PUBLIC SUMMARY DOCUMENT
Product: Paclitaxel, powder for I.V. infusion (suspension), 100 mg, Abraxane®
Sponsor: Specialised Therapeutics Australia Pty Ltd.
Date of PBAC Consideration: November 2008

1. Purpose of Application

The submission sought an Authority Required listing for advanced breast cancer after failure of prior therapy which includes an anthracycline.

2. Background

This formulation of paclitaxel had not previously been considered by the PBAC.

Paclitaxel solution concentrate for I.V. infusion has been listed on the PBS since 1 October 1994.

3. Registration Status

Nanoparticle albumin-bound (nab) paclitaxel (Abraxane®) 100mg powder for injection (suspension) was registered by the TGA on 17 October 2008 for the treatment of metastatic carcinoma of the breast after failure of anthracycline therapy.

4. Listing Requested and PBAC's View

Authority Required
Advanced breast cancer after failure of prior therapy which includes an anthracycline.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Breast cancer is the most common invasive cancer and the most common cause of cancer-related death among Australian women. This formulation of paclitaxel provides a treatment alternative for patients with metastatic breast cancer following failure of prior therapy which includes an anthracycline.

Existing paclitaxel products have been formulated with Cremophor to improve water solubility. However, Cremophor is associated with hypersensitivity reactions. Paclitaxel powder for I.V. infusion contains paclitaxel bound to albumin to overcome the solubility and hypersensitivity problems. The albumin-bound formulation allows shorter infusion times and avoids the use of in-line filters and special tubing.

6. Comparator

The submission nominated the current PBS listings of solvent-based paclitaxel as the main comparator. Docetaxel was nominated as secondary comparator. This was accepted as appropriate by the PBAC.

7. Clinical Trials

The submission presented two key randomised trials (CA012 & CA201) comparing nab-paclitaxel 260 mg/m^2 every 3 weeks (q3w) with solvent-based paclitaxel 175 mg/m^2 q3w in patients with metastatic breast cancer, and a supplementary randomised trial (CA204) comparing nab-paclitaxel in 3 different dose regimens (300 mg/m^2 q3w, 100 mg/m^2 weekly and 150 mg/m^2 weekly) with docetaxel 100 mg/m^2 q3w.

The trials published at the time of submission are listed as below:

Trial ID/ Author	Protocol title/ Publication title	Publication citation
Direct randomised trials (nab-paclitaxel vs. paclitaxel)		
CA012	Clinical Study Report Final A controlled randomised Phase III, Multicentre, open label study of AB1-007 (a Cremophor®-free protein stabilized, nanoparticle paclitaxel) and Taxol® in patients with metastatic breast cancer.	February 2004
O'Shaughnessy J et al.	ABI-007 (ABRAXANE™), a nanoparticle albumin-bound (*nab*) paclitaxel demonstrates superior efficacy vs taxol in MBC: a phase III trial.	26th Annual San Antonio Breast Cancer Symposium December 2003.
Gradishar W et al.	Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.	*J Clin Oncol* 2005; 23: 7794-803.
CA201	CA201 Clinical Study Report A controlled, randomized, open label study to evaluate the efficacy and safety of capxol (a Cremophor-free, nanoparticle paclitaxel) and Cremophor-formulated paclitaxel injection in patients with metastatic breast cancer.	January 2007
Guan Z et al.	Randomized study comparing *nab*-paclitaxel with solvent-based paclitaxel in Chinese patients with metastatic breast cancer [poster].	American Society of Clinical Oncology Meeting; June 1-5, 2007; Chicago, IL. Abs 1038
Supplementary randomised trial (nab-paclitaxel vs. docetaxel)		
CA024	Protocol CA024 Amendment 4 A randomized Phase II study of weekly or every 3 weeks ABI-007 versus every 3 weeks Taxotere as first line therapy of Stage IV (metastatic) breast cancer	6 April 200**7**
Ranganathan A et al.	Randomized phase II trial of weekly or every-3-week albumin-bound paclitaxel versus every-3-week docetaxel as first-line therapy in patients with metastatic breast cancer.	*Clin Breast Cancer*. 2007; 7: 445-6
Gradishar W et al.	A randomised Phase 2 study of weekly or every-3-week *nab*-Paclitaxel versus every-3-week docetaxel as first-line therapy in patients with metastatic breast cancer.	San Antonio Breast Cancer Conference Plenary Session, December 2006

8. Results of Trials

Nab-paclitaxel vs. paclitaxel

Results of overall response rates derived from fixed effect meta-analyses using the ITT population and a range of subgroups are summarised in the table below. Response rates were statistically significantly higher for nab-paclitaxel compared with paclitaxel.

Data on overall response rates are shown in the table below.

Patients with overall response (invORR*, investigator assessment of overall response rate)

Study	*nab*-paclitaxel n/N (%)	Paclitaxel n/N (%)	OR (95% CI)	RR (95% CI)	p value
All patients (ITT)					
CA012	76/229 (33.2)	42/225 (18.7)	2.16 (1.40, 3.34)	1.78 (1.28, 2.47)	0.001
CA201	54/104 (53.8)	29/106 (29.2)	2.87 (1.61, 5.09)	1.90 (1.32, 2.72)	<0.001
Total			2.39 (1.69, 3.39)	1.83 (1.43, 2.33)	<0.0001
Patients receiving 1st line therapy					
CA012	41/97 (42.3)	24/89 (27.0)	1.98 (1.07, 3.68)	1.57 (1.04, 2,37)	0.029
CA201	33/61 (54.1)	17/64 (26.6)	3.26 (1.54, 6.89)	2.04 (1.27, 3.25)	0.001
Total			2.42 (1.51, 3.90)	1.75 (1.29, 2.39)	0.0004
Patients receiving > 1st line therapy					
CA012	35/132 (26.5)	18/136 (13.2)	2.37 (1.26, 4.44)	2.00 (1.20, 3.35)	0.006
CA201	21/43 (48.8)	12/42 (28.6)	2.39 (0.97, 5.86)	1.71 (0.97, 3.02)	0.122
Total			2.37 (1.42, 3.97)	1.88 (1.28, 2.77)	0.001
Patients with prior anthracycline therapy (adjuvant or metastatic)					
CA012	60/176 (34.1)	32/175 (18.3)	2.31 (1.41, 3.79)	1.86 (1.28, 2,71)	0.002
CA201	28/60 (46.7)	22/72 (30.6)	1.99 (0.97, 4.06)	1.53 (0.98, 2.37)	0.097
Total			2.20 (1.47, 3.31)	1.73 (1.30, 2.31)	0.002
Patients with prior metastatic anthracycline therapy					
CA012	31/115 (27.0)	18/130 (13.8)	2.30 (1.20, 4.38)	1.95 (1.15, 3.29)	0.010

Abbreviations: invORR: overall response rate based on Investigator Response Assessment Dataset i.e. the proportion of patients who achieved complete or partial overall response;
OR: odds ratio; RR: relative risk.

Patient survival and median time to death in Trials CA012 and CA201 are shown below.

Patient survival

Trial	*Nab*-paclitaxel n/N (%)	paclitaxel n/N (%)	OR (95% CI)	RR (95% CI)	P Value
Proportion of patients who died					
All patients (ITT)					
CA012	172/229 (75)	175/225 (78)	0.86 (0.56, 1.33)	0.97 (0.87, 1.07)	
CA201	20/104 (19)	13/106 (12)	1.70 (0.80, 3.63)	1.57 (0.82, 2.98)	
Total			1.13 (0.59, 2.16)	1.12 (0.70, 1.79)	0.90
Patients receiving 1st line therapy					
CA012	73/98 (74)	60/89 (67)	1.41 (0.75, 2.66)	1.10 (0.92, 1.33)	0.29
Patients receiving > 1st line therapy					
CA012	99/131 (76)	115/136 (85)	0.56 (0.31, 1.04)	0.89 (0.79, 1.01)	0.07
Patients who failed anthracyclines					
CA012	98/127 (77)	119/142 (84)	*0.65 (0.36, 1.20)*	*0.92 (0.82, 1.04)*	0.23

Median time to death – weeks						
	N	***nab*-paclitaxel median (95% CI)**	**N**	**paclitaxel median (95% CI)**	**Hazard Ratio (95% CI)**	**P Value**
All patients (ITT)						
CA012	229	65.0 (53.4, 76.9)	225	55.3 (48.0, 66.4)	0.899 (0.728, 1.110)	0.322
CA201[a]	104	>58.9 (47.3, >58.9)	106	>80.0	1.512 (0.752, 3.040)	0.242
Patients receiving 1st line therapy						
CA012	98	71.0 (59.4, 87.7))	89	77.9 (58.1, 98.0)	1.215 (0.863, 1.709)	0.264
Patients receiving > 1st line therapy						
CA012	131	56.4 (45.1, 76.9)	136	46.7 (39.0, 55.3)	0.726 (0.553, 0.952)	0.020
Patients who failed anthracyclines						
CA012	*127*	57.0 (45.1, 76.6)	*142*	46.7 (38.3, 55.3)	0.762 (0.582, 0.997)	0.047

Abbreviations: OR: odds ratio; RR: relative risk.

Only a subgroup of patients recruited in CA012 (prior anthracycline failure subgroup) was representative of the target population for whom the listing was sought. Survival data relevant to this subgroup showed no statistically significant difference in overall survival (77% vs. 84%, p=0.23). The proportions of patients who had died were substantially different in trials CA012 and CA201 (this may reflect the immature data in CA201).

Median time to death was significantly prolonged in the nab-paclitaxel arm for the subgroup who failed anthracycline therapy. However, the upper limit of the confidence interval was very close to 1.0 (HR: 0.762, 95% CI: 0.582, 0.997). Given that no adjustment for multiplicity in the multiple subgroup analyses had been conducted, the US Food and Drug Administration (FDA) had expressed the view that the p value presented for overall survival was not interpretable.

Nab-paclitaxel vs. docetaxel

Data on overall response, progression free survival and overall survival in Trial C204 are presented below.

Patients with overall response (invORR)

	300mg/m^2 q3w n/N (%)	***nab*-paclitaxel 100mg/m^2 wkly n/N (%)**	**150mg/m^2 wkly n/N (%)**	**docetaxel 100mg/m^2 q3w n/N (%)**	**OR (95% CI)**	**p[b] value**	***p[c] Value***
Responders[a]	35/76 (46)	48/76 (63)	55/74 (74)	29/74 (39)	2.43 (1.42, 4.16)	<0.001	*<0.001*
CR	1/76 (1)	2/76 (3)	2/74 (3)	2/74 (3)		0.029	*0.9197*
PR	34/76 (45)	46/76 (61)	53/74 (72)	27/74 (36)		0.010	*<0.0001*

Abbreviations: OR: odds ratio; CR: complete response; PR: partial response
[a]Patients with confirmed complete or partial overall response
[b]p values are based on a Cochran-Mantel-Haenszel (CMH) test stratified by study site
[c]p values are based on a Fisher exact test undertaken in the evaluation

Progression-free survival and median survival

	nab-paclitaxel			**docetaxel 100mg/m2 q3w**	**p[a] value**	**p[b] Value**
	300mg/m^2 q3w	**100mg/m^2 wkly**	**150mg/m^2 wkly**			
Investigator Assessed Progression-Free Survival						
Pts who progressed or died n/N (%)	44/76 (58)	59/76 (78)	36/74 (49)	44/74 (59)		0.0024
Median (95% CI) PFS (months)	10.9 (8.9, 14.6)	7.5 (7.2, 9.3)	14.6 (10.0, 18.9)	7.8 (6.3, 11.0)	0.008	
Patient Survival						
Patients who died n/N (%)	24/76 (32)	32/76 (42)	19/74 (26)	26/74 (35)		0.1933
Median (95% CI) survival (months)	21.7 (21.7, >23.7)	>23.0 (16.6, >23.0)	>22.7	19.7 (18.0, >21.2)	0.111	

Abbreviations: PFS, progression free survival.
[a] p values are based on a log rank test and refer to the overall p values
[b]p values are based on a Fisher exact test undertaken in the evaluation

It was difficult to interpret the results given the different dose regimens of nab-paclitaxel used and combination across three weekly and weekly dosage administration schedules. Overall

response rates were similar between nab-paclitaxel 300mg/m^2 three weekly and docetaxel 100mg/m^2 three weekly. A more relevant comparison may be nab-paclitaxel 100mg/m^2 weekly and docetaxel administered weekly. However, there was no significant difference in patient survival among the four treatment arms. No results related to the target population for whom the listing was sought were presented in the submission.

The PBAC noted nab-paclitaxel had a different safety profile compared to paclitaxel, with statistically significantly higher incidence of sensory neuropathy, fatigue and gastrointestinal toxicities reported.

9. Clinical Claim

The submission claimed nab-paclitaxel was superior in terms of comparative effectiveness over paclitaxel. The PBAC considered that this may not be reasonable. The PBAC concluded that, based on the clinical evidence presented, the claim of a clinically significant benefit for treatment with nab-paclitaxel over paclitaxel and docetaxel had not been substantiated, and therefore that the presented cost-effectiveness analysis (CEA) lacked an adequate basis.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

A trial based economic evaluation was presented. A cost-effectiveness analysis was performed to obtain costs per life-year gained based on overall survival (OS) in CA012.

The submission compared costs and outcomes for all patients dosed in CA012, and for patients with prior anthracycline exposure and patients who were on >1st line therapy. However, none of the three groups presented in the economic evaluation fully represented the population for whom the listing was sought.

Total costs were calculated per cycle to 18 cycles (52 weeks) from the perspective of the health care system as no patients continued treatment after 18 cycles of therapy. Overall survival estimates were based on CA012 for both treatment arms until 150 weeks with no further extrapolation beyond the trial horizon.

The incremental cost per life year saved for the ITT population was between $45,000 and $75,000. The sensitivity analysis presented indicated that the ICER was highly sensitive to the estimate of survival.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated a financial cost to the PBS of less than $10 million per year. The PBAC considered the submission's estimates were uncertain with potential for usage beyond the requested restriction.

12. Recommendation and Reasons

The PBAC noted that nab-paclitaxel was an albumin bound form of paclitaxel and was likely to have a higher uptake by cancer cells due to increased transendothelial transport on albumin. The PBAC also noted that nab-paclitaxel has a different safety profile and a different dosage to paclitaxel. The new formulation was noted to have potential advantages

which included: no cremophor EL or ethanol in the formulation which reduced hypersensitivity reactions, no requirement for premedications, a shorter infusion time, and the possibility of using standard drip sets.

The PBAC also noted that the requested listing for nab-paclitaxel was for advanced breast cancer which is consistent with the current listing of the comparator, paclitaxel. However, *nab*-paclitaxel's TGA registration is for "metastatic breast cancer" and in its pre-subcommittee response the sponsor acknowledged this discrepancy and had no objection to limiting the PBS indication to patients with metastatic breast cancer if recommended for listing.

The PBAC agreed that paclitaxel was the appropriate main comparator and that docetaxel was an appropriate secondary comparator, with data from three studies presented: one randomised comparative study of nab-paclitaxel and paclitaxel in patients with metastatic breast cancer (CA021) with mature survival data, and two other ongoing, randomised trials comparing *nab*-paclitaxel with paclitaxel (CA201) and docetaxel (CA204), respectively, in which the survival data are immature.

The primary outcome of the clinical trials of *nab*-paclitaxel with paclitaxel (CA012 and CA201) was response rate and the PBAC agreed that in the meta-analysis, response rates were statistically significantly higher for *nab*-paclitaxel compared with paclitaxel in the ITT population and for the subgroup of patients from trial CA012 with prior anthracycline failure who were representative of the target population for whom the listing is sought.

However this subgroup showed no statistically significant difference in the more patient relevant endpoint of overall survival (77% vs. 84%, p=0.23), nor was a statistically significant difference in overall survival seen in the ITT populations from either trial CA012 or CA201. Although the PBAC noted that the median time to death in trial CA012 was significantly greater in the *nab*-paclitaxel treatment arm for patients receiving second or greater line therapy (p = 0.020) and in patients who had received prior anthracycline therapy (p = 0.047), the later result was of marginal statistical significance and in addition, the p value presented was not interpretable given that there was no adjustment for multiplicity in the multiple subgroup analyses conducted (the Pre-Sub-Committee response argument that multiple testing adjustments were not necessary as the multiple nested testing analysis in Study CA012 reduced the false discovery rate was not accepted by the Committee).

In addition, the PBAC noted that there was no significant difference in patient survival in study CA204 among the four treatment arms (*nab*-paclitaxel 300 mg/ m^2 q3w, 100 mg/ m^2 wkly, 150 mg/ m^2 wkly and docetaxel 100 mg/m^2 q3w), although it was accepted that the survival data from this trial were immature. Furthermore, no results related to the target population for whom the listing was sought were presented in the submission.

The PBAC also noted that nab-paclitaxel had a different safety profile to paclitaxel with more GIT toxicity, fatigue and sensory neuropathy reported but that no comparative safety claim was provided in the submission.

Thus the Committee concluded that, based on the clinical evidence presented, the claim of a clinically significant benefit for treatment *with* nab-paclitaxel over paclitaxel and docetaxel had not been substantiated, and therefore that the presented cost-effectiveness analysis (CEA) lacked an adequate basis. In addition, the presented sensitivity analysis indicated that the

ICER was highly sensitive to the estimate of survival, with a difference of 3.65 days increasing or decreasing the ICER by $10,000, increasing the uncertainty further.

The PBAC also noted that ESC had raised a number of other areas of clinical and economic uncertainty and agreed these would need to be addressed by any future submissions.

Therefore, the PBAC rejected the submission on the basis of uncertainty in clinical benefits and uncertain cost-effectiveness. However, the Committee indicated it would be prepared to consider a submission presenting a cost-minimisation analysis of nab-paclitaxel versus paclitaxel at its 11 December Special meeting.

Recommendation
Reject

Further Information
Further to the PBAC's consideration of this product at the 5-7 November 2008 meeting (at which the committee rejected the submission, but indicated its willingness to consider a submission presenting a cost minimisation analysis), the sponsor presented a re-submission to the PBAC Special Meeting held in December 2008. The re-submission presented a cost minimisation of nab-paclitaxel versus paclitaxel. The equi-effective doses used were 260 mg/m^2 of nab-paclitaxel and 175 mg/m^2 of paclitaxel with additional cost offsets claimed for drug administration, premedications and adverse events.

No new clinical data were presented.

Differences from the previous submission in the assumptions and inputs in the pricing calculations compared with the economic model related to body surface area, incidence of adverse events and paclitaxel price.

The re-submission estimated the number of patient treatment cycles to be less than 10,000 by Year 5 of listing. It estimated there would be a net cost saving to the PBS of less than $500,000 per year by Year 5 achieved through a reduction in the use of other taxanes and concomitant medications.

The PBAC recommended the listing of nab-paclitaxel on the PBS for metastatic breast cancer after failure of prior therapy which includes an anthracycline on a cost-minimisation basis with paclitaxel using the price per mg methodology and the equi-effective doses being 260 mg/m^2 of nab-paclitaxel and 175 mg/m^2 of paclitaxel.

The PBAC considered that a maximum quantity of 1 is more appropriate as the dose will vary according to the body surface area of the patient and that a prescriber can request the appropriate number of vials at the time of the authority application. The PBAC also noted that submission sought listing in patients with metastatic breast cancer as opposed to advanced breast cancer as requested in November 2008. The PBAC considered that metastatic breast cancer was the more appropriate of the two as this is consistent with the TGA registration.

The PBAC noted that the clinical data presented in the submission was the same as that considered in the November 2008 major submission. Consequently, the PBAC's conclusion

from November 2008 that there is no clinically significant benefit in treatment with nab-paclitaxel over paclitaxel, remained. Although the claim of a clinically significant benefit for treatment with nab-paclitaxel over paclitaxel was maintained in the submission, in the context of a cost-minimisation analysis, the PBAC did not consider this to be directly relevant to its deliberations and the sponsor indicated a willingness to accept listing on this basis. As a result of this, the PBAC was interested in whether nab-paclitaxel outcomes are no worse than paclitaxel outcomes and from the trial results presented, the PBAC concluded that this was the case. However, the PBAC did consider the possibility that nab-paclitaxel may produce better outcomes than paclitaxel but as outlined previously in the November 2008 PBAC meeting minutes, uncertainty existed over the validity of this claim.

The PBAC also recalled that the ESC had raised a number of other areas of clinical and economic uncertainty in the November 2008 submission needing addressing, but again, in the context of a cost-minimisation analysis, the PBAC did not consider these issues relevant.

The PBAC noted that the adverse events experienced in the first treatment cycle were used to estimate the incidence of toxicities per treatment cycle as opposed to the total trial period as used in the November 2008 submission. By using adverse events experienced in the first treatment cycle only, the adverse events costs associated with nab-paclitaxel changed from a cost to a saving. However, the PBAC considered that this had little impact on the analysis.

Recommendation
NAB-PACLITAXEL, powder for I.V. infusion (suspension), 100 mg

Restriction:	Authority Required Metastatic breast cancer after failure of prior therapy which includes an anthracycline
Maximum quantity:	1
Number of repeats:	Nil

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
Specialised Therapeutics is pleased to have been able to work with the PBAC to make Abraxane available to Australian women with metastatic breast cancer.