

## **PUBLIC SUMMARY DOCUMENT**

**Product:** Ibandronic acid, tablet, 50 mg, Bondronat<sup>®</sup>

**Sponsor:** Hospira Pty Ltd

**Date of PBAC Consideration:** November 2008

### **1. Purpose of Application**

The submission requested a Restricted Benefit listing for patients with bone metastases from breast cancer.

### **2. Background**

This was the second submission for ibandronic acid 50 mg tablets for the treatment of bone disease in patients with breast cancer. The PBAC rejected a submission in March 2008 because of inadequate evidence that ibandronic acid was not inferior to the comparator, clodronate. The PBAC noted that the indirect comparison presented was based upon two ibandronic acid trials and three clodronate trials, which varied considerably in their study designs, age of the trials and exclusion criteria (See also Public Summary Document of March 2008).

An injectable form of ibandronic acid was recommended for listing by PBAC at its March 2004 meeting as a Section 100 (Highly Specialised Drug) item for bone metastases from breast cancer on a cost-minimisation basis against disodium pamidronate. It was listed on 1 March 2008. Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities

### **3. Registration Status**

The ibandronic acid 50 mg tablet was registered by the TGA on 24 August 2006 for the treatment of metastatic bone disease in patients with breast cancer.

### **4. Listing Requested and PBAC's View**

#### Restricted Benefit

Bone metastases from breast cancer

*See Recommendation and Reasons for PBAC's view.*

### **5. Clinical Place for the Proposed Therapy**

The submission stated that oral ibandronate is a more palatable tablet and has more convenient dosing than oral clodronate. In addition, compared to IV administration, it allows the option of long term maintenance at home.

### **6. Comparator**

The submission nominated IV ibandronate as the primary efficacy comparator with IV zoledronic acid and oral clodronate as secondary or supportive efficacy comparators. As oral ibandronate is largely expected to replace oral clodronate on the PBS, the submission used clodronate as the pricing comparator.

The PBAC considered that, in accordance with the 2007 PBAC Guidelines, oral clodronate was the appropriate main comparator. Given that the indirect comparison of ibandronate and clodronate previously presented was not considered by the PBAC to be sufficient evidence to

support the claim of non-inferiority, the submission's revised approach to compare oral ibandronate with IV ibandronate was reasonable.

## 7. Clinical Trials

The submission presented two Phase III oral ibandronate trials (MF4414 and MF4434, presented in the previous submission) and one Phase III IV ibandronate trial (MF4265). These trials form the basis of an indirect comparison between 50 mg oral and 6 mg IV ibandronate, with placebo as the common comparator. Additional supporting evidence was provided in the form of the previously presented indirect comparison of the two Phase III oral ibandronate trials (MF4414 and MF4434) and three oral clodronate trials (Kristensen et al. 1999; Paterson et al. 1993a and 2001; and Tubiana-Hulin et al. 2001), as well as a newly presented direct head-to-head trial comparing oral ibandronate against IV zoledronic acid (Body et al, 2007).

The trials published at the time of the submission were:

<b>Trial ID /Author</b>	<b>Protocol title/Publication title</b>	<b>Publication citation</b>
<b>Oral ibandronate versus placebo</b>		
Tripathy D, et al. MF4434 Study Group.	Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomised double-blind placebo-controlled trial.	<i>Annals of Oncology</i> 2004; 15(5):743-50.
Body JJ, et al.	Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised placebo-controlled phase III studies.	<i>British Journal of Cancer</i> 2004a; 90: 1133-1137.
Body JJ, et al.	Oral ibandronate improves bone pain and preserves quality of life in patients with skeletal metastases due to breast cancer.	<i>Pain</i> 2004b; 111(3): 306-312.
McLachlan SA, et al.	Safety of oral ibandronate in the treatment of bone metastases from breast cancer: Long-term follow-up experience.	<i>Clinical Drug Investigation</i> 2006; 26(1): 43-48.
<b>Clodronate versus placebo</b>		
Kristensen et al.	Oral clodronate in breast cancer patients with bone metastases: a randomised study.	<i>Journal of Internal Medicine</i> 1999; 246(1):67-74.
Paterson et al.	Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer.	<i>Journal of Clinical Oncology</i> 1993a; 11(1): 59-65.
Paterson et al.	Double-blind trial of oral clodronate in breast cancer patients with bone metastases.	<i>Bulletin du Cancer</i> 1993b; 80(10 Suppl):50-6.
Paterson et al.	Effect of clodronate on time to occurrence of skeletal complications in patients with breast cancer and bone metastases.	<i>Breast Cancer Research &amp; Treatment</i> 2001; 69(3):305.
Tubiana-Hulin et al.	Double-blinded controlled study comparing clodronate versus placebo in patients with breast cancer bone metastases.	<i>Bulletin du Cancer</i> 2001; 88(7):701-7.
<b>IV ibandronate</b>		

Body JJ et al.	Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases.	<i>Annals of Oncology</i> 2003; 14(9): 1399-1405.
Pecherstorfer M et al.	Long-term safety of intravenous ibandronic acid for up to 4 years in metastatic breast cancer.	<i>Clin Drug Invest</i> 2006; 26(6): 315-22
Lyubimova NV et al.	Renal safety of intravenous ibandronic acid in breast cancer patients with metastatic bone disease.	<i>Clin Drug Invest</i> 2003; 23(1): 707-16.
<b>Oral ibandronate versus IV zoledronic acid (direct head-to-head trial used as supportive evidence)</b>		
Body JJ, et al.	Oral ibandronate is as active as intravenous zoledronic acid for reducing bone turnover markers in women with breast cancer and bone metastases.	<i>Annals of Oncology</i> 2007; 18: 1165-1171.

## 8. Results of Trials

The results of the indirect comparison for oral and IV ibandronate showed no statistically significant difference between the two ibandronate formulations for the four designated outcomes:

- Mean number of events calculated using Poisson multivariate regression analysis (with covariates included), indirect relative risk (IRR) = 1.03 (95% CI: 0.68, 1.58);
- Mean number of 12-week periods with events calculated using Poisson multivariate regression analysis (with covariates included), IRR = 0.89 (95% CI: 0.64, 1.25);
- A multiple events analysis assessed using the Anderson-Gill approach (Tripathy et al, 2004), IRR = 0.87 (95% CI: 0.60, 1.27); and
- Proportion of patients assessed through logistic regression adjusted for baseline characteristics, IRR = 1.25 (95% CI: 0.68, 2.29).

The PBAC noted that the results for mean number of 12 week periods with events (Poisson multivariate regression with covariates) and the multiple events analysis using the Anderson-Gill approach supported the claim that oral ibandronate was non-inferior to IV ibandronate. The PBAC noted that in accordance with good methodological practice, the results of key outcomes, new bone events and the number of 12-week periods with new bone events for trial MF4265 should have been presented with and without co-variate adjustment.

The re-submission presented further safety information to that presented in the previous submission. The PBAC noted that overall, the clinical safety profile of oral ibandronate was typical of bisphosphonates, with similar levels of adverse events having been presented previously for clodronate and in the re-submission for IV ibandronate and zoledronic acid. In the extended assessment of safety, information and concerns regarding osteonecrosis of the jaw have been updated.

## 9. Clinical Claim

The re-submission stated that oral ibandronate was no worse than IV ibandronate and oral clodronate. This was considered reasonable by the PBAC.

## 10. Economic Analysis

The submission presented a cost-minimisation analysis. The equi-effective doses were estimated as oral ibandronate 50 mg daily for long-term administration and clodronate

1600 mg daily for long-term administration. This approach was unchanged from the previous submission.

#### **11. Estimated PBS Usage and Financial Implications**

The submission estimated the likely number of patients per year to be < 10,000 in Year 5, The estimate provided by the re-submission appeared to be reasonable.

#### **12. Recommendation and Reasons**

The PBAC recommended ibandronic acid tablets for listing on the PBS on a cost-minimisation basis compared with oral clodronate and recommended that the equi-effective doses were ibandronic acid 50 mg daily and clodronate 1600 mg daily, both for long term administration.

The PBAC agreed that intravenous ibandronic acid was the appropriate primary efficacy comparator and zoledronic acid and oral clodronate were the appropriate secondary comparators, as the previous comparison of oral ibandronic acid and clodronate was not considered to be sufficient to support the claim of non-inferiority.

The PBAC considered that the analyses presented in the submission, together with the clarifications provided in the Pre-Sub-Committee Response, supported the claim of non-inferiority against IV ibandronic acid and, by extension, oral clodronate.

Lastly, the PBAC agreed with the pre-PBAC response that the restriction for oral ibandronate should be consistent with other PBS agents listed for the same indication.

#### **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**

The sponsor has no comment.