

PUBLIC SUMMARY DOCUMENT

Product: Risedronate sodium, tablet, 5 mg, (Actonel[®]) and 35 mg (Actonel Once-a-week[®]), Risedronate sodium and Calcium carbonate, pack containing 4 tablets risedronate sodium 35 mg and 24 tablets calcium carbonate 1.25 g (equivalent to 500 mg calcium), (Actonel Combi[®])

Sponsor: Sanofi Aventis Australia Pty Ltd

Date of PBAC Consideration: July 2008

1. Purpose of Application

The re-submission sought to extend the current authority required (STREAMLINED) listing of risedronate sodium and risedronate sodium and calcium carbonate to include the treatment of corticosteroid-induced osteoporosis (CIO) in patients on long term (≥ 3 months) high dose (≥ 7.5 mg / day prednisolone or equivalent) corticosteroid therapy and a Bone Mineral Density (BMD) T-score ≤ -1.5 .

2. Background

At the September 2000 meeting, the PBAC recommended listing risedronate for the treatment of established postmenopausal osteoporosis (PMO) on a cost-minimisation basis that risedronate 5 mg daily is similar to alendronate sodium 10 mg daily. Listing was implemented on 1 February 2001.

The use of risedronate sodium for patients undergoing long-term treatment with high dose corticosteroids which sought to extend listing to all corticosteroid induced osteoporosis (CIO) patients for both primary and secondary prevention was rejected by the PBAC at its March 2001 meeting, due to uncertainties over the extent of clinical benefit in the proposed restriction. At the December 2001 PBAC meeting, the PBAC recommended the listing of the 5 mg tablet for established corticosteroid-induced osteoporosis in patients with fracture due to minimal trauma. This was implemented on 1 August 2002.

Risedronate 35 mg tablet (Actonel Once-a-Week[®]) was recommended at the September 2002 PBAC meeting on a cost-minimisation basis, with the 35 mg tablet taken weekly accepted as providing similar safety and efficacy to a 5 mg tablet taken daily. The listing was effective from 1 February 2003. The PBAC also recommended removal of the wording 'post-menopausal or established corticosteroid-induced' in the Authority required listing of 5 mg risedronate tablet and its replacement with 'established osteoporosis'.

At the November 2005 meeting, the PBAC recommended listing risedronate 35 mg with calcium carbonate 1.25 mg (Actonel-Combi[®]) on a cost-minimisation basis compared to the risedronate 35 mg once weekly preparation, which is currently listed on the PBS. The PBAC considered and rejected three applications (at the June 2003, March 2005 and July 2006 meetings) which sought to extend the listing of this drug for use prior to first fracture.

At the March 2007 meeting, the PBAC recommended extending the listing as an authority required benefit to allow subsidised use in the primary treatment of osteoporosis on a cost-minimisation basis as compared to alendronate.

At the March 2008 meeting, the PBAC recommended an Authority required (Streamlined) listing for risedronate 75 mg tablet for the same indications as the current listings for risedronate 5 mg tablet on a cost-minimisation basis compared with risedronate 5 mg tablet.

3. Registration Status

5 mg daily tablets (Actonel[®]), 35 mg weekly tablets (Actonel Once-a-Week[®]) and Risedronate 35 mg with calcium carbonate 1.25 g (Actonel-Combi[®]) were TGA registered on 14 August 2000, 12 November 2002 and 20 October 2005, respectively, for the following indications:

- Treatment of osteoporosis.
- Treatment of glucocorticoid-induced osteoporosis.
- Preservation of bone mineral density in patients on long-term corticosteroid therapy.

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)

Treatment of corticosteroid-induced osteoporosis in a patient on long-term (≥ 3 months), high-dose (≥ 7.5 mg/day prednisolone or equivalent) corticosteroid therapy with a Bone Mineral Density (BMD) T-score of -1.5 or less.

The length and dose of corticosteroid therapy along with the date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement must be documented in the patient's medical records when treatment is initiated.

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Risedronate would provide treatment for corticosteroid-induced osteoporosis in patients on long term corticosteroid therapy, who are at risk of fracture.

6. Comparator

The submission nominated placebo as the main comparator. The PBAC considered that this was appropriate.

7. Clinical Trials

The basis of the current submission was two direct randomised comparative trials and a meta-analysis of the same trials from the March 2001 submission comparing risedronate and placebo.

The two direct randomised trials and meta-analysis published at the time of submission are as follows:

Trial ID/First author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
RCT 009893 Reid D.M.	Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: A randomised trial.	Journal of Bone and Mineral Research 2000; 15 (6): 1006-1013.

Trial ID/First author	Protocol title/ Publication title	Publication citation
RCP 009993 Cohen S.	Risedronate therapy prevents corticosteroid-induced bone loss: A twelve-month, multicentre, randomised, double-blind, placebo-controlled, parallel-group study.	Arthritis & Rheumatism 1999;42 (11): 2309-2318
Meta-analyses of direct randomised trials		
Wallach 2000	Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy.	Calcified Tissue International 2000;67:277-285.
Systematic review		
Kanis 2007	Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis. (Includes all trials listed above).	Health Technol Assess 2007:11(7)

8. Results of Trials

The majority of the subjects recruited in the trials were representative of those for whom PBS listing was sought. However, around one third of the subjects over the two trials had a prevalent vertebral fracture at baseline, a group of patients for whom risedronate is already PBS listed. The results across the direct randomised trials showed that, overall, treatment with risedronate reduces the risk of new vertebral fractures. However, no distinction was made in the submission between morphometric (diagnosis made on X-ray) versus clinical vertebral fractures (those which produce symptoms of pain and/or loss of function).

The results of new non-vertebral fractures across the direct randomised trials did not demonstrate a statistically significant effect on non-vertebral fractures.

No new toxicity data were presented in the re-submission.

For PBAC's comments on these results, see Recommendations and Reasons.

9. Clinical Claim

The re-submission described risedronate as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over placebo.

The PBAC accepted that risedronate is superior to placebo in the reduction of fractures in patients on long-term high-dose corticosteroid therapy, but did not accept that risedronate has equivalent safety to placebo. *For PBAC's view, see Recommendations and Reasons.*

10. Economic Analysis

The re-submission estimated the risk of fracture in high-dose, long-term corticosteroid users with a BMD T-score ≤ -1.5 by applying the relative risks of vertebral fracture in the population sought to the vertebral fracture risk seen in the general Australian population using age and gender specific estimates.

A new modelled economic evaluation was presented which used a Markov model and included three health states: well (free from vertebral fracture), post-vertebral fracture and death. The model had a 60 year time horizon, with a 5 year cycle length.

The results of the stepped multivariate sensitivity analyses estimated the base case incremental cost-effective ratio (ICER) to be in the range of \$15,000- \$45,000.

11. Estimated PBS Usage and Financial Implications

The submission estimated the financial costs per year to the PBS to be less than \$10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the extension of the authority required listing on the PBS of risedronate sodium and risedronate sodium with calcium carbonate to include the treatment of corticosteroid-induced osteoporosis (CIO) in patients currently on at least 3 months high dose corticosteroids with a bone mineral density of -1.5 or less on the basis of an acceptable, although uncertain cost effectiveness ratio in the context of a high and unmet clinical need.

The PBAC noted the clinical evidence presented in this re-submission was limited and of poor quality. The trial populations included patients who were not representative of those in whom PBS listing is sought, with both pivotal trials including subjects with prevalent vertebral fractures at baseline, and not distinguishing between clinical (symptomatic) and morphometric (diagnosis made on x-ray) fractures. On the other hand, the clinical use of the bisphosphonates in this condition is widely accepted thus making the availability of further studies unlikely on ethical grounds. The Committee further noted that Kanis (2007) pooled and compared all available data for all bisphosphonates in CIO and PMO and concluded that the fracture risk reductions seen in the two populations were of the same magnitude and that the lack of statistical significance observed in CIO only reflected the smaller sample size within the CIO trials. The overall conclusion from Kanis (2007) was that there was no evidence to support the hypothesis that the effects of bisphosphonates (and risedronate in particular) on fracture risks (including non-vertebral fractures) differ between CIO and post-menopausal osteoporosis (PMO). Overall the PBAC agreed that the relative risk reduction in this indication should be the same if the baseline risk of fracture is equivalent.

The re-submission estimated the risk of fracture in high-dose, long-term corticosteroid users with a BMD T-score ≤ -1.5 by applying the relative risks of vertebral fracture in the population sought to the vertebral fracture risk seen in the general Australian population using age and gender specific estimates.

Although this analysis was subject to a number of uncertainties, the Committee considered that on balance, patients on high dose corticosteroid treatment appeared to have a similar risk of fracture compared to the population for whom risedronate is currently listed on the PBS for the primary prevention of osteoporosis.

The PBAC did not accept that risedronate has equivalent safety to placebo, and this resubmission did not present any new safety data to substantiate this claim. Risedronate has a number of emerging adverse effects, including osteonecrosis of the jaw (ONJ). Concerns regarding the possible increased risk of adverse effects, such as ONJ, in patients on long term corticosteroids are relevant to the patient population covered by this listing.

The PBAC noted that patients in the two direct randomised trials presented, RCT009893 and RCP009993, were currently on corticosteroids, and that the PBS listing should reflect this by

requiring patients to be currently treated with corticosteroids at the time bisphosphonate treatment is initiated.

Recommendation

RISEDRONATE SODIUM and CALCIUM CARBONATE, pack containing 4 tablets risendronate sodium 35 mg and 24 tablets calcium carbonate 1.25 g (equivalent to 500 mg calcium).

Restriction: Authority required (STREAMLINED)
Treatment as the sole PBS-subsidised anti-resorptive agent for corticosteroid-induced osteoporosis in a patient currently on long-term (at least 3 months), high-dose (at least 7.5 mg per day prednisolone or equivalent) corticosteroid therapy with a Bone Mineral Density (BMD) T-score of -1.5 or less.

The duration and dose of corticosteroid therapy together with the date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement must be documented in the patient's medical records when treatment is initiated.

Maximum quantity: 28 (5 mg) 4 (35 mg)
Repeats: 5

Maximum quantity: 1 (Pack containing 4 tablets risedronate sodium 35 mg and 24 tablets calcium carbonate 1.25 g (equivalent to 500 mg calcium))
Repeats: 5

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

Sanofi-aventis welcomes the PBAC's decision to recommend PBS listing of risedronate for use in patients on long-term, high-dose corticosteroid therapy.