

PUBLIC SUMMARY DOCUMENT

Product: Zoledronic acid, solution for I.V. infusion, 5 mg (as monohydrate) in 100 mL, Aclasta®

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

Date of PBAC Consideration: November 2009

1. Purpose of Application

To request an extension to the current authority required PBS listing for zoledronic acid to include an authority required (STREAMLINED) listing for symptomatic Paget disease of bone.

2. Background

This drug had not previously been considered by the PBAC for this indication.

3. Registration Status

Zoledronic acid 5 mg in 100 mL was TGA registered on 27 May 2009 for the treatment of Paget disease of bone.

Zoledronic acid 5 mg in 100 mL is also registered for the following indications:

- Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures, treatment should be restricted to three annual doses;
- Treatment of osteoporosis in patients over 50 years of age with a history of at least one low trauma hip fracture, to reduce the incidence of further fractures, treatment should be restricted to three annual doses;
- To increase bone mineral density in men with osteoporosis;
- To increase bone mineral density in patients with osteoporosis associated with long term glucocorticoid use; and
- To prevent glucocorticoid induced bone mineral density loss.

4. Listing Requested and PBAC's View

Authority required (STREAMLINED)

Symptomatic Paget's disease of bone.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Paget disease is a chronic skeletal disorder characterised by localised areas of increased bone remodelling, bone hypertrophy, abnormal bone structure and structural weakness. It is characterised by periods of active, symptomatic disease interspersed with periods of disease remission. The aims of treatment are to achieve clinical remission (relief of symptoms), biochemical remission and radiological remission.

Therapy is aimed at decreasing abnormal bone turnover, and therefore, treatment usually involves anti-resorptive therapy such as alendronate, risedronate, tiludronate (oral therapy) and pamidronate (intravenous therapy) as standard therapy.

Zoledronic acid would provide an alternative intravenous treatment for Paget disease.

6. Comparator

The submission nominated risedronate as the main comparator (direct comparison) and pamidronate as a secondary comparator (indirect comparison).

For PBAC's view see Recommendation and Reasons.

7. Clinical Trials

The submission presented a direct comparison of zoledronic acid with risedronate (pooled Trials 2304 and 2305), an indirect comparison of zoledronic acid with pamidronate using risedronate as common comparator (pooled data from Trials 2304/2305, and pamidronate data from Rendina 2004), and an extension study of treatment responders of Trials 2304 and 2305 (unpublished). The outcomes of Merlotti 2007 (zoledronic dose of 4 mg) were included in the evaluation as supplementary data.

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

Trial ID / First author	Protocol title / Publication title	Publication citation
Zoledronic acid 5 mg vs. risedronate		
Trial 2304 Reid IR et al	Comparison of a Single Infusion of Zoledronic Acid with Risedronate for Paget's Disease.	NEJM 2005; 353(9):898-908
Trial 2304 Reid IR	Zoledronate: Efficacy and Safety	J Bone & Mineral Research 2006; 21(Supp 2):P83-P87
Trial 2305 Reid IR et al	Comparison of a Single Infusion of Zoledronic Acid with Risedronate for Paget's Disease.	NEJM 2005; 353(9):898-908
Trial 2305 Reid IR	Zoledronate: Efficacy and Safety	J Bone & Mineral Research 2006; 21(Supp 2):P83-P87
Extension Study 2304/2305 (interim results) Hosking D et al	Long-Term Control of Bone Turnover in Paget's Disease With Zoledronic Acid and Risedronate.	Journal of Bone and Mineral Research 2007, 22(1):142-148
Pamidronate vs. risedronate		
Rendina D et al	Risedronate and pamidronate treatment in the clinical management of patients with severe Paget's disease of bone and acquired resistance to bisphosphonates.	Calcified Tissue International 2004 75:189-196
Zoledronic acid 4 mg versus pamidronate		
Merlotti D et al	Comparison of different intravenous bisphosphonate regimens for Paget's disease of bone.	J Bone & Mineral Research 2007;22(10);1510-17

8. Results of Trials

The primary outcome of the Trials 2304 and 2305 was the proportions of patients achieving $\geq 75\%$ reduction from baseline in total serum alkaline phosphatase (SAP) excess at baseline by 6 months. This outcome has been previously accepted by the PBAC as an adequate indicator of disease activity in Paget disease of bone.

The primary outcomes at 6 months in the pooled Trials 2304 and 2305 for zoledronic acid compared with risedronate are summarised in the table below.

Proportion of patients achieving $\geq 75\%$ reduction from baseline in total SAP excess at 6 months in pooled Trials 2304 & 2305

Trial	Treatment	N	Proportion n (%)	Difference in proportions (95% CI)	Odds ratio (95% CI)	Relative risk* (95% CI)
2304/2305*	Zoledronic acid	176	169 (96)	0.22 (0.14, 0.30)	8.44 (3.90, 21.09)	1.29 (1.19, 1.43)
	Risedronate	171	127 (74)			

* From Reid 2005

There were statistically significant differences in the proportion of patients responding to zoledronic acid compared with risedronate (relative risk 1.29 [95% CI 1.19, 1.43]).

The results of the indirect comparison of zoledronic acid with pamidronate, via risedronate as common comparator, using the secondary outcome of 100% reduction from baseline in total SAP excess at 6 months are shown in the following table.

Indirect comparison of zoledronic acid and pamidronate via risedronate: proportion of patients achieving 100% reduction from baseline in total SAP excess at 6 months

Trial	Zoledronic acid n/N (%)	Risedronate n/N (%)	Pamidronate n/N (%)	OR (95% CI)	RR (95% CI)
2304/2305*	156/176 (88.6)	99/171 (57.9)		5.7 (3.3,9.9)	1.53 (1.33,1.76)
Rendina 2004		13/15 (86.6)	12/15 (80.0)	0.6 (0.2,4.3)	0.92 (0.67,1.27)
Indirect odds ratio (95% CI)				9.2 (1.2, 70.3) p = 0.032	
Indirect Relative risk (95% CI)					1.66 (1.17, 2.35) p = 0.046

* From Reid 2005

There was a substantial difference in the proportions of responders in the two risedronate study groups (57.9% and 86.6%) that made the indirect comparison difficult to interpret. There was clinical heterogeneity with sub-optimal dosing of risedronate in Trials 2304 and 2305, and possible risedronate resistance. The clinical heterogeneity between studies and the wide confidence intervals around the estimates (due to small sample sizes in Rendina 2004) made this comparison difficult to interpret. The Rendina 2004 study included patients with relatively high SAP levels, consistent with relatively extensive and/or relatively active disease. In addition, the inclusion criteria specified that the percent of total skeletal volume involved in Paget's disease of bone in each patient was greater than 40%, which would not be common in clinical practice.

The table below shows the proportions of responders in the subgroups of patients with and without previous anti-pagetic therapy in the pooled Trials 2304 and 2305.

Proportion of responders (i.e. patients achieving $\geq 75\%$ reduction from baseline in total SAP excess at 6 months) in pooled Trials 2304 & 2305, and subgroups of patients with and without previous anti-pagetic therapy

Trial	Zoledronic acid n/N (%)	Risedronate n/N (%)	Odds ratio (95% CI)	Relative risk (95% CI)
Trials 2304/2305 combined*	169/176 (96)	127/171 (74)	8.44 (3.90,21.09)	1.29 (1.19,1.43)
Previous anti-pagetic therapy**	89/94	62/95 (65)	9.47	1.45

	(95)		(3.50,25.62)	(1.24,1.69)
No previous anti-pagetic therapy**	80/82 (98)	65/76 (86)	6.77 (1.45,31.63)	1.14 (1.03,1.26)

* From Reid 2005

** From Reid 2006

Patients in the risedronate group who had previous anti-pagetic therapy were less likely to achieve a therapeutic response than those who did not have previous therapy, which may be due to risedronate resistance.

The table below shows the outcomes for zoledronic acid and pamidronate from Merlotti 2007. Similar to the above table, patients in the pamidronate group were less likely to respond to treatment if they had a history of previous bisphosphonate therapy compared with no previous therapy (26% vs. 81% response respectively).

Proportion of patients achieving \geq 75% reduction from baseline in total SAP excess at 6 months in Merlotti 2007

Trial	Zoledronic acid n/N (%)	Pamidronate n/N (%)	RR (95% CI)
All patients	28 / 29 (97%)	27 / 60 (45%)	2.15 (1.64, 2.93)
Previous bisphosphonate therapy	Not reported*	10 / 39 (26%)	-
No previous bisphosphonate therapy	Not reported*	17 / 21 (81%)	-

* Merlotti 2007 states that response rates in the zoledronic acid group were not significantly different in the previous or no previous treatment subgroups.

The clinical trial and post-marketing data suggested that zoledronic acid may be similar to other bisphosphonates in adverse event profile, with the exception of the acute phase reaction after infusion.

For PBAC's view see Recommendation and Reasons.

9. Clinical Claim

The submission claimed non-inferiority of zoledronic acid compared with other bisphosphonates in terms of comparative effectiveness, but stated that this claim is conservative as superiority of zoledronic acid was demonstrated compared with risedronate and pamidronate. The submission described zoledronic acid as equivalent in terms of safety compared with other bisphosphonates.

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis compared with risedronate, given that equi-effective doses of zoledronic acid and pamidronate could not be calculated from the indirect analysis. The equi-effective doses were estimated as 1 mg zoledronic acid to 627 mg risedronate. The submission calculated the equi-effective doses solely by comparing the time to loss of therapeutic response in an extension study of patients who were classified as "responders" in Trials 2304 and 2305.

For PBAC's view see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated less than 10,000 patients per year in 2010. This estimate was considered uncertain given that it was back-calculated from the estimated cost of other substituted bisphosphonates.

The submission estimated savings of less than \$10,000 in 2010. The estimate was considered uncertain, as they are based on assuming that listing zoledronic acid would be cost neutral to the PBS, and that the cost of administration of zoledronic would be included in a specialist or GP consultation of less than 20 minutes.

12. Recommendation and Reasons

The PBAC recommended the listing of zoledronic acid for the treatment of Paget disease on a cost-minimisation basis compared to disodium pamidronate. The equi-effective doses in the context of cost-minimisation were determined to be one infusion of zoledronic acid 5 mg was equivalent to two infusions of disodium pamidronate 60 mg.

The submission nominated risedronate as the main comparator (direct comparison) and pamidronate as a secondary comparator (indirect comparison). The submission considered the main comparator would be pamidronate based on similar indications and similar routes of administration. However, the only direct trial evidence is against risedronate, so this was presented as the primary comparison, with the indirect comparison with pamidronate presented as a secondary comparison. The PBAC considered that pamidronate was the appropriate main comparator as is given by a similar route of administration, and the most likely therapy to be replaced by zoledronic acid.

In the indirect comparison the PBAC noted that the heterogeneity of trials 2304/2305 and Rendina 2004, and the lack of power of Rendina 2004, hindered the interpretation of the results. However, the PBAC considered that the evidence supported a conclusion of non-inferiority between zoledronic acid and pamidronate.

In the direct comparison, the PBAC noted there were statistically significant differences in the proportion of patients responding to zoledronic acid compared to risedronate (relative risk 1.29 [95% CI 1.19, 1.43]). However, as re-treatment was not offered in the risedronate group if the response was inadequate, as would occur in clinical practice, and the study population may have included patients who had been treated with bisphosphonates previously and were resistant to risedronate, meant that the efficacy of zoledronic acid compared to risedronate may have been over-estimated.

The PBAC accepted that clinical trial and post-marketing data indicated the adverse event profile of zoledronic acid is similar to other bisphosphonates with the exception of acute phase reaction after infusion. The PBAC noted that the incidence of osteonecrosis of the jaw (ONJ) in patients treated for Paget disease is more common than in those treated for osteoporosis, however zoledronic acid has not been shown, to date, to be associated with an excess risk of ONJ compared to other bisphosphonates.

The submission requested that the equi-effective doses be determined by comparing the time to loss of therapeutic response in an extension study of patients classified as 'responders' in trials 2304 and 2305. On this basis the equi-effective doses were estimated in the submission as 1 mg of zoledronic acid to 627 mg of risedronate.

However, on the basis that pamidronate is the appropriate comparator, the PBAC considered the equi-effective doses to be one infusion of zoledronic acid 5 mg was equivalent to two infusions of sodium pamidronate 60 mg. In coming to this conclusion the PBAC noted the following:

- time for re-treatment in the extension study was determined by biochemical parameters alone (serum alkaline phosphatase level) rather than symptomatic and suggested that re-treatment with zoledronic acid occurs every 3.4 years (1233 days) and with risedronate every 1.9 years (708 days);
- that Paget's Disease management guidelines (Selby et al. Guidelines on the Management of Paget's Disease of Bone, Bone 31,3, Sep 2002,10-19; 2002) suggest that symptoms drive treatment and this is confirmed in Walsh et al (Walsh JP et al Treatment of Paget's disease of bone: A survey of clinical practice in Australia. Bone 42; 1219-1225; 2008) in its description of Australian practice; and
- in Walsh et al the re-treatment intervals for pamidronate were quoted as being between 3 and 12 months, suggesting that a 12 months re-treatment interval based on symptoms (with or without SAP level measurement) may be reasonable compared with a six months re-treatment interval for pamidronate.
- In addition, the Pricing Authority accepts that a 60 mg infusion of pamidronate = three months of alendronate = 1.5 months of tiludronate = 1.5 months of risedronate; applying the Pricing Authority relativities to the extension study outcomes, it was calculated that time to re-treatment with one pamidronate infusion 60 mg would be 531 days (based on 60 days of risedronate providing 708 days, and one pamidronate 60 mg infusion being equivalent to 1.5 months of risedronate treatment), and two pamidronate infusions would provide treatment for 1062 days, which is close to the 1233 days time to treatment calculated for zoledronic acid.

The PBAC considered that given the variability in dosing and dosing intervals with pamidronate and clinical practice in the treatment of Paget's disease that a therapeutic relativity of one 5 mg zoledronic acid infusion to two 60 mg pamidronate infusions was appropriate.

Recommendation:

ZOLEDRONIC ACID, solution for I.V. infusion, 5 mg (as monohydrate) in 100 mL,
Extend the current restriction to include:

Restriction: Authority required
Symptomatic Paget disease of bone.

Only 1 treatment each year per patient will be PBS-subsidised.

Maximum quantity: 1
Repeats: nil

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 welcomes the PBAC's decision to make zoledronic acid 5 mg available on the PBS for the treatment of Paget's disease of bone.