PUBLIC SUMMARY DOCUMENT

Product: PACLITAXEL-NANOPARTICLE ALBUMIN BOUND, 100 mg injection, 1 x 100 mg vial, 250 mg injection, 1 x 250 mg vial, Abraxane®
Sponsor: Specialised Therapeutics Australia Pty Ltd
Date of PBAC Consideration: March 2014

1. Purpose of Application

The submission requested an Authority Required listing for first line treatment of locally advanced, unresectable or metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

2. Background

The PBAC had not previously considered *nab*-paclitaxel for this indication.

3. Registration Status

The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, a positive TGA Delegate's overview was available for the 100 mg vial.

The PBAC noted that the 250 mg vial of *nab*-paclitaxel is not currently TGA-registered, having been submitted to the TGA on 24 January 2014.

As of 21 March 2014, paclitaxel-nanoparticle albumin bound 100 mg vial was TGA registered for the following indications.

- treatment of metastatic carcinoma of the breast after failure of anthracycline therapy.
- first-line treatment, in combination with carboplatin, of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation.
- first-line treatment, in combination with gemcitabine of patients with metastatic adenocarcinoma of the pancreas.

4. Listing Requested and PBAC's View

Authority required

First-line treatment of locally advanced unresectable or metastatic adenocarcinoma of the pancreas in combination with gemcitabine

The PBAC noted that the proposed maximum amount of 580mg is the same as for the current PBS listing for the treatment of breast cancer. The PBAC also noted that the dose and frequency of administration of *nab*-paclitaxel in breast cancer is 260 mg/m^2 every three weeks, whereas the proposed dose for the treatment of adenocarcinoma of the pancreas is 125 mg/m^2 on days 1, 8 and 15 of a 28 day cycle. The PBAC recommended a maximum amount based on a maximum patient body surface area of 2.2 m^2 (equivalent to 120 kg), equating to a maximum amount of 275 mg.

The PBAC agreed with the Secretariat's suggestion to increase the number of repeats to 11, which would allow for a total of four cycles. This was consistent with the treatment duration of 3.9 months in the trial.

The PBAC noted the TGA indication proposed by the Delegate, in which treatment is limited to patients with metastatic disease. The PBAC therefore recommended that the PBS restriction limit PBS-subsidised access to patients with metastatic (Stage IV) disease.

The PBAC recommended that PBS subsidy for *nab*-paclitaxel be ceased upon disease progression.

The PBAC noted that the proposed restriction and TGA indication place *nab*-paclitaxel as first-line treatment of Stage IV pancreatic cancer. The PBAC considered this appropriate, and recommended that the PBS restriction require that the patient has not received any other PBS-subsidised treatment for the treatment of metastatic disease.

The PBAC recommended that the restriction exclude the possibility of use in an adjuvant or neoadjuvant setting.

The PBAC noted that the proposed restriction did not include a performance score. The PBAC recommended that PBS subsidy be restricted to patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less.

The PBAC noted that only the 100 mg vial of *nab*-paclitaxel has been approved by the TGA, and considered that the absence of the 250 mg vial may increase wastage.

5. Clinical Place for the Proposed Therapy

Stage IV pancreatic cancer is surgically unresectable and has a very low 5-year survival rate. Gemcitabine monotherapy is the current standard of care for stage IV pancreatic cancer.

The submission proposed that *nab*-paclitaxel would be used in combination with gemcitabine for first-line treatment for stage IV pancreatic cancer.

6. Comparator

The submission nominated gemcitabine monotherapy as the main comparator, arguing that gemcitabine monotherapy is the only therapy currently listed on the PBS for locally advanced unresectable or metastatic adenocarcinoma of the pancreas.

The PBAC considered that gemcitabine monotherapy was the appropriate comparator.

The PBAC considered that FOLFIRINOX (folinic acid, fluorouracil, irinotecan and oxaliplatin) may potentially be a comparator, however noted that this regimen is not PBS-subsidised and treatment with this combination is associated with significant side effects.

7. Clinical Trials

The submission presented a single randomised, open-label, multi-centre study: CA046. The associated reports presented in the submission are shown in the following table:

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
CA046 Abraxis BioScience	Clinical Study Report 05 February 2013 Abraxis BioScience. A Randomised Phase II Study of Weekly AB1-007 plus Gemcitabine versus Gemcitabine Alone in Patients with Metastatic Adenocarcinoma of the Pancreas.	Clinical Study Report CA046, 05 February 2013.
Goldstein D	Evaluation of Peripheral Neuropathy in a Phase III Trial (MPACT) of Weekly nab-Paclitaxel (nab-P) plus Gemcitabine (Gem) vs Gem Alone for Patients With Metastatic Adenocarcinoma of the Pancreas	ECCO 2013 Abstract 2.577
Ramanathan RK	Positron Emission Tomography (PET) Response from a Randomized Phase III Trial (MPACT) of Weekly *nab*-Paclitaxel (*nab*-P) plus Gemcitabine (Gem) vs Gem Alone for Patients (pts) With Metastatic Adenocarcinoma of the Pancreas.	ECCO 2013 Abstract 2.577
Scheithauer W	Dose Delivery in a Phase III trial (MPACT) of Weekly *nab*-Paclitaxel (*nab*-P) plus Gemcitabine (Gem) vs Gem Alone for Patients With Metastatic Adenocarcinoma of the Pancreas.	ECCO 2013 Abstract 2.586
Von Hoff DD	Increased Survival in Pancreatic Cancer with *nab*-Paclitaxel plus Gemcitabine.	N Engl J Med 2013.
Von Hoff DD	Randomized phase III study of weekly *nab*-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT)	J Clin Oncol 2013;31(4).
Von Hoff DD	Results of a randomized phase III trial (MPACT) of weekly *nab*-paclitaxel plus gemcitabine versus gemcitabine alone for patients with metastatic adenocarcinoma of the pancreas with PET and CA19-9 correlates.	J Clin Oncol 2013;31(15).
Goldstein D	Updated survival from a randomized phase III trial (MPACT) of *nab*-Paclitaxel plus gemcitabine vs gemcitabine alone for patients (pts) with metastatic adenocarcinoma of the pancreas.	Submitted to ASCO-GI 2014.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
***Nab*-paclitaxel+gemcitabine vs. gemcitabine monotherapy.**						
Von Hoff DD 2013, Goldstein 2013	861 (120 Australia)	R, OL MC 24 months (36 month recent follow-up)	Low	Locally advanced unresectable/ metastatic	OS/PFS	Survival gain

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised;
Source: compiled during the evaluation

The sponsor did not request a hearing.

The PBAC noted the consumer comments received in support of this item. Comments were received from one individual, five health care practitioners and one organisation (the Medical Oncology Group of Australia). The PBAC particularly noted the views that *nab*-paclitaxel is a treatment that improves survival for patients with stage IV pancreatic cancer.

8. Results of Trials

The results for comparative effectiveness of *nab*-paclitaxel plus gemcitabine for progression free survival (PFS) and overall survival (OS) from the trial are presented in the table below:

Results of PFS/OS across the direct randomised trials

	***nab*-paclitaxel/ gemcitabine n=431**	**Gemcitabine n=430**	**Absolute difference RD**	**HR (95% CI)**	**p value[a]**
Overall Survival					
ITT					
Events n (%)	333/431 (77)	359/430 (83)	6		
Censored n (%)	98/431 (23)	71/430 (17)	6		
Median, months (95% CI)	8.5 (7.89, 9.53)	6.7 (6.01, 7.23)	1.8	0.72 (0.617, 0.835)	<0.001
75th Percentile	14.8 (13.6, 15.7)	11.4 (10.1, 12.6)	3.4		
Updated ITT					
Events n (%)	380/431 (88)	394/430 (92)	4		
Median, months (95% CI)	8.7	6.6	2.1	0.72 (0.620, 0.825)	<0.0001
Progression free Survival					
ITT					
Events n (%)	277/431 (64)	265/430 (62)	2		
Censored n (%)	154/431 (36)	165/430 (38)	2		
Median, months (95% CI)	5.5 (4.47, 5.95)	3.7 (3.61, 4.04)	2.2	0.69 (0.581, 0.821)	<0.001

The PBAC considered that the trial presented in the submission was of good quality and provided mature data on PFS and OS. The PBAC noted that a median treatment duration of 3.9 months with *nab*-paclitaxel plus gemcitabine resulted in a median PFS gain of 1.8 months in the intention to treat (ITT) population compared with gemcitabine monotherapy. A median gain of 2.1 months OS was noted in the ITT population in the updated analysis (i.e. an increase from 6.6 to 8.7 months). The updated survival analysis also revealed an overall survival rate of 4% at 3 years in the *nab*-paclitaxel/gemcitabine arm compared with 0% in the gemcitabine alone arm.

The PBAC noted that no quality of life data were collected during the trial, and that therefore it was not possible to assess the effect of drug toxicity and adverse events that may counterbalance a gain in survival.

With regard to comparative harms, the PBAC considered that *nab*-paclitaxel has a different safety profile to gemcitabine, with a higher incidence (≥10% difference) of grade 3 treatment related adverse events neutropenia, fatigue, peripheral neuropathy, thrombocytopenia and anaemia. There was no difference in patients with at least 1 adverse event leading to death.

The PBAC noted the submission presented data from the most recent Periodic Safety Update Report, which took account of an estimated 182,439 patients that have been exposed to *nab*-paclitaxel through both study participation and clinical use globally. The PBAC noted the following ongoing identified risks

- Myelosuppression
- Neurotoxicity
- Gastrointestinal events
- Myalgia and arthralgia
- Hypersensitivity reactions
- Cranial nerve palsies
- Cardiotoxicity
- Stevens-Johnson syndrome/toxic epidermal necrolysis

A summary of the comparative benefits and harms for paclitaxel plus gemcitabine versus gemcitabine monotherapy is presented in the table below.

Benefit/harm summary

Outcome[a]	N (1)[b]	RR (95%CI)[c]	Event rate/100 patients		Increment
			Nab-paclitaxel+ gemcitabine[e]	Gemcitabine[d]	
Benefits					
Overall Survival					
Dead at Month 24	861	0.92 (0.88,0.96)	38.6	41.7	3.1
Dead at Month 36	861	0.96 (0.92,1.00)	29.3	30.5	1.2
Harms[g]					
Neutropenia Grade 3	823	1.55 (1.22,1.95)	16.4	10.6	5.8
Fatigue	823	1.98 (1.38,2.87)	6.1	3.1	3.0
Peripheral neuropathy	823	32.47 (4.46,236.06)	2.7	0.08	2.6

Source: compiled during the evaluation
[a] OS:Primary outcome of the trial
[b] one trial CA046
[c] relative risk. At 36 months 0% of gemcitabine patients were alive.
[d] based on duration of trial (24 months) and at follow up (36 months)
[e] As for above, based on intervention group.
[g] most frequent grade 3 and above adverse events.

The PBAC noted that based on these trials, for every 100 patients treated with *nab*-paclitaxel plus gemcitabine compared to gemcitabine monotherapy:

- 3 additional patients would survive to 24 months;
- 1 additional patient would survive to 36 months;
- 6 patients would experience grade 3 neutropenia;
- 3 patients would experience fatigue;
- 3 patients would experience peripheral neuropathy.

The PBAC noted the combination of *nab*-paclitaxel and gemcitabine was associated with significant toxicity which would likely impact on quality of life. Of particular note, was the fact that an additional 10% of patients had grade 3 (severe) fatigue. This equates to a reduction of two points in a patient's Eastern Cooperative Oncology Group (ECOG) status.

Overall, the PBAC considered that in light of the safety data presented, a substantial impact on quality of life may be exchanged for the incremental survival benefit with *nab*-paclitaxel plus gemcitabine. Quality of life data would have been informative in better assessing the benefits and harms of this new treatment combination.

9. Clinical Claim

The submission described *nab*-paclitaxel plus gemcitabine as superior in terms of comparative effectiveness and 'comparable' in terms of comparative safety over gemcitabine monotherapy.

The PBAC considered that the claim of superior comparative effectiveness was supported in patients with metastatic disease.

The PBAC considered that the claim of comparable comparative safety was not adequately supported, noting the quality of life impact that would be incurred in exchange for the demonstrated survival benefit.

The PBAC noted the advice of the ESC that the clinical claim was not adequately supported for patients with locally advanced unresectable disease, since these patients were excluded from the trial. The PBAC noted, however, that the proposed TGA indication limits treatment to patients with stage IV disease, and that consideration of locally advanced disease was no longer a relevant consideration.

10. Economic Analysis

The submission presented a trial-based economic analysis, consistent with the clinical evidence. The outcomes were presented in Life Years Saved (LYS). The key drivers of the model were overall survival and treatment costs. The PBAC considered that the model structure was reasonable.

In the base case economic analysis, the submission used the time horizon directly from the trial data (186 weeks (3.58 years) in the treatment arm and 150 weeks (2.88 years) in the comparator arm). The ICER for the primary analysis in the ITT population was between $45,000 and $75,000 per LYS. The PBAC considered this analysis was a reasonable approximation of the ICER/LYS, noting that at 3 years, 90% of all events had occurred (4% patients were alive at 3 years in the experimental arm).

The submission also presented a secondary analysis, based on the ITT population, where patients are censored at the point of subsequent treatment. This analysis relied on trial data (up to 143 weeks in the treatment arm and 104 weeks in the comparator arm) with no further extrapolation. The ICER for this secondary analysis was between $45,000 and $75,000 per LYS.

The PBAC considered that the use of LYS only was a significant concern. The PBAC noted the sponsor's claim in its pre-PBAC response that LYS would be the most appropriate measure. The PBAC also noted the advice of the ESC that inclusion of utilities to generate a cost per quality adjusted life year (QALY) would increase the ICER. For example, the ICER would be over $100,000 per QALY gained using the 'late cancer' (pancreatic cancer) utility of 0.5 from the Tufts Cost-Effectiveness Analysis Registry/ Das et al (2009). Although this ICER was generated using only one possible utility value, the PBAC considered that given the impact on the ICER, as for all its assessments, it was not appropriate to accept LYS without quality adjustment.

The PBAC recalled that although the November 2008 submission for use of *nab*-paclitaxel in breast cancer had presented an ICER in terms of cost/LYS, the PBAC had rejected that submission on the basis of uncertainty in clinical benefits and uncertain cost-effectiveness. The PBAC further recalled that the positive recommendation made at the December 2008 Special Meeting had been based on cost minimisation to paclitaxel, and that therefore the ICER presented in terms of cost/LYS had not been accepted.

The PBAC noted that the 250 mg vial of *nab*-paclitaxel has not yet been approved by the TGA, and noted that a sensitivity analysis in which this strength is not available produced an ICER of between $75,000 and $105,000 per LYS.

The PBAC considered that the base case ICER of between $45,000 and $75,000 per LYS for the primary analysis of the ITT population was the most reasonable estimate of the cost-effectiveness of *nab*-paclitaxel. The PBAC considered, however, that this figure should be adjusted using standard methods for quality adjustment to appropriately capture the impacts of adverse events and drug toxicity on a patient's quality of life.

The PBAC considered that at an ICER of between $45,000 and $75,000 per LYS, *nab*-paclitaxel would not be cost effective under the sponsor's pricing proposal. The PBAC considered that the cost-effectiveness of *nab*-paclitaxel would be acceptable if the ICER was between $50,000 and $90,000 per QALY, which would be comparable with that of other recent medicines where there is a high unmet clinical need. The PBAC considered that as the submission only presented an ICER in terms of cost per LYS, an ICER in the range of $15,000 to $45,000 per LYS would be appropriate to account for the lack of adjustment for quality of life.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated by the submission to be less than 10,000 in Year 5 of listing, at an estimated net cost per year to the PBS of between $10 million and $30 million in Year 5.

The PBAC considered that the number of eligible patients was overestimated in the submission because Stage III patients were included, but overall considered the predicted estimates of use to be reasonable.

The PBAC noted that the overall cost was driven by the estimated market share. The PBAC noted that increasing the estimated market share, increased the cost to the PBS.

12. PBAC Outcome

The PBAC recommended the listing of *nab*-paclitaxel injection 100 mg vial only, on the basis that it should be made available only under special arrangements under Section 100 (Efficient Funding of Chemotherapy).

The PBAC was satisfied that *nab*-paclitaxel in combination with gemcitabine provides, for some patients, a significant improvement in efficacy over gemcitabine monotherapy.

The PBAC noted the clinical need for new treatments for pancreatic cancer. The PBAC noted and appreciated the consumer comments received on this item, in particular the view that *nab*-paclitaxel provides a survival benefit in this disease.

The PBAC considered that the clinical data presented in the submission were mature and demonstrated a benefit in OS and PFS. The PBAC considered that the most reliable estimate of the OS gain was the uncensored increment of 2.1 months, observed in more than 50% of the participants in the trial.

The PBAC noted significant toxicity and adverse events with *nab*-paclitaxel plus gemcitabine compared with gemcitabine monotherapy. In particular, the PBAC noted the incidence of neutropenia, fatigue and peripheral neuropathy and the consequent effect on a patient's quality of life. The PBAC considered that the lack of quality of life data from the trial was a significant limitation.

The PBAC considered that the claim of superior comparative effectiveness of *nab*-paclitaxel plus gemcitabine over gemcitabine was adequately supported, but that the claim of comparable safety was not adequately supported.

The PBAC noted that as the 250 mg vial of *nab*-paclitaxel was not TGA registered at the time of consideration, it was not able to make a recommendation to list this strength.

The PBAC advised the Minister that under Section 101 3BA of the *National Health Act*, *nab*-paclitaxel should not be treated as interchangeable on an individual patient basis with any other drug(s) or medicinal preparation(s).

The PBAC recommended that nab-paclitaxel is not suitable for prescribing by nurse practitioners.

The PBAC considered that the Safety Net 20 Day Rule should not apply

Recommendation:
Add new item:

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Proprietary Name and Manufacturer
PACLITAXEL NANOPARTICLE ALBUMIN BOUND Injection, 100 mg, 1 x 100 mg vial	275 mg	11	Abraxane TS

Severity:	Stage IV (metastatic)
Condition:	Adenocarcinoma of the pancreas
Restriction:	Section 100 (Efficient Funding of Chemotherapy) Authority Required *(private hospitals)* Authority Required (STREAMLINED) *(public hospitals)*

Clinical criteria:	Treatment must be in combination with gemcitabine AND The condition must not have been treated previously with PBS subsidised therapy. AND Patient must have an ECOG performance status score of 2 or less
Administrative advice	**Note** A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug **Note** Not for use as neoadjuvant or adjuvant therapy

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 Australia (STA) thanks the PBAC for their positive recommendation. In the past three months, STA and The Department of Health have worked together to reach a mutually satisfactory position on a number of conditions for the listing. STA is very pleased that an in principle agreement has been achieved with Department of Health, subject to final Cabinet approval.