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 80 mg (anhydrous) in 2 mL and 1 single use vial solvent 6 mL, Taxotere®
Sponsor:	Sanofi-aventis Group
Date of PBAC Consideration:	March 2006

1. Purpose of Application

The submission requested an extension of the current authority required listing for docetaxel to include the adjuvant treatment of operable, node positive, oestrogen receptor (ER) positive breast cancer.

2. Background

Docetaxel currently has authority required listings on the Pharmaceutical Benefits Scheme (PBS) for:

- use in advanced breast cancer after failure of prior therapy which includes an anthracycline;
- locally advanced or metastatic non-small cell lung cancer (NSCLC);
- advanced metastatic ovarian cancer after failure of prior therapy which includes a platinum compound.

At the July 2005 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) deferred a submission to extend the current authority required listing for docetaxel to include the adjuvant treatment of operable node positive breast cancer due to considerable uncertainty about the incremental cost-effectiveness of TAC (docetaxel, doxorubicin and cyclophosphamide) over FAC (fluorouracil, doxorubicin and cyclophosphamide) because of problems with the economic model.

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.

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

Adjuvant treatment of operable node-positive, oestrogen receptor positive, breast cancer administered in combination with an anthracycline (e.g. doxorubicin) and cyclophosphamide.

The PBAC considered that "doxorubicin" could be replaced with "an anthracycline", as in practice, the drugs classified as anthracyclines are used interchangeably and that the word "operable" was redundant, as adjuvant treatment was given after the patient had had breast cancer surgery. The PBAC also did not agree that docetaxel should be restricted to oestrogen receptor (ER) positive patients *(See Recommendation and Reasons).*

5. Clinical Place for the Proposed Therapy

Docetaxel will be used in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of node positive breast cancer.

6. Comparator

The submission nominated FAC (fluorouracil + doxorubicin + cyclophosphamide) as the comparator for the docetaxel regimen for the adjuvant treatment of node positive oestrogen-receptor positive breast cancer.

The PBAC accepted that this was the appropriate comparator, regardless of ER status *(See Recommendation and Reasons).*

7. Clinical Trials

The submission presented the results of a head-to-head randomised trial over a mean of 55 months comparing six cycles of TAC (docetaxel + doxorubicin + cyclophosphamide) with six cycles of FAC (fluorouracil + doxorubicin + cyclophosphamide) as adjuvant treatment of operable node-positive breast cancer patients.

This trial had been published at the time of submission, as follows:

Trial/first author	Protocol/Publication title	Publication citation
Martin M et al., on behalf of the TAX316/BCIRG 001 investigators.	TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up.	San Antonio Breast Cancer Symposium, Abstract No. 43, December 2003.
Martin et al.	Adjuvant docetaxel for node-positive breast cancer.	N Engl J Med 2005; 352: 2302-2313.

8. Results of Trials

In the key trial comparing TAC and FAC there was a statistically significant difference in disease free survival favouring TAC in the primary analysis. There was a 28% reduction in disease relapse for TAC compared to FAC (23% vs 30%; hazard ratio = 0.72; 95% CI: 0.59 – 0.88) for 5-year disease free survival. There was a statistically significant difference in the secondary outcome of overall survival favouring TAC, with a 30% improvement in survival associated with TAC compared with FAC (12% vs 17%; hazard ratio 0.70, 95%CI: 0.53, 0.91).

There were 28% and 31% reductions in disease relapse for TAC compared to FAC in ER-positive and ER-negative patients, respectively (hazard ratios ER-positive = 0.72; 95% CI: 0.56 – 0.92; ER-negative = 0.69 95% CI: 0.49 – 0.97) for 5-year disease free survival.

In the key trial, TAC was more toxic than FAC with more frequent febrile neutropenia, more Grade 3/4 neutropenia and more infections. TAC was also associated with a higher incidence of long-term amenorrhoea, alopecia, and neurosensory effects.

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

9. Clinical Claim

The submission claimed that docetaxel had significant clinical advantages over anthracycline-based therapy, but had more toxicity for the treatment of operable node-positive oestrogen receptor positive breast cancer.

The PBAC accepted this claim.

10. Economic Analysis

A new preliminary (trial-based) economic evaluation was presented. Australian patterns of resource use were applied in the updated trial-based economic model.

Two modelled economic evaluations were provided to address the concerns raised by the PBAC at the July 2005 meeting. In the first, referred to as the 2-part parametric model, the base case modelled incremental discounted cost per extra discounted quality-adjusted life-year gained was in the range $15,000 - $45,000 for ER-positive and ER-negative patients combined.

Sensitivity analyses of various sub-groups were performed with a second model.

11. Estimated PBS Usage and Financial Implications

The submission estimated the number of patients with operable ER positive breast cancer eligible for TAC to be <10,000 in year 4 of listing. The incremental cost to the PBS, inclusive of granulocyte colony stimulating factor (G-CSF) costs, was estimated to be in the range $10 – 30 million in year 4 of listing.

12. Recommendation and Reasons

The PBAC recommended listing on the basis of acceptable cost-effectiveness comparing docetaxel + doxorubicin + cyclophosphamide (TAC) with fluorouracil + doxorubicin + cyclophosphamide (FAC) for the adjuvant treatment of node-positive breast cancer, irrespective of oestrogen receptor (ER) status. The PBAC accepted that the appropriate comparator was that proposed in the submission, regardless of ER status. Although, as a taxane, paclitaxel is a close pharmacological analogue of docetaxel, the PBAC considered that its use as sequential therapy after adjuvant therapy was sufficiently different in therapeutic intent and clinical impact to docetaxel's use as part of adjuvant therapy to justify not applying this criterion in determining the main comparator for the recommended restriction.

The PBAC considered that the available evidence did not support a conclusion that ER status is a treatment effect modifier in either the primary outcome of disease-free survival or the

secondary outcome of overall survival. The PBAC also concluded that, in isolation, ER status was not a sufficiently strong prognostic variable to justify using different placebo rates of disease-free survival or overall survival to predict different absolute risk reductions with sufficient confidence to justify differentiating a restriction based on ER status.

The PBAC noted the results of the 2-part parametric modelled evaluation and that the revised model provided a better fit from the overall intention-to-treat (ITT) survival data from Trial TAX 316 than in the previous submission. The PBAC considered that the results of this model supported a conclusion that docetaxel was acceptably cost-effective for the combined population of ER negative and ER positive patients.

The PBAC requested that the sponsor confirm the existence of one or more ongoing trials of TAC compared with AC followed by four or more cycles of paclitaxel or other taxane agent. If such trials exist, the PBAC requested that the sponsor provide regular updates to the PBAC of the results of these trials by presenting the observed disease-free survival and overall survival results measured in these trials as plots superimposed on those observed from the TAC versus FAC trial and on those projected by the 2-part parametric model. The PBAC further requested that the sponsor confirm whether there is ongoing follow-up of the TAC vs FAC trial. If so, then the PBAC similarly requested that the sponsor provide regular updates to the PBAC of the results of these trials by presenting the future observed disease-free survival and overall survival results measured in this trial as plots superimposed on those projected by the 2-part parametric model.

Recommendation
Add the following restriction to the current listing:

Restriction	<u>Authority required</u> Adjuvant treatment of node-positive breast cancer in combination with an anthracycline and cyclophosphamide.
Maximum Quantity:	2 for 20 mg; 1 for 80 mg
Repeats	0

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 acknowledges the PBAC's conclusion that docetaxel is both clinically effective and cost effective in the adjuvant treatment of breast cancer regardless of the number of positive nodes or the ER status. We also note that the cost effectiveness of docetaxel remains in the same range as presented at the July 2005 PBAC meeting and look forward to working with the Department of Health to ensure that PBS listing occurs as soon a possible.