PUBLIC SUMMARY DOCUMENT
Product: Risedronate sodium, tablets, 5mg Actonel®, tablet 35mg (enteric coated) Actonel EC®, tablet 150mg Actonel Once-a-Month®
Risedronate sodium and calcium carbonate, tablets (+/- enteric coated), 4 x 35mg risedronate with 24 x 1.25 g calcium carbonate, Actonel Combi® and Actonel EC Combi®
Risedronate sodium and calcium carbonate with colecalciferol, tablets (enteric coated) and sachets, 4 x 35mg risedronate with 24 x sachets 2.5g calcium and 22mcg colecalciferol, Actonel EC Combi D®
Sponsor: Sanofi-Aventis Australia Pty Ltd
Date of PBAC Consideration: March 2013

1. Purpose of Application
The submission sought to extend the current Authority required (STREAMLINED) listing for the treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis to include patients aged 70 years of age or older with a bone mineral density (BMD) T-score less than or equal to -2.5.

2. Background
An application for use of risedronate for this extended treatment group had not previously been considered by the PBAC.

3. Registration Status
Risedronate is TGA-approved for the treatment of osteoporosis, treatment of glucocorticoid-induced osteoporosis, preservation of bone mineral density in patients on long-term corticosteroid therapy as well as the treatment of Paget disease.

4. Listing Requested and PBAC's View
Authority required (STREAMLINED)
Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a patient aged 70 years of age or older with a Bone mineral Density T-score of -2.5 or less. 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.

No changes were requested to the current restrictions for corticosteroid-induced osteoporosis or osteoporosis in patients with fracture due to minimal trauma.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Osteoporosis is a disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and increased fracture risk. Loss of bone strength occurs gradually over many years and usually shows no symptoms. Many people are not diagnosed with osteoporosis until a fracture occurs.

The Royal Australian College of General Practitioners (RACGP) osteoporosis guidelines identify risedronate as a potential treatment option in patients with a BMD T-score of -2.5 or less.

6. Comparator
The nominated comparator of alendronate was considered appropriate by the PBAC.

7. Clinical Trials

The submission presented an indirect comparison of fracture outcomes between risedronate (BMD-NA, BMD-MN, VERT-NA and HIP trials) and alendronate (FIT-CFA trial), with placebo as the common comparator, in a subgroup of osteoporosis patients without prevalent fracture.

The PBAC noted that this indirect comparison was presented to the PBAC in March 2007 to support the listing of risedronate for the primary prevention of fracture.

Details of the trials and associated reports presented in the submission are in the table below.

Trial ID	Protocol title/ Publication title	Publication citation
Risedronate vs. Placebo trials		
BMD NA 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. Abstract P269
BMD MN Fogelman et al (2000)	Risedronate reverses bone loss in post-menopausal women with low bone mass	The Journal of Clinical Endocrinology and Metabolism 85: 1895-1900
VERT NA Harris et al (1999)	Effect of risedronate treatment on vertebral and non-vertebral fracture in women with postmenopausal osteoporosis	Journal of the American Medical Association 282: 1344-1352
HIP McClung et al (2001)	Effect of risedronate on the risk of hip fracture in elderly women.	New England Journal of Medicine 344: 333-340
Risedronate meta-analyses		
Heaney et al (2002)	Risedronate reduces the risk of first vertebral fracture in osteoporotic women	Osteoporosis International 13: 501-505
Alendronate vs. Placebo trials		
FIT-CFA Cummings et al (1998)	Effect of Alendronate on risk of fracture in women with low bone density but without vertebral fractures	Journal of the American Medical Association 280: 2077-2082
Black et al (2000).	Fracture risk reduction with alendronate in women with osteoporosis: The Fracture Intervention Trial	The Journal of Clinical Endocrinology and Metabolism 85: 4118-4124

8. Results of Trials

The PBAC noted the presented trial data did not match the target patient population i.e. patients aged ≥70 years, with BMD T-scores between -3.0 and -2.5, without prevalent fracture. The PBAC, however, recalled that it had previously accepted that risedronate was non-inferior to alendronate in the primary prevention setting for osteoporosis. The PBAC accepted that there was no pharmacological reason to expect any difference in treatment effect between the target population and the broader primary prevention population.

The results of the indirect comparison indicated that there was no statistically significant difference in vertebral fractures, non-vertebral fractures and hip fractures between risedronate and alendronate. The results are shown in the table below.

Indirect comparison of fracture outcomes

Trial	Risedronate	Placebo	Alendronate	Treatment effect RR (95% CI)
Proportion of patients with new morphometric vertebral fractures [n/N (%)] Subgroup with no prevalent fracture and BMD ≤ -2.5				
BMD-MN	2/68 (2.9)	6/69 (6.7)	-	0.34 (0.08, 1.40)
BMD-NA	1/73 (1.4)	2/64 (3.1)	-	0.44 (0.06, 3.28)
VERT-NA	1/55 (1.8)	5/54 (9.3)	-	0.20 (0.03, 1.21)
HIP	2/132 (1.5)	9/125 (7.2)	-	**0.21 (0.05, 0.84)**
FIT-CFA	-	44/763 (5.8)	22/757 (2.9)	**0.50 (0.30, 0.83)**[a]
Meta-analysis of risedronate trials [RR (95% CI)]				**0.27 (0.11, 0.66)**
Indirect estimate of effect [RR (95% CI)]				0.51 (0.19, 1.43)
Proportion of patients with any non-vertebral fracture [n/N (%)] Subgroup with no prevalent fracture and BMD ≤ -2.5				
BMD-MN	0/79 (0.0)	8/83 (9.6)	-	0.06 (0.00, 1.05)
BMD-NA	3/102 (2.9)	6/97 (6.2)	-	0.48 (0.12, 1.85)
VERT-NA	6/60 (10.0)	9/67 (13.4)	-	0.74 (0.28, 1.97)
HIP	15/172 (8.7)	11/159 (6.9)	-	1.26 (0.60, 2.66)
FIT-CFA	-	150/812 (18.5)	101/819 (12.3)	**0.64 (0.50, 0.83)**[a]
Meta-analysis of risedronate trials [RR (95% CI)]				0.69 (0.31, 1.56)
Indirect estimate of effect [RR (95% CI)]				1.04 (0.59, 1.83)
Proportion of patients with any hip fracture [n/N (%)] HIP study:				

Trial	Risedronate	Placebo	Alendronate	Treatment effect RR (95% CI)
subgroup with no prevalent fracture; FIT-CFA study: Subgroup with no prevalent fracture and BMD ≤ -2.5				
HIP	14/1773 (0.8)	12/875 (1.4)	-	0.58 (0.27, 1.22)
FIT-CFA	-	18/812 (2.2)	8/819 (1.0)	**0.44 (0.19, 1.01)[a]**
Indirect estimate of effect [RR (95% CI)]				1.31 (0.42, 4.04)

Abbreviations: CI, confidence interval; RR, relative risk

[a] Submission has re-calculated the published RR estimates for the FIT-CFA trial. The difference in estimates is marginal with the exception of hip fracture results which switch from statistically significant (published estimate RR 0.44; 95% CI 0.18-0.97) to non-significant (submission estimate RR 0.44; 95% CI 0.19-1.01).

In relation to comparative harms, the submission claimed that both treatments appear to have similar safety profiles. The PBAC considered the toxicity of bisphosphonates was well recognised. The PBAC noted it had previously accepted risedronate as no worse than alendronate and noted no new safety issues with risedronate were identified in the submission.

9. Clinical Claim

The submission claimed that risedronate is non-inferior in terms of effectiveness and similar in terms of safety compared to alendronate in the target population (no prevalent fracture, BMD T-score between -3.0 and -2.5, aged ≥ 70 years.

For PBAC's view, see Recommendation & Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis of risedronate compared to alendronate based on a non-inferiority claim.

The proposed equi-effective doses were based on the established therapeutic relativity between risedronate (5mg daily/35mg weekly/150mg monthly) and alendronate (70mg weekly) in osteoporosis. There was an assumption that risedronate combination products (calcium with or without colecalciferol) were equivalent to alendronate combination products (colecalciferol with or without calcium).

For PBAC's view, see Recommendation & Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of risedronate PBS prescriptions in the target population per year to be 100,000 – 200,000 in Year 5.

The submission stated that the requested extension of listing for risedronate would be associated with a small cumulative net saving over five years.

For PBAC's view, see Recommendation & Reasons.

12. Recommendation and Reasons

The PBAC recommended extending the current listing of risedronate and its combinations for treatment of osteoporosis to include treatment of patients aged 70 years of age or older with a bone mineral density (BMD) T-score less than or equal to -2.5, on a cost-minimisation basis with alendronate monotherapy.

The PBAC noted from the PBS therapeutic relativity sheets that risedronate and alendronate combination products for osteoporosis were recommended on a cost-minimisation basis against their respective monotherapies. Therefore, the PBAC considered it appropriate for risedronate and its combinations to be cost-minimised to alendronate monotherapy in the requested extended population.

The PBAC accepted the submission's claim that risedronate is non-inferior in terms of effectiveness, and similar in terms of safety, compared to alendronate in the target population.

The PBAC considered the estimated financial saving to the PBS were highly uncertain due to assumptions regarding utilisation, distribution of scripts across formulations, potential for switching between monotherapy/combination therapy, patient co-payments and the uncertain overall weighted price of risedronate. The PBAC requested the Pharmaceutical Benefits Pricing Authority determine the appropriate weightings across indications for risedronate, consistent with the approach used for denosumab**.**

The PBAC considered it would be useful to review the clinical value and place of combination therapies (calcium, with or without colecalciferol) in light of changing evidence regarding the use of calcium and vitamin D.

Recommendation:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
RISEDRONATE SODIUM Tablet 5 mg	28	5	Actonel	SW
Tablet 35 mg (enteric coated)	4	5	Actonel EC	SW
Tablet 150 mg	1	5	Actonel Once-a-Month	SW
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)	ǂ1	5	Actonel Combi	SW
Pack containing 4 enteric coated tablets risedronate sodium 35 mg and 24 tablets calcium carbonate 1.25 g (equivalent to 500 mg calcium)	ǂ1	5	Actonel EC Combi	SW
RISEDRONATE SODIUM and CALCIUM CARBONATE with COLECALCIFEROL Pack containing 4 enteric coated tablets risedronate sodium 35 mg and 24 sachets containing granules of calcium carbonate 2.5 g (equivalent to 1 g calcium) with colecalciferol 22 micrograms	ǂ1	5	Actonel EC Combi D	SW

Condition/Indication:	Osteoporosis
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	Patient must have a Bone Mineral Density (BMD) T-score of -2.5 or less. AND Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this condition.
Population criteria:	Patient must be aged 70 years or older.
Prescriber Instructions:	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.
Administrative advice:	Anti-resorptive agents in established osteoporosis include alendronate sodium, risedronate sodium, denosumab, raloxifene hydrochloride, strontium ranelate and zoledronic acid.

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 recommendation to make Actonel available to more patients at risk of fracture due to osteoporosis.