Public Summary Document

Product:	Paclitaxel, solution concentrate for I.V. infusion, 30 mg in 5 mL, 100mg in 16.7 mL, 150 mg in 25 mL and 300 mg in 50 mL, Anzatax®
Sponsor:	Mayne Pharma Pty Ltd
Date of PBAC Consideration:	March 2006

1. Purpose of Application

The submission requested a change to the current Pharmaceutical Benefits Scheme (PBS) authority required listing for paclitaxel by removing the oestrogen receptor (ER) negative requirement in the adjuvant treatment of node-positive breast cancer, i.e. allowing treatment of ER positive patients.

2. Background

Paclitaxel was initially listed on the PBS on 1 October 1994 as an authority benefit for advanced metastatic ovarian carcinoma after failure of standard therapy including a platinum compound. In February 1996, the authority listing was extended to include treatment of advanced metastatic breast cancer after failure of standard therapy including an anthracycline, and in May 1998 for primary treatment of ovarian cancer in combination with a platinum compound.

In September 2000, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended an extension to the authority required listing to include the adjuvant treatment of node-positive, ER negative, breast cancer administered sequentially to doxorubicin and cyclophosphamide on the basis of acceptable cost-effectiveness in node positive, ER negative, breast cancer only.

3. Registration Status

Paclitaxel is registered for:

- the primary treatment of ovarian cancer in combination with a platinum agent;
- treatment of metastatic ovarian cancer and metastatic breast cancer, after failure of standard therapy;
- treatment of locally advanced or metastatic non-small cell lung cancer;
- for adjuvant treatment of node positive breast cancer administered sequentially to doxorubicin and cyclophosphamide;
- for the treatment of metastatic cancer of the breast, in combination with trastuzumab (Herceptin®), in patients who have tumours that over-express HER-2 and who have not received previous chemotherapy for their metastatic disease.

4. Listing Requested and PBAC's View

Authority required:

Adjuvant treatment of node positive breast cancer administered sequentially to doxorubicin hydrochloride and cyclophosphamide.

For PBAC's views see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Early breast cancer patients who have had surgery have a 30-60% chance of disease recurrence. The role of systemic adjuvant therapy is the elimination of micrometastatic disease which results in death in the majority of women in whom it is present at diagnosis. Paclitaxel is one of a number of chemotherapy drugs which may be used in adjuvant therapy.

6. Comparator

The submission nominated no sequential therapy following standard chemotherapy with doxorubicin hydrochloride and cyclophosphamide (AC) as the main comparator for paclitaxel in the adjuvant setting. The PBAC accepted this as appropriate.

7. Clinical Trials

The submission presented two randomised trials (CALGB 9344 and NSABP B-28) comparing paclitaxel sequentially administered to doxorubicin and cyclophosphamide (AC) with AC alone in node-positive breast cancer patients over a 7-year period. This group included both ER-positive and ER-negative cancer patients. The dosage of paclitaxel was 175mg/m^2 and 225mg/m^2 in the CALGB 9344 and NSABP B-28 trials, respectively. Three different doses of doxorubicin (60, 75, 90mg/m^2) were used in the CALGB 9344 trial. Only one dose of doxorubicin (60mg/m^2) was used in the NSABP B-28 trial. The dose of cyclophosphamide 600mg/m^2 was the same for both trials.

These trials had been published at the time of submission as follows:

Trial/First author	Protocol title	Publication citation
CALGB 9344 Henderson IC	Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer.	Journal of Clinical Oncology, 21(6): 976–83, 2003
CALGB 9344 Berry DA	Effects of improvements in chemotherapy on disease free and overall survival of estrogen-receptor negative, node-positive breast cancer: 20-year experience of the CALGB and U.S. Breast Intergroup	Proceedings of the San Antonio Breast Cancer Symposium, 2004
NSABP B-28 Mamounas EP	Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28.	Journal of Clinical Oncology, 23(16):3686–96, 2005

8. Results of Trials

The results of the key trials for all node-positive patients are summarised in the following table.

Results of disease-free survival and overall survival in node-positive patients from the comparative randomised trials (intention-to-treat population at median 5 years' follow-up)

Trial	AC + PTX	AC	ARD (95% CI)	RR (95% CI)	HR (95% CI)	NNT [§] (95% CI)
Disease-free survival (risk of DFS failure events)						
CALGB 9344	491/1590 (31%)	563/1580 (36%)	-0.05 (-0.08, -0.01)	0.87 (0.78, 0.96)	0.83 (0.73, 0.94) [1]	20 (13, 100)
NSABP B-28	400/1531 (26%)	463/1528 (30%)	-0.04 (-0.07, -0.01)	0.86 (0.77, 0.97)	0.83 (0.72, 0.95) [2]	25 (14, 100)
Pooled *			-0.04 (-0.07, -0.02)	0.86 (0.80, 0.93)	0.83 (0.76, 0.91)	25 (14, 50)
Overall survival (risk of death)						
CALGB 9344	342/1590 (22%)	400/1580 (25%)	-0.04 (-0.07, -0.01)	0.85 (0.75, 0.96)	0.82 (0.71, 0.95) [1]	25 (14, 100)
NSABP B-28	243/1531 (16%)	255/1528 (17%)	-0.01 (-0.03, 0.02)	0.95 (0.81, 1.12)	0.93 (0.78, 1.12) [2]	100 (NNTB 33 to ∞ to NNTH 50)
Pooled *			-0.02 (-0.04, 0.00)	0.89 (0.80, 0.98)	0.86 (0.77, 0.97)	50 (25, ∞)

AC = doxorubicin + cyclophosphamide; PTX = paclitaxel; ARD = absolute risk difference; RR = relative risk; HR = hazard ratio; DFS = disease-free survival

* fixed and random effects models produced same results; heterogeneity test p>0.10

[§] all point estimates are number needed to treat to benefit (NNTB), unless otherwise stated; NNTH = number needed to treat to harm

[1] HR adjusted in the model according to the number of positive nodes, the square root transformation of tumour size, and age at study entry.

[2] HR stratified by type of surgery performed (lumpectomy, mastectomy), number of positive nodes (1-3, 4-9, 10+) removed after surgery and tamoxifen assigned per protocol.

Although the pooled analyses showed statistically significant reductions in the risk of disease-free survival failure events (recurrence, secondary primary cancer and death) and in the risk of death with AC + paclitaxel over AC alone, absolute reductions in risks over 5 years are small (4% for disease-free survival failure events and 2% for death).

The submission also provided a post-hoc sub-group meta-analysis for ER-positive and ER-negative patients at median 5 years'follow-up. The sub-group analysis of ER-positive and ER-negative patients was conducted post-hoc for CALGB 9344, but was pre-specified for NSABP B-28.

Comparison of sub-group analyses of ER status and use or not of tamoxifen by CALGB 9344 and NSABP B-28

Sub-group	HR (95% CI)	
	CALGB 9344 (median 69 month follow-up)	NSABP B-28 (median 64 month follow-up)
ER-positive	0.91 (0.78, 1.07)	0.77 (0.65, 0.92)
ER-negative	0.72 (0.59, 0.86)	0.90 (0.72, 1.12)
Received tamoxifen	0.92 (0.79, 1.08)	
Received no tamoxifen	0.69 (0.57, 0.84)	

Based on the comparative trials, alopecia, granulocytopenia and sensory neurological disturbances were found to be more prevalent in patients taking AC + paclitaxel compared to those patients receiving AC alone. More toxicity-related treatment discontinuations occurred among patients receiving AC + paclitaxel than those receiving AC alone.

9. Clinical Claim

The submission claimed that paclitaxel following standard chemotherapy with doxorubicin hydrochloride and cyclophosphamide (AC) had significant clinical advantages over no sequential therapy following standard chemotherapy with AC in the adjuvant setting. It was significantly more effective and had similar or less toxicity.

For PBAC's views see Recommendations and Reasons.

10. Economic Analysis

A preliminary economic evaluation was presented. The choice of the cost-effectiveness approach was considered valid. The treatment outcomes were disease-free survival and overall survival based on pooled data over 7 years for all the node-positive population and over 6 years for the node-positive, ER-positive patients. The resources included were drug costs, drug administration costs, pre-medication costs, co-administered drug costs and costs of hospitalisation.

The trial-based incremental discounted cost per extra discounted life-years gained for all node-positive patients was in the range $105,000 - $200,000 over the trial duration of 7 years; and for node-positive ER-positive patients was in the range of $105,000 - $200,000 over 6 years.

The trial-based incremental discounted cost per extra discounted disease-free years gained for all node-positive patients was in the range $45,000 - $75,000 over 7 years; and for node-positive ER-positive patients was in the range of $105,000 - $200,000 over 6 years.

Two separate, but related, modelled economic evaluations using a cost-utility approach were presented.

- Scenario 1 considered ongoing treatment effects that extended beyond the end of the trial until Year 10; and
- Scenario 2 assumed that the treatment effects stop at the end of the trial (7 years) and both groups become identical in terms of survival.

The base case modelled incremental discounted cost per extra discounted quality-adjusted life-years gained for all node-positive patients was in the range of $15,000 - $45,000 for both scenario 1 and scenario 2.

The base case modelled incremental discounted cost per extra discounted quality-adjusted life-years gained for node-positive ER-positive patients was in the range of $15,000 - $45,000 for both scenario 1 and scenario 2.

11. Estimated PBS Usage and Financial Implications

The submission estimated that < 10,000 additional patients each year would receive paclitaxel adjuvant chemotherapy from 2006, if listed. The net cost to the PBS was estimated to be < $10 million in year 4 of listing.

12. Recommendation and Reasons

The PBAC recommended extension to the current listing as requested in the submission to allow for the adjuvant treatment of node positive breast cancer irrespective of oestrogen receptor status, on a cost-effectiveness basis as compared to no sequential therapy following an anthracycline and cyclophosphamide.

The PBAC considered that the updated and new evidence did not support the previous 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 further 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 Committee therefore considered that there was no longer sufficient reason to deny treatment of ER positive patients with this regimen, and that by doing so would raise an equity of access issue with respect to the current PBS availability of this drug for ER negative patients.

However, the PBAC expressed concern regarding the overall cost-effectiveness of sequential paclitaxel in the treatment of breast cancer given new evidence that has become available since its initial PBS listing. This was for a number of reasons, including that the 5 year follow-up data presented in the current submission were less favourable that the 30 month data relied upon for the node positive ER-negative group.

The Committee thus foreshadowed that it would be appropriate for sequential paclitaxel in early breast cancer to be selected for a review of its cost-effectiveness under the *Cost-Effectiveness Review* mechanism. The Department was requested to advise whether such a review would be feasible and give an indication of the possible timing.

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

No comment.