetaxel every 3 wk	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

Source: Tannock, 2004

For the TAX 327, treatment with docetaxel plus prednisone resulted in a statistically significant improvement in all secondary outcomes which included pain response rate, prostate specific antigen (PSA) response rate and median tumour progression-free survival compared to the mitozantrone/prednisone arm. The percentage of patients with an improvement in quality of life (QoL) score during the trial was also significantly higher in the docetaxel arm.

See Recommendations and Reasons.

9. Clinical Claim

The submission claimed that compared with mitozantrone/prednisone, docetaxel plus prednisone significantly extends overall survival and improves Quality of Life (QoL), but was associated with a higher rate of adverse events**.**

The PBAC considered this claim appropriate.

10. Economic Analysis

An updated preliminary economic evaluation was presented. The re-submission updated the costs of drugs.

An updated modelled economic evaluation was presented.

The base case modelled incremental undiscounted cost/extra undiscounted QALY was estimated to be in the range of $15,000- $45,000 (ITT population) and between $15,000- $45,000 (excluding patients with crossover) based on utilities generated by the re-submission; $45,000 – $75,000 and $75,000 – $105,000 respectively if based on utilities used by the PBAC previously; $15,000 - $45,000 and $45,000 – $75,000 respectively if based on utilities referenced from the Tufts-New England Medical Center CEA registry.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated to be < 10,000 patients in Year 4.

The financial cost/year to the PBS was estimated to be in the range $30 – 60 million in Year 4.

12. Recommendation and Reasons

The PBAC considered it may be appropriate to restrict treatment to patients with a Karnofsky's performance score of at least 60%, which is compatible with the trial data; and to 10 cycles, as it is rare for patients to tolerate more than six 3-weekly cycles of docetaxel.

The PBAC noted that there were no changes to the trial data presented in the previous submission, but that the original data were supplemented by a post hoc analysis excluding patients who crossed over to the other treatment. Docetaxel plus prednisone achieved an overall statistically significant median survival benefit of 2.43 months compared with mitozantrone plus prednisone. The PBAC considered this survival benefit to be small and the gain was at the expense of the high toxicity of treatment with docetaxel. The median survival benefit of 2.43 months was shown when crossover patients were included (ITT), and a median survival benefit of 3.78 months (statistically significant also) when crossover patients were excluded. The PBAC considered the ITT analysis to be more appropriate. The ITT population, i.e. including crossovers, is more appropriate for use in an economic analysis as it is intended to evaluate the cost-effectiveness of the drug in clinical practice (under usual conditions). Based on the benefit in median survival in the ITT population (2.43 months over mitozantrone plus prednisone), the submission estimated a mean survival difference of 3.73 months using a Weibull model, which was accepted by the PBAC.

The PBAC noted that the re-submission presented the incremental cost/QALY gained based on a Quality-adjusted Time Without Symptoms and Toxicity (Q-TWiST) analyses. Three sets of utility values were used in the model, including those used by the PBAC in an exploratory Q-TWiST analysis reported in the PBAC short minutes of July 2005, secondly, values sourced from the Tufts-New England Medical Centre CEA registry, and finally, those generated for the re-submission using a Standard Gamble method, in which 100 Australian men from the general population were interviewed.

The PBAC discounted the analysis based on its July 2005 exploratory utility values as highly uncertain. It also noted that not all of the utility values for the Tufts registry were matched to the population in the model presented. Thus the results from this analysis were also considered uncertain.

The PBAC agreed with the ESC advice about the high uncertainty of the utility values in the Australian Health Utility study. The PBAC considered there were also a number of problems with the survival estimates used in the Q Twist analysis presented in the submission. These survival results could not be reproduced during the evaluation. Thus the quality adjusted survival derived from uncertain utilities and uncertain estimates of survival was also considered to be uncertain.

Therefore, the PBAC rejected the submission because of uncertain cost-effectiveness.

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 is disappointed with this outcome as we believe docetaxel to be the **only** drug that has been able to demonstrate a survival benefit (associated with an improvement in quality of life) in the treatment of androgen independent prostate cancer (AIPC), the most common cancer in Australian men, and the second leading cause of male cancer deaths. This clinical benefit has been acknowledged by the PBAC.

However, and despite the fact that Taxotere is already reimbursed for lung cancer, ovarian cancer, breast cancer and that the price of Taxotere is now lower compared to when it was listed for these other cancer types, the PBAC has rejected reimbursement for Taxotere in AIPC for a second time. Sanofi-aventis is committed to continue working with the PBAC in order to provide equitable access to Taxotere for AIPC patients.