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 2009

1. Purpose of Application
The submission requested to extend the current authority required listing for docetaxel to include adjuvant treatment of operable breast cancer in combination with cyclophosphamide.

2. Background
Docetaxel has not previously been considered by the PBAC for adjuvant treatment of operable breast cancer in combination with cyclophosphamide.

3. Registration Status
The TGA registration for docetaxel was extended on 21 August 2009 to include the adjuvant treatment of operable breast cancer with a primary tumour of greater than or equal to 1 cm and less than 7 cm, in combination with cyclophosphamide; Doxorubicin and cyclophosphamide followed by docetaxel in combination with trastuzumab (AC-TH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumours overexpress HER2 and docetaxel in combination with carboplatin and trastuzumab (TCH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumours overexpress HER2.

Docetaxel was first TGA registered on 6 February 1996, and 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.

Head and neck cancer:
Locally advanced, squamous cell carcinoma.

4. Listing Requested and PBAC's View

Authority Required
Adjuvant treatment of operable breast cancer in combination with cyclophosphamide.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Breast cancer is the most notifiable cancer for women in Australia, accounting for more than one in four of all female cancers, and the most common cause of cancer-related death.

In patients with early breast cancer, the cancer is operable and is restricted to the breast. The exception is in women with 'node positive' disease, where the cancer involves the lymph nodes. The primary treatment in most situations is surgery. Treatment given subsequent to surgery is referred to as 'adjuvant' and aims to achieve total disease control. Doxorubicin (an anthracycline) plus cyclophosphamide (AC) is the most common adjuvant treatment of breast cancer. However, there are long term cardiotoxicity and bone marrow toxicity risks with anthracycline use.

Docetaxel plus cyclophosphamide (TC) regimen would provide an alternative non-anthracycline adjuvant treatment of operable breast cancer.

6. Comparator

The submission nominated the chemotherapy regimen of doxorubicin plus cyclophosphamide (AC) as the main comparator.

The PBAC considered that the comparator AC was appropriate but that a wider range of therapies might be utilised in clinical practice in this patient population.

7. Clinical Trials

The submission presented one randomised trial comparing docetaxel (75 mg/m^2) plus cyclophosphamide (600 mg/m^2) with doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2), administered intravenously every 21 days for four cycles, in patients with operable breast cancer as adjuvant treatment, over a follow-up of seven years.

The key trials published at the time of submission are shown in the table below:

Trial ID/First author	Full Title	Publication citation
Full report of 5-year follow-up		
Jones et al. 2006	Phase III trial comparing doxorubicin plus cyclophosphamide as adjuvant therapy for operable breast cancer.	Journal of Clinical Oncology 24(34):5381-5387

Abstract reports of 5-year follow-up		
Jones et al. 2001	Preliminary results of a prospective randomized trial of adjuvant chemotherapy for patients with stage I-III operable, invasive breast cancer comparing four courses of Adriamycin/cyclophosphamide (AC) to four courses of Taxotere/cyclophosphamide (TC).	Proceedings of the American Society of Clinical Oncology 2001, Vol 20, Part 1, p 33a, Abstract Number 128. 37th Annual Meeting of ASCO, San Francisco (May 12-15, 2001)
Jones et al. 2003	Three year results of a prospective randomized trial of adjuvant chemotherapy for patients (pts) with stage I-III operable, invasive breast cancer comparing 4 courses of doxorubicin/cyclophosphamide (AC) to 4 course of docetaxel/cyclophosphamide (TC).	Proc Am Soc Clin Oncology 22:15, 2003 (abstract 59)
Jones et al. 2005	Final analysis: TC (docetaxel/cyclophosphamide, 4 cycles) has a superior disease-free survival compared to standard AC (doxorubicin/cyclophosphamide) in 1016 women with early stage breast cancer.	Breast Cancer Res Treat 2005; 94(Suppl 1): S20, Abs: 40 Presented at the 28th Annual San Antonio Breast Cancer Symposium, December 8-11, 2005
Full report of 7-year follow-up		
Jones et al. 2009	Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Adjuvant trial 9735.	Journal of Clinical Oncology 27(8): 1177-1183
Abstract report of 7-year follow-up		
Jones et al. 2007	Extended follow-up and analysis by age of the US Oncology Adjuvant trial 9735: docetaxel/cyclophosphamide is associated with an overall survival benefit compared to doxorubicin/cyclophosphamide and is well tolerated in women 65 or older.	Breast Cancer Res Treat 2007; 106(Suppl 1): S5, Abs: 12. 30th Annual San Antonio Breast Cancer Symposium (SABCS), San Antonio, TX (Dec 2007)

ASCO = American Society of Clinical Oncology; TX = Texas

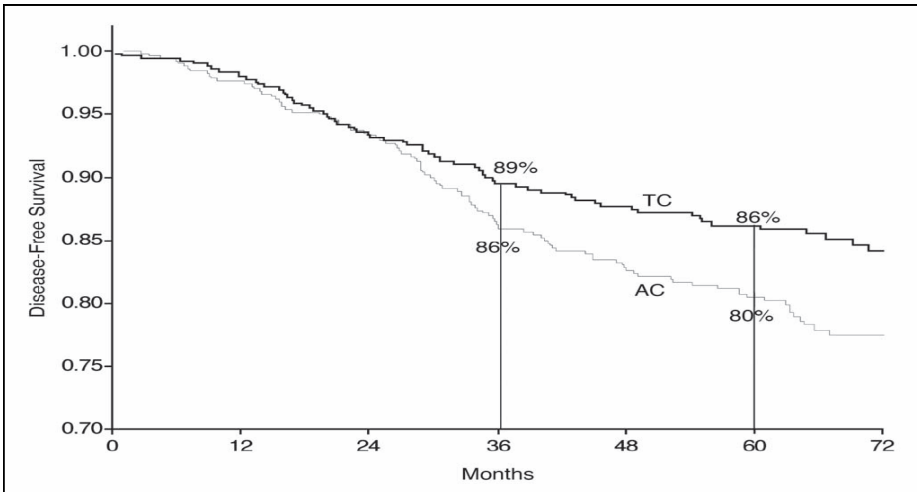
8. Results of Trials

The submission conducted analyses of disease-free survival and overall survival at 5 and 7 years follow up.

Five-year analyses

The disease-free survival (primary outcome) and overall survival (secondary outcome) at 5 years are presented in the figures below.

Disease-free survival at 5 years

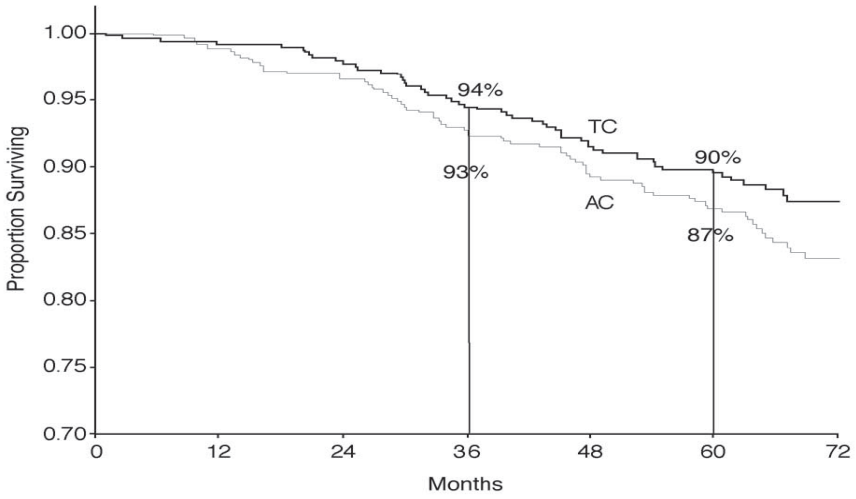


Arm	N	Relapse	Months	12	24	36	48	60	72	*P*
TC	506	71	% DFS	98	93	89	88	86	84	.015
AC	510	103	% DFS	98	93	86	83	80	78	

Patients at risk per year:

	12 Months	24 Months	36 Months	48 Months	60 Months	72 Months
TC	506	478	440	409	374	317
AC	510	483	450	401	369	307

Overall survival at 5 years



Arm	N	Deaths	Months	12	24	36	48	60	72	*P*
TC	506	55	% Survival	99	98	95	92	90	87	.13
AC	510	73	% Survival	99	97	93	90	87	83	

Patients at risk per year:

	12 Months	24 Months	36 Months	48 Months	60 Months	72 Months
TC	506	483	459	431	389	332
AC	510	489	466	433	400	335

TC = docetaxel plus cyclophosphamide; AC = doxorubicin plus cyclophosphamide

The disease-free survival rate for patients taking TC was 86% compared with 80% for patients receiving AC at 5 years (hazard ratio (HR) = 0.67, 95% confidence intervals (CI) 0.50, 0.94, p=0.015).

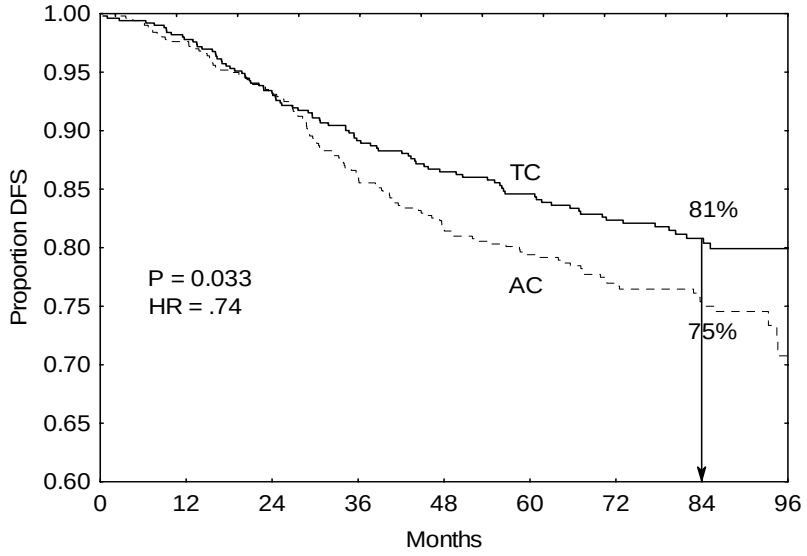
The overall survival rate for women treated with TC was 90% compared with 87% for women treated with AC (HR 0.76, 95% CI 0.52, 1.1, p = 0.13) at the 5-year follow-up. There were no statistically significant differences in overall survival between the two treatment arms at 5 years.

Seven-year analyses

The submission claimed that overall survival became a primary outcome in the seven-year follow-up analysis, after the trial protocol was amended. The PBAC noted that the protocol amendment did not specify that overall survival became a primary outcome in the 7-year analysis. Therefore, the Committee considered that overall survival should be treated as a secondary outcome, but was the more informative analysis.

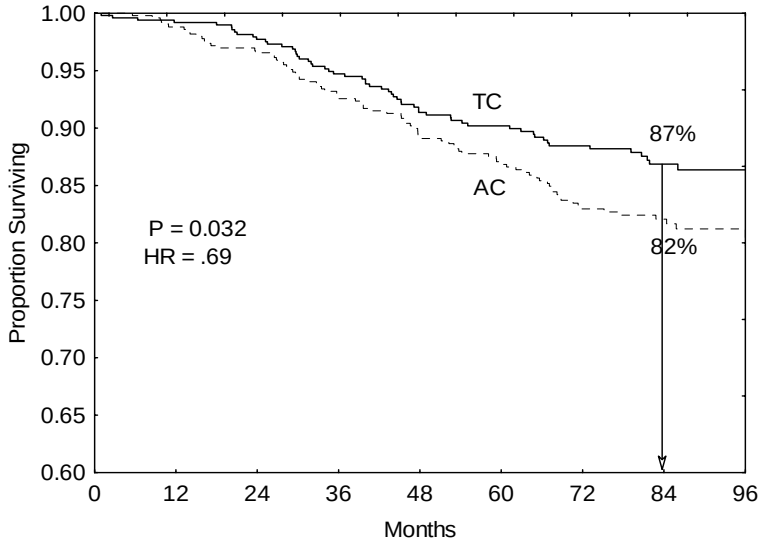
The disease-free survival and overall survival curves are presented below.

Disease-free survival at 7-year follow-up



At Risk									
	TC	506	481	442	410	378	349	320	195
	AC	510	483	449	405	372	343	303	194

Overall survival at 7-year follow-up



At Risk	TC	506	487	461	434	398	371	344	207
	AC	510	488	464	438	407	375	327	210

TC = docetaxel + cyclophosphamide; AC = doxorubicin + cyclophosphamide; HR = hazard ratio

The disease-free survival rate for women treated with TC was 81% compared with 75% for women treated with AC (HR 0.74, 95% CI 0.56, 0.98, p = 0.033) at 7-year follow-up.

The PBAC noted that the survival rate was 87% for patients treated with TC and 82% for those in the AC arm (HR = 0.69, 95% CI 0.50, 0.97, p=0.032; 58 vs 24 deaths), with a reduction in risk of relapse of approximately 20%, which was similar to that seen with second generation chemotherapy protocols such as 5-fluorouracil, epirubicin and cyclophosphamide (FE(100)C) x 6 cycles.

The trial results showed that TC patients experienced significantly more Grade 1 and 2 oedema, myalgia and arthralgia (p<.01), whereas AC patients had more Grade 1 to 4 nausea and vomiting (p<.01). More fever and neutropenia was observed with TC (25 patients, 5%) compared with AC (13 patients, 2.5%, p=0.07). Two patients died while receiving TC (one unrelated cardiac death and one death with sepsis and neutropenia). No patients died during the treatment with AC. It appears that TC is associated with increased short-term toxicities compared with AC.

There were three late deaths without relapse in the AC arm and the submission claimed that these three deaths were likely to be related to treatment. One of the deaths was from cardiomyopathy and congestive heart failure, and two died of complications related to myelodysplasia and myelofibrosis respectively. As there was no formal comparison of cardiac function at each assessment visit between treatment arms in the trial, the causal relation between AC treatment and these deaths is uncertain.

The submission provided additional data on potential safety concerns beyond those identified in the clinical trial. The submission stated that the Periodic Safety Update Report, which monitored the post-marketing safety of docetaxel over 15 years, did not identify new safety issues for docetaxel. The submission claimed that the use of anthracycline increases the risk

of cardio-toxicity, congestive heart failure and bone marrow toxicity. Long term cardio-toxicity of doxorubicin has been confirmed in the Product Information of doxorubicin.

For PBAC's comments, see Recommendation and Reasons.

9. Clinical Claim

The submission described docetaxel in combination with cyclophosphamide as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over doxorubicin in combination with cyclophosphamide.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

A modelled stepped economic evaluation was presented. The model estimated the proportion of patients (at monthly intervals) in both TC and AC arms who are alive, and who have recurrent disease (local or distant) based on Kaplan-Meier curves. Differences in mean survival between TC and AC were estimated as the area under the Kaplan-Meier curve for overall survival.

Within the trial period of 7 years, a curve of relapse was derived from the disease-free survival (DFS) curve. After the trial period of 7 years, it was assumed that no patients will relapse. Time spent in a health state of being alive or of relapse, which was estimated from the area under the Kaplan-Meier curves, was transformed to quality adjusted life years by using utility values generated in an Australian utility valuation study.

The time horizon in the modelled economic evaluation was 35 years.

The trial based cost-effectiveness ratio (including wastage) was in the range $45,000 - $75,000 per QALY gained.

The modelled cost-effectiveness ration (including wastage) was less than $15,000 per QALY gained.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be less than 10,000 in Year 5. The submission's estimate was considered to be uncertain.

The financial cost per year to the PBS was estimated to be less than $10 million in Year 5. The submission's estimate was considered to be uncertain.

12. Recommendation and Reasons

The PBAC recommended listing of docetaxel on the PBS for the adjuvant treatment of operable breast cancer in combination with cyclophosphamide on the basis of an uncertain but acceptable cost-effectiveness ratio compared with the chemotherapy regimen doxorubicin with cyclophosphamide (AC) given every 21 days for 4 cycles. The PBAC advised that it would be appropriate for the Pricing Authority to apply its usual methodology when considering the price for this extension to listing, which has substantial financial implications.

The PBAC considered that the comparator AC was appropriate but that a wider range of therapies might be utilised in clinical practice in this patient population, as acknowledged in the sponsor's Pre-Sub-Committee Response. However, the PBAC noted that TC has a survival rate at 7 years of 87% compared with 82% for AC [HR 0.69, 95% CI 0.50, 0.97, p = 0.032], a reduction in risk of relapse of approximately 20%, which is similar to that seen with second generation chemotherapy protocols such as FE(100)C x 6 cycles. However, the cost-effectiveness of TC versus second generation protocols such as FE(100)C is unknown. Therefore, the PBAC considered that the number of cycles of TC should be limited to 4, consistent with the number of cycles administered in the trial, which may decrease the uncertainty associated with the cost effectiveness.

The PBAC noted that the list of side effects in the trial was incomplete and did not include common side effects of docetaxel such as peripheral neuropathy, nail changes, constipation, skin eruptions and fatigue. The PBAC considered that the rates of febrile neutropenia were underestimated and that this may have been due to the fact that the use of prophylactic antibiotics was permitted in the trial. The PBAC considered that the disutility of the side effects from docetaxel was underestimated and that the ICER was therefore uncertain and likely to be higher.

Further, it was assumed that the cost of treating local recurrence is the same as that of distant recurrence. However, the two types of recurrence are likely to have different survival, quality of life and treatment costs. The PBAC noted there is a higher proportion of local relapse in the AC arm than in the TC arm. However, the submission uses an average value across both treatment arms to estimate the split of local and distant recurrence in order to derive the weighted utility for recurrence. The PBAC considered that this was not appropriate and was likely to bias the result in favour of TC, as TC has a higher distant recurrence than AC and distant recurrence has a lower utility than local recurrence.

The PBAC agreed with the ESC that none of the four extrapolation methods presented in the submission were conservative and that the incremental cost-effectiveness ratios calculated represented best-case scenarios. Extrapolation from a trial-duration of 7 years to a time horizon of 35 years had driven the model from an incremental cost of between $45,000 – $75,000/QALY to less than $15,000/QALY. However, the PBAC considered that the duration of extrapolation meant that the results are subject to considerable uncertainty and that the ICER could be higher than those estimated in the submission, although unlikely to be higher than the trial-based ICER of between $45,000 – $75,000/QALY which was high but acceptable.

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

Extend the current restriction to include:

Restriction:	<u>Authority Required</u> Adjuvant treatment of operable breast cancer in combination with cyclophosphamide.

NOTE:
A maximum of four cycles of treatment will be authorised under this restriction.

Maximum quantity:	2 (20 mg in 0.5 mL) 1 (80 mg in 2 mL)
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 welcomes the PBAC's decision to recommend PBS listing of docetaxel in combination with cyclophosphamide for use as adjuvant chemotherapy treatment of patients with operable breast cancer.