6.18 NAB-PACLITAXEL
nanoparticle albumin bound 100 mg injection, 1 x 100 mg vial Abraxane®, Specialised Therapeutics Australia

1 Purpose of Application

1.1 To request the PBAC to reconsider the exclusion of *nab*-paclitaxel (Abraxane®) from use in combination with trastuzumab, in the treatments of patients with human epidermal growth factor receptor 2 (HER-2) positive metastatic breast cancer and to reflect on the March 2011 amendment to the *nab*-paclitaxel PBS listings.

2 Requested listing

2.1 The submission requested changes to the existing trastuzumab restrictions arising from the November 2014 PBAC meeting which prevented its PBS-subsidised use in combination with *nab*-paclitaxel. The PBS listing for *nab*-paclitaxel is as follows:

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Dispensed Price for Max. Amount (Published*)	Proprietary Name and Manufacturer
NAB-PACLITAXEL nanoparticle albumin bound 100 mg injection **Authority Required** Metastatic breast cancer Treatment of HER2 positive breast cancer in combination with trastuzumab	580 mg	5	$2,491.55 (Public) $2,562.86 (Private)	Abraxane Specialised Therapeutics Australia

* Effective prices apply under a special pricing arrangement across the two listed cancers for *nab*-paclitaxel (breast cancer and prostatic cancer). As each cancer is associated with a different dose and thus a different maximum amount, it is not straightforward to present a single effective dispensed price for maximum amount.

2.2 The submission requested an amendment to the current trastuzumab restriction to exclude the following wording:

- AND
  The treatment must not be in combination with *nab*-paclitaxel

2.3 The PBAC rejected the request to allow *nab*-paclitaxel from use in combination with trastuzumab, in the treatment of patients with human epidermal growth factor receptor 2 (HER-2) positive metastatic breast cancer.

2.4 The minor submission offered a price reduction for the use of *nab*-paclitaxel in the treatment of patients with HER-2 positive metastatic breast cancer in combination with trastuzumab.

For more details on PBAC's view, see section 7 "PBAC outcome".

3 Background

3.1 *nab*-paclitaxel (nanoparticle albumin-bound paclitaxel) 100 mg powder for injection (suspension) was registered by the TGA in October 2008 for the treatment of metastatic carcinoma of the breast after failure of anthracycline therapy.

3.2 The PBAC considered *nab*-paclitaxel in November 2008. The PBAC rejected the submission, but indicated its willingness to consider a submission presenting a cost minimisation analysis of *nab*-paclitaxel versus solvent-based paclitaxel.

3.3 The PBAC recommended the listing of *nab*-paclitaxel on the PBS at its December 2008 Special Meeting for the treatment of metastatic breast cancer after failure of prior therapy which includes an anthracycline, on a cost-minimisation basis with solvent-based 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 solvent-based paclitaxel.

3.4 At its March 2011 meeting, the PBAC recommended a change to the circumstances under which *nab*-paclitaxel was made available, and the restriction was amended and extended to include the treatment of HER-2 positive breast cancer in combination with trastuzumab.

3.5 In the previous major re-submission for pertuzumab, trastuzumab and trastuzumab emtansine considered by PBAC in November 2014, the PBAC recommended the listing of pertuzumab for the treatment of HER-2 positive metastatic breast cancer in combination with trastuzumab and a taxane, in the first line setting. The PBAC noted in the economic model that the ICER varied between $45,000/QALY - $75,000/QALY (final analysis of data from CLEOPATRA and modifying to a broad taxane restriction). The PBAC noted that the latter ICER included 22.14% use of *nab*-paclitaxel, but rejected this because the increased cost of *nab*-paclitaxel, at more than 30 times the cost of solvent-based paclitaxel, which had price reductions due to PBS reforms means that *nab*-paclitaxel should be excluded from use with pertuzumab + trastuzumab by the pertuzumab restriction (Public Summary Document – November 2014 PBAC meeting items 7.5 & 7.8).

3.6 The PBAC recommended that "*nab*-paclitaxel should be excluded from use with pertuzumab + trastuzumab by the pertuzumab restriction". Further, the PBAC "noted that the restrictions should reflect current evidence and legitimise clinical practice by allowing use of trastuzumab beyond progression and a range of partner chemotherapy options, with the exception of *nab*-paclitaxel" (Public Summary Document – November 2014 PBAC meeting items 7.5 & 7.8).

For more details on PBAC's view, see section 7 "PBAC outcome".

4 Clinical place for the proposed therapy

4.1 The submission requested inclusion of *nab*-paclitaxel as a clinical option for later lines of therapy in combination with trastuzumab.

5 Comparator

5.1 The comparators for the minor submission are solvent-based paclitaxel and docetaxel.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (3) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with *nab*-paclitaxel including the ease of administration and better tolerability to the currently available alternatives.

6.3 The PBAC noted the advice received from Medical Oncology Group of Australia and Breast Cancer Network Australia requesting clarification on the likely use of *nab*-paclitaxel in clinical practice; and supporting the relisting of *nab*-paclitaxel in combination with trastuzumab. The PBAC specifically noted the discussion on some anomalies pertaining to the implementation of HER-2 Metastatic Program and advice with reference to utilisation of other drugs in the Program, diagnostic testing and grandfathering.

6.4 The PBAC noted and welcomed the input.

Clinical trials

6.5 The minor submission presented two single-arm studies:

Table 1: Trials and associated reports presented in the re-submission

Study	Protocol title/ Publication title	Publication citation
Mirtsching et al	Open-label, phase II, non-randomised study that evaluated weekly nab-paclitaxel with or without trastuzumab as first-line treatment of advanced breast cancer	2011
Colin et al	Open-label, phase II study of nab-paclitaxel with trastuzumab and carboplatin as first-line therapy for women with HER-2 positive metastatic cancer	2010

Source: p4 & 5 of the submission

6.6 Results of the study end points included objective response rates (ORR), progression-free survival (PFS), and 1- and 2-year overall survival (OS) rates.

Comparative effectiveness

6.7 The study results (Mirtsching et al) of response rates after a median of six cycles (range, 1-22 cycles) of treatment for *nab*-paclitaxel ± trastuzumab therapy are summarised in the table below.

Table 2: Response rates for *nab*-paclitaxel ± trastuzumab therapy

	Evaluable population (n = 64)	HER-2 positive (n = 21)	HER-2 negative (n = 42)
Overall response, n (%)	27 (42.2)	11 (52.4)	16 (38.1)
Complete response	5	3	2
Partial response	22	8	14
Stable disease	17	4	12
Progressive disease	20	6	14
	ITT (n = 72)	**HER-2 positive [a] (n = 21)**	**HER-2 negative [a] (n = 42)**
Median PFS, months (range)	14.5 (1-49.3)	18.7	12.8
Median OS, months (range)	29 (1-49.3)	36.8	27.3

Adapted from Mirtsching et al. 2011

[a] No significant difference in PFS or OS between HER-2 positive and HER-2 negative groups.

Abbreviations: ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival

6.8 The submission proposed that there was a trend favouring improved OS and PFS in the HER-2 positive cohort, but this did not reach statistical significance.

6.9 The overall response rate in the study conducted by Colin et al was 63% with 3 confirmed complete responses and 17 partial responses with a median PFS of 16.6 months.

6.10 As this was a minor submission, the results have not been independently evaluated. Their relevance to the comparison with solvent-based paclitaxel and docetaxel in the context of trastuzumab is not clear. However, the submission has confirmed that studies have been conducted involving *nab*-paclitaxel and trastuzumab in advanced breast cancer.

Clinical claim

6.11 The November 2008 submission claimed that *nab*-paclitaxel offers numerous clinical advantages (i.e. superior response rates, progression-free survival, overall survival, reduced adverse events, and greater convenience in administration) over solvent-based paclitaxel (Minutes, December 2008 PBAC Meeting).

6.12 At the November 2008 PBAC meeting, the *nab*-paclitaxel 'formulation was noted to have potential advantages over solvent-based paclitaxel 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' (Minutes, November 2008 PBAC meeting).

Estimated PBS usage & financial implications

6.13 The submission acknowledged the disparity in price between *nab*-paclitaxel and solvent-based paclitaxel, and so proposed a price reduction for the use of *nab*-

paclitaxel in the HER-2 positive metastatic breast cancer patient population (in combination with trastuzumab).

6.14 The minor submission estimated that the lowest price that could be provided for *nab*-paclitaxel was the same as the current reimbursed price for patients with metastatic pancreatic cancer, $[redacted] per vial (ex-manufacturer). The submission observed that there will be a further 5% mandatory price cut in April 2016, which will further lower the price of *nab*-paclitaxel in this setting. At the proposed ex-manufacturer price of $[redacted] per vial, the corresponding dispensed price for maximum amount of 580 mg (for breast cancer) in the private hospital setting was $[redacted].

6.15 To illustrate the current situation, the analysis below shows the current weighted dispensed price between the two indications for *nab*-paclitaxel (i.e. breast and pancreatic cancer) for private hospital services using latest available Medicare data.

Table 3: Weighted dispensed price of *nab*-paclitaxel between two indications

nab-paclitaxel	Breast cancer	Pancreatic cancer
Ex-man per vial	$[redacted]	$[redacted]
Maximum amount	580 mg	275 mg
Dispensed price (effective)	$2,562.86	$[redacted]
Medicare services split [1]	58%	42%
Weighted dispensed price (effective)	$[redacted]	

[1] Medicare data between November 2014 – August 2015.

6.16 By comparison, the corresponding dispensed price for an adjusted amount of solvent-based paclitaxel equivalent to 580 mg of *nab*-paclitaxel is $[redacted] The calculation of this price reflects the PBAC-accepted equi-effective doses of 260 mg/m^2 of *nab*-paclitaxel and 175 mg/m^2 of solvent-based paclitaxel, such that the amount of solvent-based paclitaxel equivalent to the maximum amount of 580 mg of *nab*-paclitaxel is 303 mg solvent-based paclitaxel.

6.17 The submission requested a modification to the special pricing arrangement should the PBAC be willing to accept the proposed price for this patient population, where the published price would remain at the price for metastatic breast cancer patients.

6.18 The submission proposed that it was difficult to estimate the cost of retaining the listing of *nab*-paclitaxel for patients with HER-2 positive metastatic breast cancer as the data for this population is not captured by a separate item number. However, the submission made a reference to the DUSC estimates that *nab*-paclitaxel was previously co-administered with 22.14% of patients on HER-2 blockade therapy (Public Summary Document - November 2014 PBAC Meeting Items 7.5 & 7.8).

6.19 The submission proposed that utilisation data presented at the May 2014 Stakeholder's meeting estimated that there were approximately 40 new patients per month. On this basis, the submission claimed that the cost of re-listing *nab*-paclitaxel for this population would be approximately $1.4 million per year. The submission stated that this price would not come at an additional cost to the PBS. Moreover, it was proposed that there would be a 15% saving (including the mandatory 5% price cut) relative to the expenditure that applied before pertuzumab was listed.

6.20 The submission claimed that the costs associated with *nab*-paclitaxel listing would be slightly offset by reduction in use of docetaxel and solvent-based paclitaxel, and associated reductions in the use of steroids and resources.

Table 4: Estimated financial implications for the PBS

	Per Year
Incident patients on trastuzumab per year	[redacted]
Proportion of patients receiving Abraxane in combination with trastuzumab	22.14%
Patients receiving Abraxane in combination with trastuzumab	[redacted]
Number of Abraxane cycles/patient (total)	6
Total number of cycles	[redacted]
Cost of Abraxane (prior to mandatory 5% price cut)	**$**[redacted]

6.21 As this was a minor submission, these estimates were not independently evaluated.

For more details on PBAC's view, see section 7 "PBAC outcome".

7 PBAC Outcome

7.1 The PBAC rejected the request for PBS subsidy of the use of *nab*-paclitaxel in combination with trastuzumab, in the treatment of patients with human epidermal growth factor receptor 2 (HER-2) positive metastatic breast cancer.

7.2 In making this recommendation, the PBAC recalled its decision on a resubmission for pertuzumab, trastuzumab and trastuzumab emtansine considered at the November 2014 PBAC meeting. At the time, the PBAC recommended that "*nab*-paclitaxel should be excluded from use with pertuzumab + trastuzumab by the pertuzumab restriction" (Public Summary Document - November 2014 PBAC Meeting Items 7.5 & 7.8). To be consistent with this restriction wording, the November 2015 PBAC meeting recommended that the *nab*-paclitaxel restriction "Treatment of HER2 positive breast cancer in combination with trastuzumab" be changed to "HER2 positive breast cancer".

7.3 The PBAC reaffirmed that there was no basis for the cost of *nab*-paclitaxel to be greater than that of either solvent-based paclitaxel or docetaxel because the resubmission did not present any clear evidence for improved efficacy of *nab*-paclitaxel used in combination with trastuzumab over either of the comparators.

7.4 The PBAC referred to its previously determined equi-effective doses being 260 mg/m^2 of *nab*-paclitaxel and 175 mg/m^2 of solvent-based paclitaxel from the November 2008 consideration. The PBAC considered that the resubmission did not provide any justification to change this determination.

7.5 The PBAC rejected the resubmission because there was no basis to justify, in terms of clinical benefits, the price advantage even after the price reduction offered for *nab*-paclitaxel when compared with the corresponding price of solvent-based paclitaxel. However, the Committee indicated its willingness to consider a submission presenting a price reduction of *nab*-paclitaxel so that it is the same price as solvent-based paclitaxel.

7.6 The PBAC noted that the submission is eligible for an independent review.

Outcome:
Rejected.

8 Recommended listing

8.1 Amend existing PBS items 4531L, 7270P as follows:

The Authority Required (Streamlined) restriction code 3956 to be changed from:

"Treatment of HER2 positive breast cancer in combination with trastuzumab" to

"HER2 positive breast cancer".

9 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.

10 Sponsor's Comment

The sponsor had no comment.