

PUBLIC SUMMARY DOCUMENT

Product: Ibandronic acid, tablet, 50 mg, Bondronat[®]

Sponsor: Hospira Pty Ltd

Date of PBAC Consideration: March 2008

1. Purpose of Application

The submission sought a Restricted benefit listing for patients with bone metastases from breast cancer.

2. Background

This formulation of ibandronic acid has not previously been considered by the PBAC.

Ibandronic acid as 6 mg per 6 mL injection was considered by PBAC at its March 2004 meeting for a Section 100 (Highly Specialised Drug) Private hospital authority required listing for bone metastases from breast cancer. The PBAC recommended listing on a cost-minimisation basis against disodium pamidronate with the equi-effective doses being ibandronic acid 6 mg IV and pamidronate 90 mg IV. Listing was effective from 1 March 2008.

3. Registration Status

Bondronat 50 mg tablets were 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.

The PBAC had no objection to the requested wording of the restriction.

5. Clinical Place for the Proposed Therapy

Ibandronic acid 50 mg tablets would provide an alternative to treatment with oral clodronate or intravenous pamidronate and zoledronic acid for patients with bone metastases from breast cancer.

6. Comparator

The submission nominated oral sodium clodronate as the comparator. This is the only currently available oral bisphosphonate indicated for bone metastases from breast cancer. The PBAC accepted that oral clodronate was an appropriate comparator for the listing requested, but that oral ibandronic acid may also substitute for intravenous bisphosphonates in the PBS population who currently prefer intravenous agents over oral clodronate.

7. Clinical Trials

The submission presented an indirect comparison of two 96 week double-blind, placebo controlled, randomised efficacy and safety studies comparing ibandronate (ibandronic acid) 50 mg versus placebo, MF4414 and MF4434, and three randomised trials comparing clodronate 1600 mg with placebo, in patients with bone metastases from breast cancer.

The following table lists the trials as published at the time of submission.

Trial/Author	Protocol title/Publication title	Publication citation
Trial MF4434 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.
Trials MF4414 and 4434 Pooled Body JJ, et al. Body JJ, et al. McLachlan SA, 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. Oral ibandronate improves bone pain and preserves quality of life in patients with skeletal metastases due to breast cancer. Safety of oral ibandronate in the treatment of bone metastases from breast cancer: Long-term follow-up experience.	<i>British Journal of Cancer</i> 2004a; 90: 1133-1137. <i>Pain</i> 2004b; 111(3): 306-312. <i>Clinical Drug Investigation</i> 2006; 26(1): 43-48.
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. Paterson et al. Paterson et al.	Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. Double-blind trial of oral clodronate in breast cancer patients with bone metastases. Effect of clodronate on time to occurrence of skeletal complications in patients with breast cancer and bone metastases.	<i>Journal of Clinical Oncology</i> 1993a; 11(1): 59-65. <i>Bulletin du Cancer</i> 1993b; 80(10 Suppl):50-6. <i>Breast Cancer Research & 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.

8. Results of Trials

The principal analysis used the data from the pooled analysis of the ibandronate trials adjusted for baseline characteristics and excluding the first 12 weeks due to confounding factors. The submission claimed this to be the most appropriate comparison to use for a true assessment of non-inferiority as it minimises the influence of the confounding factors in the ibandronate trials. The PBAC was advised that although this may reduce confounding factors and account for pre-scheduled radiotherapy events within the ibandronate trials, it is an inappropriate comparison given the clodronate trials, with the exception of the Tubiana-Hulin (2001) trial, recorded all skeletal-related events from the start of the trials. The second comparison used the meta-analysis of all the ibandronate data (random effects model). The submission claimed this represents the “worst case” scenario, due to the confounding factors in the first 12 weeks of the study.

Using a conventional approach in interpreting the data presented, a statistically significant difference was observed in the pooled analysis of the clodronate trials, RR=0.85 (95% CI: 0.73, 0.99) and the pooled analysis of the ibandronate trials (when the first 12 weeks were excluded and the results were adjusted for baseline characteristics), RR=0.637 (95% CI: 0.435, 0.932), in favour of the treatment arms compared with placebo. The pooled analysis

of “all data” from the ibandronate trials showed no statistically significant difference between ibandronate and placebo. The indirect comparison of ibandronate and clodronate indicated no statistically significant differences between the treatments when “all data” and when data adjusting for baseline characteristics and the first 12 weeks were excluded, RR= 1.11 (95% CI: 0.50, 1.13), respectively.

With respect to the secondary efficacy endpoint of bone pain, oral ibandronate produced significant reductions in pain scores to below baseline that were maintained throughout two years of treatment, whereas a gradual increase in bone pain scores was observed for placebo-treated patients at study end.

The clinical safety profile of ibandronate was typical of oral bisphosphonates and comparable to clodronate. Major adverse events reported for ibandronate were mainly gastrointestinal but did not reach statistical significance. Hypocalcaemia was the only reported adverse event of statistical significance. These effects were similar in prevalence to the clodronate trials. In the extended assessment of safety, concerns regarding osteonecrosis of the jaw were raised. It was noted that there is continuing uncertainty around the issue of osteonecrosis of the jaw, and as such, it remains a long term safety concern.

For PBAC’s comments on the results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed ibandronic acid was non-inferior to clodronate in terms of comparative effectiveness.

The PBAC considered it difficult to describe ibandronic acid as non-inferior in terms of comparative effectiveness due to the variability of the evidence presented and errors in the analysis of results.

For further details of PBAC’s view see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses in terms of cost-minimisation were claimed by the submission to be ibandronic acid 50 mg daily and clodronate 1600 mg daily, both for long-term administration. These are the TGA approved doses for bone metastases from breast cancer.

11. Estimated PBS Usage and Financial Implications

The submission estimated the financial cost per year to the PBS minus any savings in use of other drugs to be less than \$10 million in Year 5.

12. Recommendation and Reasons

The PBAC accepted that oral clodronate is an appropriate comparator for the listing requested, but that oral ibandronic acid may also substitute for intravenous bisphosphonates in the PBS population who currently prefer intravenous agents over oral clodronate. This is because ibandronic acid tablets appear to have advantages compared to clodronate tablets in size and because the former may be taken just 30 minutes prior to a meal, whereas the latter needs to be taken one hour prior or two hours after a meal.

The PBAC noted that the indirect comparison was based upon two ibandronate trials and three clodronate trials, which vary considerably in their study designs, age of the trials and exclusion criteria. The indirect comparison was based upon a commonly reported outcome, the proportion of patients with skeletal-related events, excluding hypercalcaemia. Definitions amongst the trials of a skeletal-related event differed and recording of the frequency of events also varied. Additionally, the indirect comparison was inappropriate given that the first 12 weeks of skeletal events were excluded from the ibandronate trials and the first month of events were excluded from one of the clodronate trials (Tubiana-Hulin). The other clodronate trials did not specify exclusion of events. This made it difficult to compare the different trials and favourably biases ibandronate. The PBAC expressed concerns about the indirect comparison.

The heterogeneity in the trials and the problems in the handling of the trial data made it difficult to interpret the results of the indirect comparison. For example, although the indirect comparison shows that a statistically significant difference was observed in the pooled analysis of the clodronate trials, RR=0.85 (95% CI: 0.73, 0.99) and the pooled analysis of the ibandronate trials (when the first 12 weeks were excluded and the results were adjusted for baseline characteristics), RR=0.637 (95% CI: 0.435, 0.932), in favour of the treatment arms compared with placebo, the pooled analysis of “all data” from the ibandronate trials showed no statistically significant difference between ibandronate and placebo. The indirect comparison of ibandronate and clodronate indicated no statistically significant differences between the treatments when “all data” and when data adjusting for baseline characteristics and the first 12 weeks were excluded, RR=1.11 (95% CI: 0.85, 1.43) and RR=0.75 (95% CI: 0.50, 1.13), respectively. However, considering the wide confidence interval around the point estimate of relative risk in the “all data” analysis, the possibility that ibandronate is worse than clodronate could not be excluded.

Although the PBAC acknowledged the reanalysis presented using only the results of the Tubiana-Hulin (2001) study for clodronate may provide better support for a conclusion of non-inferiority (in both the analysis including the first 12 weeks of data and the analysis excluding these data), the Committee could not justifiably make a recommendation upon these results alone.

The PBAC therefore rejected the submission to list ibandronic acid 50 mg tablets for the treatment of patients with bone metastases from breast cancer because of inadequate evidence that it is not inferior to the comparator, clodronate.

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 will be considering its position regarding any future course of action.