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: July 2007

1. Purpose of Application

The resubmission sought to extend 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 they considered that there are other therapies available to treat the condition. *(See also Public Summary Document for July 2005)*

At the November 2006 meeting, the PBAC rejected a second submission to extend the authority required PBS listing for docetaxel to include the treatment of hormone refractory prostate cancer because of uncertain cost-effectiveness. The PBAC suggested that any new submission should address all of the issues raised about the Australian Health Utility study and that the Q-TWIST analysis should be presented in such a way that the incremental cost effectiveness ratios (ICERs) generated by the analysis can be verified during the evaluation process. *(See also Public Summary Document for November 2006)*

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;
Taxotere in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with node positive breast cancer;
Taxotere 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.
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: Taxotere is indicated for the 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.

The PBAC considered that any restriction on the listing of docetaxel should stipulate use as first-line chemotherapy, a minimum Karnofsky score of 60%, that dosing must be on a 3-weekly basis (there was no survival difference when using weekly dosing) and a maximum of 10 cycles.

5. Clinical Place for the Proposed Therapy

Prostate cancer is the most common cancer in Australian men and the second leading cause of cancer deaths in males. 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, they all of 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

Appropriately, the submission nominated mitozantrone as the comparator. This is as previously agreed by the PBAC.

7. Clinical Trials

No changes were made to the trial data presented in the previous submissions and the PBAC noted that no new efficacy data had been presented.

Analysis of the intention-to-treat population remained the primary analysis.

8. Results of Trials

The results presented were not changed from previous submissions, treatment with docetaxel and prednisone resulted in a 24% improvement in overall survival [Hazard Ratio (HR) = 0.76; 95% CI: 0.62, 0.94] compared to treatment with mitozantrone and prednisone in the key trial TAX 327. Similar results were found in the supportive trial. Analysis showed that docetaxel plus prednisone achieves an overall median survival benefit of 2.43 months, and an overall mean survival benefit of 3.73 months, compared with mitozantrone plus prednisone.

The PBAC noted that no new toxicity data were presented in the re-submission.

9. Clinical Claim

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

The PBAC accepted this claim.

10. Economic Analysis

The submission presented an updated economic evaluation using a Q-TWiST analysis with the total time period (overall survival) partitioned into five health states:

- Time with treatment response and toxicity;
- Time with treatment response without toxicity;
- Time without response or progression but with toxicity;
- Time without response or progression or toxicity; and
- Disease progression.

The utility weights used in the Q-TWiST analysis were derived from a new Australian Health Utility study, which used a conventional Standard Gamble approach. The utility values were derived according to the severity of the toxicity.

Disease progression was defined as the minimum (earliest) occurrence of pain, prostate specific antigen (PSA) increase or tumour progression as reported in the trial data. Treatment response was defined as PSA response.

The base case modelled incremental undiscounted cost/extra undiscounted QALY was estimated to be in the range $75,000 – $105,000.

The sponsor argued that it was widely recognised that the measure of Quality of Life had limitations, particularly when it was evaluated in an end of life setting. The sponsor claimed that androgen independent (hormone refractory) prostate cancer (AIPC) is such a setting and for this reason considered it to be relevant that the incremental cost per quality adjusted life year (QALY) be considered alongside an incremental cost per life year gained (LYG). The base-case incremental cost per LYG for docetaxel was in the range $45,000 – $75,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated that in Year 5 of listing the likely number of patients/year would be < 10,000 and the financial cost/year to the PBS would be in the range $30 – $60 million.

12. Recommendation and Reasons

The PBAC noted that no new efficacy and safety data had been presented. The re-submission conducted a new Australian Utility study to elicit utility weights for the new Q-TWiST analysis. In this new Australian Utility study, a conventional Standard Gamble method was used to incorporate treatment response and toxicities into the same health state.

The PBAC agreed that the use of a five-state Q-TWiST analysis in this instance was reasonable, given that all the information required for the construction of the Q-TWiST were derived from the trial patient level data, with the exception of the assumption made in the

model that 'time with treatment response' is equal to 'disease free survival' for those patients who respond to treatment.

There was some uncertainty about the utility weights derived from the new Australian Health Utility study, given the lack of detailed description of adverse events in the Standard Gamble interview, and the smallness of the differences due to differing grades of toxicity. However, the worst health states appeared to be reasonably valued as being associated with worse utility values.

The PBAC did not accept the claims of the Pre-PBAC Response that a decision could be made on the basis of the cost per life year gained, particularly given the toxicity of treatment. The PBAC concluded that, overall, it was unlikely that further adjustments of the Q-TWiST analysis would alter substantially the resultant incremental cost-effectiveness ratio (ICER) which was unacceptably high.

The Committee indicated that it would be prepared to consider a price offer to make a recommendation to list out-of-session.

Following deferral of the submission at the July 2007 PBAC meeting, sanofi-aventis made a price offer for the androgen independent prostate cancer indication which resulted in an ICER in the range $45,000 – $75,000.

Recommendation and reasons arising from extraordinary PBAC meeting:
The PBAC recommended, at an extraordinary PBAC meeting, the listing of docetaxel on the PBS as an authority required benefit for the treatment of androgen independent (hormone refractory) carcinoma of the prostate in a patient with a Karnofsky performance-status score of at least 60% on the basis of an acceptable incremental cost-effectiveness ratio per quality adjusted life year at the new price proposed.

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 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®

Restriction:

Authority required
Treatment of androgen independent (hormone refractory) metastatic carcinoma of the prostate in a patient with a Karnofsky performance-status score of at least 60%. Docetaxel must be used as first line chemotherapy and administered in three weekly cycles.

NOTE: A maximum of 10 cycles of treatment with docetaxel will be authorised under this restriction.

GRANDFATHER (to be removed from Schedule on 1 May 2008)
Authority required
Treatment of androgen independent (hormone refractory) metastatic carcinoma of the prostate in a patient with a Karnofsky performance-status score of at least 60%, where the patient was receiving prior

treatment with other chemotherapy for androgen independent (hormone refractory) metastatic carcinoma of the prostate at 1 November 2007. Docetaxel must be administered in three weekly cycles.

NOTE: A maximum of 10 cycles of treatment with docetaxel will be authorised under this restriction.

Maximum quantity: 2 (20mg), 1 (80 mg)
Number of repeats: nil (both strengths)

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

On behalf of men with androgen independent prostate cancer (AIPC) and their families, sanofi-aventis welcomes the PBAC decision to recommend listing of docetaxel which is the only chemotherapy proven to extend survival and improve Quality of Life in patients with late stage prostate cancer.

We recognise that the use of the QALY as the outcome in end stage cancer is debated in the literature, but acknowledge that PBAC's desire that it be the relevant outcome for determining the cost effectiveness of medicines in prostate cancer.