PUBLIC SUMMARY DOCUMENT

Products: Vinorelbine, capsules, 20 mg and 30 mg (as tartrate), Navelbine®
Vinorelbine, solution for I.V. infusion, 10 mg in 1 mL and 50 mg in 5 mL (as tartrate) Navelbine®

Sponsor: Pierre Fabre Medicament Australia Pty Ltd

Date of PBAC Consideration: November 2012

1. Purpose of Application

The submission sought to:

1) Extend the current Authority Required listing to include an Authority Required (Streamlined) listing for the treatment of advanced breast cancer after failure of standard therapy, as a single agent or in combination.

2) Amend the wording of the current PBS restriction for vinorelbine solution for IV infusion, 10 mg in 1 mL and 50 mg in 5 mL, to remove the specification that prior therapy must include an anthracycline.

2. Background

At the June 1998 meeting, the PBAC recommended vinorelbine solution for intravenous infusion for an Authority Required listing for:

- Advanced breast cancer after failure of standard therapy which includes an anthracycline;
- Locally advanced or metastatic non-small cell lung cancer.

In March 2006 the PBAC recommended an Authority Required listing on PBS for locally advanced or metastatic non-small cell lung cancer for the soft capsule formulation on a cost-minimisation basis with intravenously administered vinorelbine.

See the March 2006 vinorelbine Public Summary Document for further information.

3. Registration Status

Intravenous vinorelbine was registered by the TGA on 16 February 1998 for advanced breast cancer after failure of standard therapy as a single agent or in combination and as first line treatment for advanced or metastatic non-small cell lung cancer as a single agent or in combination.

Vinorelbine soft capsules were registered by the Therapeutic Goods Administration (TGA) on 30 May 2005 for first line treatment of advanced non-small cell lung cancer (NSCLC), as a single agent or in combination. Vinorelbine capsules are also TGA registered for the treatment of advanced breast cancer after failure of standard therapy as a single agent or in combination.

4. Listing Requested and PBAC's View

Vinorelbine capsules:

Add the new indication, shown in italics, to the existing indication:

<u>Authority Required</u>

Locally advanced or metastatic non-small cell lung cancer.

<u>Authority Required (STREAMLINED)</u>

For the treatment of advanced breast cancer after failure of standard prior therapy, as a single agent or in combination.

NOTE:
This treatment is suitable for use in combination with trastuzumab in HER2+ ABC patients.

Vinorelbine IV solution:
Changes shown with strikethrough.

Section 100 (Efficient Funding of Chemotherapy)
Private Hospital Authority Required
Public Hospital Authority Required (STREAMLINED)
Locally advanced or metastatic non-small cell lung cancer.
Advanced breast cancer after failure of prior therapy ~~which includes an anthracycline.~~

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

The submission stated that the requested listing for oral vinorelbine will not change the current clinical place of vinorelbine but will provide an additional treatment option with greater convenience and flexibility in timing and location of treatments in addition to IV vinorelbine. Oral vinorelbine was proposed as second line therapy in advanced breast cancer after failure of standard therapies (anthracycline or taxane containing regimens), as monotherapy or in combination with another agent. Other second line therapies include IV vinorelbine and capecitabine.

6. Comparator

The sponsor nominated intravenous (IV) vinorelbine as the comparator on the basis that oral vinorelbine is the closest pharmacological analogue listed on the PBS for advanced breast cancer, and IV vinorelbine is the treatment most likely to be substituted.

The PBAC agreed that IV vinorelbine was the appropriate comparator.

7. Clinical Trials

The submission presented:

(i) one head-to-head open label randomised phase II study with oral and intravenous vinorelbine arms evaluating the efficacy of oral vinorelbine in terms of tumour response in monotherapy for advanced breast cancer previously treated with anthracycline (Trial CA-221 – this trial had not been published at the time of submission),
(ii) one supporting open label three arm randomised phase II study evaluating the disease control achieved by capecitabine and oral vinorelbine concurrently; capecitabine and docetaxel, for metastatic breast cancer previously treated with neo/adjuvant anthracyclines (Trial CA-222),
(iii) two bioequivalence studies comparing the bioavailability of the intravenous and oral forms of vinorelbine (Marty et al. 2001 and Bourgeois et al. 2007) and
(iv) three selected citations supporting the use of vinorelbine in combination with trastuzumab (Andersson et al. 2011, Burnstein et al. 2007, Bernardo et al. 2008 [conference poster only]).

The table below details the published trials presented in the submission.

Trial ID/First author	Publication title	Publication citation
Randomised controlled trials		
Trial CA-222 Campone et al.	A 3-arm randomised phase II study of oral vinorelbine (NVBo) plus capecitabine (X) versus NVBo and X in sequential versus docetaxel (D) plus X in patients with metastatic breast cancer (MBC) previously treated with anthracyclines.	*European Journal of Cancer*, Supplement (2009); 7(2-3): 259.
Supplementary bioavailability studies		
Marty et al.	Oral vinorelbine pharmacokinetics and absolute bioavailability study in patients with solid tumors.	*Annals of Oncology* (2001); 12(11):1643-1649.
Bourgeois et al.	Evaluation of oral versus intravenous dose of vinorelbine to achieve equivalent blood exposures in patients with solid tumours.	*Cancer Chemotherapy and Pharmacology* (2007); 60(3): 407-413.
Supporting publications		
Bernardo et al.	Trastuzumab plus intravenous or oral vinorelbine in chemo naive patients with HER2 overexpressing metastatic breast cancer - final results from an extended phase II trial.	Poster (2008), unknown origin.

For PBAC's view, see Recommendation and Reasons.

8. Results of Trials

Vinorelbine as monotherapy and in combination with docetaxel

The primary outcomes reported were response rate (based on RECIST criteria), median time to progression free survival and overall median time for survival. The submission did not present any comparative analyses between treatment arms.

Overall response rate (ITT; after IRP review), median time of progression free survival (ITT) and median time of overall survival (ITT) results for Trial CA-222 are shown in the table below:

	Trial CA-222 combination therapy	
Trial ID	**VRL oral+CAP (n=44)**	**DOC+CAP (n=48)**
Complete response	0	1 (2.1%)
Partial response	14 (31.8%)	16 (33.3%)
Overall response n (%), (95% CI%)	14 (31.8%) (18.6%, 47.6%)	17 (35.4%) (22.2%, 50.5%)
Stable disease	NR	NR
Disease control rate (CR+PR+SD) n (%), (95% CI)	31 (70.5%) (54.8%, 83.2%)	34 (70.8%) (55.9%, 83.1%)
Progressive disease	5 (11.4%)	2 (4.2%)
Median time of PFS months (95% CI)	7.2 months (5.3, 8.9)	8.9 months (7.2, 12.0)
Median time to TTF months n (%)	5.6 months (4.2, 6.5)	4.3 months (4.0, 5.0)

Trial ID	Trial CA-222 combination therapy	
	VRL oral+CAP (n=44)	DOC+CAP (n=48)
Median time of OS months (95% CI)	22.2 months (18.8, 29.9)	24.2 months (14.2, 38.5)
Number of events (deaths)	30 (68.2%)	29 (60.4%)

Abbreviations: VRL = Vinorelbine; DOC = Docetaxel; CAP = Capecitabine; IV = Intravenous; CR = complete response; PR = partial response; SD = stable disease; PFS = progression free survival; TTF = time to treatment failure; OS = overall survival; NR = not reported.

The PBAC noted the results of trial CA-221 (in the monotherapy setting) showed that oral vinorelbine was associated with lower rates of complete response, partial response, overall response and disease control, and with more progressive disease than IV vinorelbine. Median progression free survival and median time of overall survival were shorter for patients taking oral vinorelbine.

In the monotherapy trial (CA-221), patients taking oral vinorelbine reported lower scores (worse function) in overall quality of life, role functioning and emotional functioning and more severe gastrointestinal symptoms (nausea/vomiting, appetite loss, diarrhoea, fatigue) compared to baseline as well as compared to patients using IV vinorelbine, at both 6 and 12 weeks.

Quality of life measures for Trial CA-222 were not reported as 36.7% of patients failed to complete the questionnaire instrument at baseline and at least once during the study.

Given the limited trial data presented in the submission and the request for price parity with oral vinorelbine in non-small cell lung cancer, the results of Trial CA-205 (pivotal trial in the March 2006 submission comparing oral and IV vinorelbine in non-small cell lung cancer) are compared with Trial CA-221.

The results of Trial CA-205 in non-small cell lung cancer numerically favoured oral vinorelbine over IV vinorelbine in partial response rates, stable disease, longer PFS and less progressive disease. In Trial CA-221 in advanced breast cancer, the estimates for partial response, progressive disease, PFS and median survival favour IV vinorelbine.

Combination therapy with trastuzumab

Bernardo (2008), the only study including oral vinorelbine in combination with trastuzumab, was an unpublished observational study presented as a conference poster only. The submission did not provide data supporting the cost effectiveness of vinorelbine in combination with trastuzumab.

Removal of the requirement for prior therapy with anthracyclines for IV vinorelbine

No clinical evidence was presented in the submission, supporting the removal of the requirement for prior therapy with anthracyclines for IV vinorelbine.

Adverse events were consistent with those reported in the pivotal trial for oral vinorelbine in the March 2006 Public Summary Document (for use in non-small cell lung cancer) and the oral vinorelbine Product Information Document.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described oral vinorelbine as equivalent in terms of comparative effectiveness and comparative safety to IV vinorelbine in the treatment of advanced/metastatic breast cancer.

The submission also described oral vinorelbine in combination with trastuzumab as equivalent in terms of effectiveness of docetaxel in combination with trastuzumab in the treatment of HER2 positive advanced breast cancer.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis of vinorelbine capsules versus IV vinorelbine but requested a price based on the current PBS approved price of oral vinorelbine for non-small cell lung cancer.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

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

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC agreed that IV vinorelbine was the appropriate comparator.

The PBAC noted that the key trials comparing IV and oral vinorelbine presented in the submission (CA-221 and CA-222) were conducted in patients who had received prior anthracycline therapy and therefore considered that removal of the requirement in the restriction for patients to have failed prior therapy which includes an anthracycline was not appropriate. The PBAC noted the sponsor's acceptance in its pre sub-committee response that this requirement be retained in the restriction.

The PBAC noted the results of trial CA-221 (in the monotherapy setting) showed that oral vinorelbine was associated with lower rates of complete response, partial response, overall response and disease control, and with more progressive disease than IV vinorelbine. Median progression free survival and median time of overall survival were shorter for patients taking oral vinorelbine. The PBAC considered that these results were suggestive that oral vinorelbine may not be as effective as IV vinorelbine in advanced breast cancer. The PBAC agreed with the ESC that there was a significant risk of bias, with differences between trial arms, early termination of the trial and a lack of statistical power due to small sample sizes and thus that it was not possible to draw any confident conclusions from this study.

The PBAC noted the results of trial CA-222 (in the combination therapy setting) showed that oral vinorelbine in combination with capecitabine was associated with numerically slightly smaller but generally similar overall response rates, progression free survival and overall

survival compared to docetaxel in combination with capecitabine, and that differences between the treatment arms were not statistically significant.

The PBAC noted that there were no statistically significant differences in key adverse events between treatment arms within the trials. Patients taking oral vinorelbine reported less haematological toxicity (leukopenia, neutropenia, febrile neutropenia), alopecia and injection site phlebitis/extravasation, but more gastrointestinal toxicity (nausea, vomiting, diarrhoea, anorexia, abdominal pain) compared to patients taking IV vinorelbine or docetaxel in combination with capecitabine.

Overall, the PBAC considered that the data presented from CA-221 and CA-222 did not adequately support the claim of equivalence in terms of comparative effectiveness and comparative safety of oral and IV vinorelbine.

In relation to the submission's request to allow combination therapy with trastuzumab, the PBAC noted that the Andersson (2011) and Burnstein (2007) trials compared IV vinorelbine + trastuzumab with docetaxel + trastuzumab and docetaxel/paclitaxel + trastuzumab respectively, as first-line chemotherapy in HER2 positive advanced breast cancer. These trials did not include oral vinorelbine. In addition, both trials used dosing regimens that differ from those recommended in the relevant product information documents, treatment guidelines and Australian clinical practice. The PBAC noted that Bernardo (2008) was an unpublished observational study comparing IV vinorelbine + trastuzumab with oral vinorelbine + trastuzumab presented as a conference poster only. The submission did not provide data supporting the cost effectiveness of vinorelbine in combination with trastuzumab. Overall, the PBAC considered that the limited data presented did not support the claim of equivalence between oral vinorelbine in combination with trastuzumab and docetaxel in combination with trastuzumab. In addition, the PBAC noted that there is not currently a TGA-approved indication for this combination.

The PBAC did not consider the submission's economic claim of cost-minimisation versus IV vinorelbine, using a price based on the current PBS price of oral vinorelbine in non-small cell lung cancer to be reasonable. In the first instance, the PBAC did not accept the submission's claim of comparative efficacy and safety of oral and IV vinorelbine in advanced breast cancer. Furthermore, there have been changes to the funding of IV vinorelbine with the advent of the Section 100 Efficient Funding of Chemotherapy Program, which may mean that the previously negotiated cost-minimised price for oral vinorelbine for NSCLC may no longer be appropriate. The PBAC also considered that it was unclear whether differences in the dosing schedules of oral and IV vinorelbine used in NSCLC and advanced breast cancer would affect the pricing of oral vinorelbine for use in advanced breast cancer. The PBAC noted the cost-minimisation analysis presented in the sponsor's pre-PBAC response, which suggested that the cost of treatment with oral vinorelbine is the same as IV vinorelbine when the number of doses per cycle is assumed to be equal, but that this was higher than the cost of treatment with oral vinorelbine for NSCLC.

The PBAC considered that there was uncertainty with the submission's estimate of the number of patients treated with oral vinorelbine, as it was dependent on the proportion of use of IV vinorelbine in breast cancer. Furthermore, the submission assumed the same dose per patient and average number of cycles per patient in advanced breast cancer as in NSCLC,

which the PBAC noted is not supported by clinical guidelines, nor the doses used in the key trials.

The PBAC therefore rejected the submission on the basis of inadequate evidence to support a claim of equivalence in terms of comparative effectiveness and safety between oral and IV vinorelbine and an inappropriate cost-minimisation analysis.

Recommendation:
Reject

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

Pierre Fabre Medicament Australia is committed to collaborating with the PBAC with the aim of having oral Navelbine® subsidised on the PBS for the appropriate Australian patients with advanced breast cancer. A minor resubmission lodged in December 2012 for the March 2013 PBAC meeting is currently under review by the PBAC.