Public Summary Document

Product:	Vinorelbine tartrate, soft capsule, 20 mg and 30 mg (base), Navelbine®
Sponsor:	Pierre Fabre Medicament Australia Pty Ltd
Date of PBAC Consideration:	March 2006

1. Purpose of Application

This application sought an authority required listing on the Pharmaceutical Benefits Scheme (PBS) for locally advanced or metastatic non-small cell lung cancer.

2. Background

At the June 1998 meeting, the Pharmaceutical Benefits Advisory Committee (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.

The Committee agreed to listing on the basis of similar safety and efficacy to paclitaxel/gemcitabine or vinca alkaloid plus cisplatin and being less costly.

Vinorelbine for oral use has not previously been considered by the PBAC.

3. Registration Status

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.

4. Listing Requested and PBAC's View

Authority required

Locally advanced or metastatic non-small cell lung cancer.

The PBAC had no comments on this restriction.

5. Clinical Place for the Proposed Therapy

Chemotherapy is given in patients with advanced/metastatic NSCLC in unresectable Stage IIIB and IV who have a good performance status and are otherwise medically fit. Intravenous vinorelbine is currently a standard treatment for NSCLC, given as a single agent or in combination with other chemotherapy agents.

An oral form of vinorelbine has been developed.

6. Comparator

The submission nominated intravenous vinorelbine as the main comparator. The PBAC agreed this was appropriate.

7. Clinical Trials

The submission presented an open, randomised (2:1), phase II, head-to-head study (CA205) comparing oral vinorelbine with intravenous vinorelbine as monotherapy as the key trial, which compared 115 previously untreated patients with stage IIIB or IV NSCLC. Oral vinorelbine was administered at a dose of 60 mg/m^2 per week for 3 administrations then 80 mg/m^2 per week, in the absence of significant haematological toxicity, and 30 mg/m^2 intravenously per week. The doses of both oral and intravenous vinorelbine were adjusted on haematological response.

Six supportive single arm studies in patients with advanced NSCLC and three bioequivalence studies were also presented. The published trials forming the basis of the submission are listed below.

Trial/First author	Protocol title	Publication citation
Key trial		
Jassem J et al, 2001	A multicenter randomized phase II study of oral vs. intravenous Navelbine in advanced non-small-cell lung cancer patients. [erratum appears in Ann Oncol 2002; 13(3): 493].	Annals of Oncology 2001; 12(10):1375-81.
Supportive studies (non-randomised, single arm trials)		
Jassem J et al, 2003 (CA 202)	Oral Navelbine in combination with cisplatin: A novel active regimen in advanced non-small-cell lung cancer.	Annals of Oncology 2003; 14(11):1634-9.
De Lena M et al, 2005 (CA 206)	Phase II trial of oral Navelbine in combination with cisplatin followed by consolidation therapy with oral Navelbine in advanced NSCLC.	Lung Cancer 2005; 48(1):129-35.
O'Brien MER et al, 2004 (CA 201)	Navelbine alternating oral and intravenous plus carboplatin in advanced non-small-cell lung cancer: Results of a multicentre phase II study.	Annals of Oncology 2004; 15(6):921-7.
Gridelli C et al, 2004 (CA 208) Puozzo C,Gridelli C. 2004	Oral Navelbine given as monotherapy to advanced, elderly NSCLC patients: A multicentre phase II trial. Pharmacokinetics also published as: Non-small-cell lung cancer in elderly patients: Influence of age on Navelbine oral pharmacokinetics.	European Journal of Cancer 2004; 40(16):2424-31. Clinical Lung Cancer 2004; 5(4):237-42.
Kanard A et al, 2004	Oral Navelbine for the treatment of metastatic non-small cell lung cancer in elderly patients: A phase II trial of efficacy and toxicity.	Lung Cancer 2004; 43(3):345-53.
Bioavailability studies		
Marty et al, 2001 (CA 102)	Oral Navelbine pharmacokinetics and absolute bioavailability study in patients with solid tumours.	Annals of Oncology 2001; 12(11):1643-9.

8. Results of Trials

On an intention-to-treat basis the objective response rate (assessed after a minimum of 4 administrations of vinorelbine during the first 8 weeks of treatment) was 11.7% in the oral vinorelbine arm (95% CI: 5 to 19%) and 10.5% in the IV vinorelbine arm (95% CI: 1 to 20%); hazard ratio (HR): 1.1; 95% CI: 0.3 to 3.6). Patients in the oral vinorelbine arm experienced longer progression-free survival times than patients treated with IV vinorelbine (HR 0.65; 95% CI: 0.43 to 0.93). The overall median survival time was 9.4 months in the oral vinorelbine arm versus 7.9 months in the IV vinorelbine arm (HR 0.77; 95% CI: 0.50 to 1.18). Overall, there were no statistically significant differences between oral and IV vinorelbine in the objective response rate (assessed across complete and partial response, stable and progressive disease), overall survival, and the 1-year survival probability. Median progression-free survival favoured oral vinorelbine, but the results were of borderline statistical significance.

For the six non-randomised supportive studies, the overall response rates were variable with rates ranging from as low as 3.4% to as high as 33%. The median overall survival ranged from 7.2 to 10 months. The median progression-free survival ranged from 3.5 to 5.5 months.

For the key trial (CA 205), there appeared to be a slight reduction in the rates of neutropenia (overall rate and Grade 3-4 neutropenia) and thrombocytopenia in the oral vinorelbine arm compared to the IV vinorelbine arm. In contrast, the overall rates of nausea, vomiting, and diarrhoea were statistically significantly higher in the oral vinorelbine arm than in the IV vinorelbine arm. A more recent study incorporating administration with food and the use of anti-nauseants reduced the GI toxicities considerably.

For the six, non-randomised supportive studies, the rates of haematological toxicity (ie neutropenia, thrombocytopenia, and anaemia) and non-haematological toxicity were inconsistent across trials with no clear trends emerging.

9. Clinical Claim

The submission claimed oral vinorelbine was no worse than intravenous vinorelbine in terms of effectiveness and toxicity. The PBAC accepted this claim.

10. Economic Analysis

The submission presented a cost-minimisation analysis as the preliminary economic evaluation which compared the cost of treatment with oral vinorelbine with intravenous vinorelbine based on the regimens used in the pivotal trial study CA 205 over 3 cycles (the median length of treatment in the study).

The only cost off-set in the economic evaluation was administration cost for IV vinorelbine. The PBAC considered that this cost was overestimated and would need to be adjusted.

11. Estimated PBS Usage and Financial Implications

The overall market was not expected to grow or to grow more rapidly as a result of listing oral vinorelbine.

12. Recommendation and Reasons

The PBAC recommended listing on a cost-minimisation basis, concluding that orally administered vinorelbine is no worse than intravenously administered vinorelbine in terms of

effectiveness and toxicity. The equi-effective doses are one 3-week cycle at 60mg/m^2 and two 3-week cycles at 80mg/m^2 for oral vinorelbine and three 3-week cycles at 30mg/m^2 for intravenous vinorelbine. The PBAC did not agree that all patients receiving IV vinorelbine would be admitted as inpatients and therefore the cost offsets claimed for oral vinorelbine that were associated with administration of the IV formulation had been over-estimated. The price should be adjusted to take into account the proportion of patients receiving IV vinorelbine in the outpatient setting in calculating the administration cost-offsets.

Recommendation

VINORELBINE TARTRATE, soft capsule, 20 mg and 30 mg (base)

Restriction:	Authority required Locally advanced or metastatic non-small cell lung cancer
Maximum Quantity	20 (20mg) 16 (30mg)
Repeats	2 (both strengths)

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

No comment.