PUBLIC SUMMARY DOCUMENT

Product: Risedronate sodium, tablet, 5 mg and 35 mg, Actonel®, Actonel Once-a-Week®, Risedronate sodium and Calcium carbonate, pack containing 4 tablets Risedronate sodium 35 mg and 25 tablets Calcium carbonate 1.25 g (equiv to 500 mg calcium) Actonel Combi®

Sponsor: Sanofi-aventis australia pty ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

The resubmission requested an extension of the Authority Required listing to include prevention of first fracture in patients aged ≥ 70 years with a bone mineral density (BMD) T-score ≤ -3.0 as determined by appropriate diagnostic tests.

2. Background

Risedronate was first listed on the Pharmaceutical Benefits Scheme (PBS) in February 2001 for the treatment of established postmenopausal osteoporosis in patients with fracture due to minimal trauma.

Actonel Once-a-Week was considered at the September 2002 PBAC meeting and listed from 1 February 2003. At the November 2005 meeting, the PBAC recommended listing of risedronate with calcium carbonate (Actonel Combi) on a cost-minimisation basis compared to the risedronate 35 mg once weekly preparation currently listed on the PBS.

The PBAC has considered and rejected previous applications which sought to extend the listings of this drug for use prior to first fracture.

A Public Summary Document for the July 2006 application is available at www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-psd-risedronate-july06

3. Registration Status

Risedronate (Actonel) has TGA approval for the treatment of osteoporosis, including glucocorticoid induced osteoporosis. The indications for risedronate sodium with calcium carbonate (Actonel Combi) are identical to those for Actonel 35 mg and 5 mg tablets, namely:

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

4. Listing Requested and PBAC's View

The resubmission proposed an Authority Required listing for:
Initial treatment of osteoporosis in patients at high risk of fracture.
A high risk of fracture is defined as:

(a) the presence of an existing fracture due to minimal trauma. The fracture must have been demonstrated radiographically and the year of plain X-ray or CT scan or MRI scan must be included in the authority application. A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or a 20% or greater reduction in any of these heights compared with the vertebral body above or below the affected vertebral body; OR
(b) a bone mineral density (BMD) T-score of –3.0 or less in a patient aged 70 years or older. The initial authority application must state the date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement.

Continuing treatment for treatment of osteoporosis in patients with fracture due to minimal trauma and/or a bone mineral density where the patient has previously been issued with an authority prescription for this drug.

See Recommendation and Reasons for PBAC's View

5. Clinical Place for the Proposed Therapy

Risedronate provides a treatment for the prevention of fracture in osteoporotic patients considered to have a similar risk of fracture as patients who have had a prior fracture due to minimal trauma.

6. Comparator

The resubmission nominated alendronate as the comparator. This was considered appropriate by the PBAC.

7. Clinical Trials

The resubmission indirectly compared the results of a previously presented post hoc subgroup analysis of four placebo-controlled risedronate trials to a subgroup analysis of the placebo controlled alendronate trial, FIT-CFA. A retrospective observational study comparing outcomes of treatment with alendronate or risedronate in women within healthcare utilisation records in the US was also presented as key data.

The studies published at the time of the submission were:

Key data	
Meta-analysis of randomised controlled trials of risedronate in the prevention of fractures in a population without prevalent fracture	
Heaney (2002)	Risedronate reduces the risk of first vertebral fracture in osteoporotic women. Osteoporosis International 2002; 13(6):501-505.
Randomised controlled trials of alendronate in the prevention of fractures in a population without prevalent fracture	
Cummings (1998)	Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures. Results from the Fracture Intervention Trial. JAMA 1998; 280(24):2077-2082.
Observational data	

Silverman (2006)	Effectiveness of bisphosphonates on nonvertebral and hip fractures in the first year of therapy: The RisedronatE and ALendronate (REAL) cohort study. ASBMR 28th Annual Meeting, 2006. Abstract SA349.
Supportive data	
Randomised controlled trials of risedronate in the prevention of fractures (in Heaney et al 2002)	
McClung et al, 1997	Risedronate increases bone mineral density at the hip, spine and radius in post menopausal women with low bone mass. ASBMR 19th Annual Meeting, 1997. Abstract P269.
Fogelman et al, 2000	Risedronate reverses bone loss in post menopausal women with low bone mass. Journal of Clinical Endocrinology and Metabolism 2000; 85(5):1895-1900.
Harris et al, 1999	Effect of risedronate treatment on vertebral and non-vertebral fracture in women with postmenopausal osteoporosis. JAMA 1999; 282(14):1344-1352.
McClung et al, 2001	Effect of risedronate on the risk of hip fracture in elderly women. NEJM 2001; 344(5):333-340.
Randomised controlled trials of alendronate in the prevention of fractures (in Cummings et al 1998)	
Black et al, 2000	Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. Journal of Clinical Endocrinology and Metabolism 2000; 85:4118-4124.
Black et al, 1996	Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. The Lancet 1996; 348(9041):1535-1541.
Meta-analyses: Risedronate vs. alendronate	
Cranney et al, 2002	Summary of meta-analyses of therapies for postmenopausal osteoporosis. Endocrine Reviews 2002; 23(4):570-578.
Boonen et al, 2005	Effect of osteoporosis treatments on risk of non-vertebral fractures: Review and meta-analysis of intention-to-treat studies. Osteoporosis International 2005; 16(10):1291-1298.
Wehren et al, 2004	Putting evidence-based medicine into clinical practice: comparing anti-resorptive agents for the treatment of osteoporosis. Current Medical Research and Opinion 2004; 20(4):525-531.
Risedronate in the prevention of fractures in a Japanese population at high risk of fracture	
Sato Y et al, 2005a	Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. Archives of Internal Medicine 2005; 165(15):1743-1748.
Sato Y et al, 2005b	The prevention of hip fracture with risedronate and ergocalciferol plus calcium supplementation in elderly women with Alzheimer disease: a randomized controlled trial. Archives of Internal Medicine 2005; 165(15):1737-1742.
Sato Y et al, 2005c	Risedronate therapy for prevention of hip fracture after stroke in elderly women. Neurology 2005; 64(5):811-816.
Observational data	
Watts NB et al, 2004	Comparison of risedronate to alendronate and calcitonin for early reduction of nonvertebral fracture risk: results from a managed care administrative claims database. Journal of Managed Care Pharmacy 2004; 10(2):142-151.

ASBMR: American Society for Bone and Mineral Research

8. Results of Trials

The key results of the indirect comparison are summarised in the table below.

Incidence of fractures: results of the indirect comparison in subgroup populations

Trial	RR (95% CI)	Risedronate n/N (%)	Placebo n/N (%)	Alendronate n/N (%)	RR (95% CI)
Vertebral fracture					
Pooled RIS	0.27 (0.11, 0.66)	6/328 (1.8%)	22/312 (7.1%)	-	-
FIT-CFA	-	-	44/763 (5.8%)	22/757 (2.9%)	0.50 (0.31, 0.83)
Indirect estimate of effect (95% CI)					0.54 (0.19, 1.50)
Non-vertebral fracture					
Pooled RIS	0.69 (0.31, 1.56)	24/413 (5.8%)	34/406 (8.4%)	-	-
FIT-CFA	-	-	150/812 (18.5%)	101/819 (12.3%)	0.67 (0.53, 0.84)
Indirect estimate of effect (95% CI)					1.03 (0.44, 2.39)
Hip fracture					
HIP	0.58 (0.27, 1.22)	14/1773 (0.8%)	12/875 (1.4%)	-	-
FIT-CFA	-	-	18/812 (2.2%)	8/819 (1.0%)	0.44 (0.20, 0.98)
Indirect estimate of effect (95% CI)					1.32 (0.44, 3.94)

From the results of the post hoc subgroup analyses of the data, the data on incidence of fracture suggest that risedronate is no worse than alendronate, as shown by the largely overlapping confidence intervals of the relative risk of each product against placebo.

9. Clinical Claim

The resubmission claimed that risedronate was no worse than alendronate in terms of effectiveness and toxicity. The PBAC considered that the resubmission had addressed the Committee's previous concerns and the sponsor's claim that risedronate was no worse than alendronate in terms of effectiveness and toxicity to be reasonable.

10. Economic Analysis

The submission sought listing for primary prevention of fracture on a cost minimisation basis compared to alendronate. The submission did not provide an updated preliminary economic evaluation and claimed that there are no differences in the costs of prescribing or administering risedronate and alendronate. The equi-effective doses in the context of cost minimisation are risedronate 35 mg weekly compared to alendronate 70 mg weekly.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year to be between 100,000 – 200,000 in the fourth year of listing. This estimate did not account for market share. The submission stated that the extension of the listing of risedronate will be cost neutral to the PBS as each prescription of risedronate will replace one current or potential prescription of alendronate.

12. Recommendation and Reasons

The PBAC considered that this resubmission had addressed the Committee's previous concerns and the sponsor's claim that risedronate is no worse than alendronate in terms of

effectiveness and toxicity to be reasonable. The PBAC recommended extending the current 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. The equi-effective doses are risedronate 35 mg weekly being equivalent to alendronate 70 mg weekly.

Recommendation
RISEDRONATE SODIUM, tablet, 5 mg and 35 mg,
RISEDRONATE SODIUM and CALCIUM CARBONATE, pack containing 4 tablets risedronate sodium 35 mg and 25 tablets calcium carbonate 1.25 g (equiv to 500 mg calcium)

Amend the restriction to read:

> Authority required
> Initial treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in patients aged 70 years of age or older and with a BMD T-score of -3.0 or less. The initial authority application must state the date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement.
>
> Continuing treatment as the sole anti-resorptive agent for osteoporosis in patients aged 70 years of age or older and with a BMD T-score of -3.0 or less where the patient has previously been issued with an authority prescription for this drug.
>
> Initial treatment as the sole PBS-subsidised anti-resorptive agent for established osteoporosis in patients with fracture due to minimal trauma. The fracture must have been demonstrated radiologically and the year of plain x-ray, or CT-scan or MRI scan must be included in the authority application.
>
> A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body;
>
> Continuing treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in patients with fracture due to minimal trauma, where the patient has previously been issued with an authority prescription for this drug.

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 make risedronate available on the PBS for primary prevention of fracture due to osteoporosis.