

PUBLIC SUMMARY DOCUMENT

Product: RISEDRONATE SODIUM, tablet, 5 mg, Actonel[®], 35 mg, Actonel Once-a-Week[®] and 150 mg, Actonel Once-a-Month[®], 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[®], RISEDRONATE SODIUM and CALCIUM CARBONATE with COLECALCIFEROL, pack containing 4 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, Actonel Combi D[®]

Sponsor: Sanofi-Aventis Australia Pty Ltd

Date of PBAC Consideration: July 2010

1. Purpose of Application

To request the PBAC re-consider its recommendation that risedronate sodium and its combination formulations are interchangeable with alendronate sodium and its combination formulations on an individual patient basis in the treatment of osteoporosis and Paget Disease.

2. Background

Paget Disease

At the September 2000 meeting, the PBAC recommended listing of risedronate 30 mg was recommended for treatment of Paget Disease on a cost-minimisation basis compared with alendronate sodium 40 mg, with two months' therapy with risedronate sodium 30 mg daily being equivalent to six months' therapy with alendronate sodium 40 mg daily. Listing was effective from 1 February 2001.

Osteoporosis

Risedronate sodium 5 mg tablet (Actonel[®]) was first listed on the PBS in February 2001 for the treatment of established postmenopausal osteoporosis in patients with fracture due to minimal trauma on a cost-minimisation basis, with risedronate 5 mg daily being similar to alendronate sodium 10 mg daily.

At the December 2001 meeting, the PBAC recommended extending the listing for risedronate 5 mg to include treatment of established corticosteroid-induced osteoporosis in patients with fracture due to minimal trauma.

Risedronate sodium 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. Listing was effective from 1 February 2003.

At the November 2005 meeting, the PBAC recommended listing risedronate sodium 35 mg with calcium carbonate 1.25 mg (Actonel-Combi[®]) on a cost-minimisation basis compared to the risedronate sodium 35 mg once weekly preparation currently listed on the PBS.

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

At the November 2007 meeting, the PBAC recommended listing a combination product containing risedronate sodium 35 mg, calcium carbonate and colecalciferol on a cost-minimisation basis compared with risedronate sodium and the combination product containing risedronate sodium and calcium carbonate.

At the March 2008 meeting, the PBAC recommended the listing of risedronate sodium 75 mg tablet on a cost-minimisation basis compared with risedronate sodium 5 mg tablet. This product has not been listed.

At the July 2008 meeting, the PBAC recommended an extension of listing for risedronate sodium (5 mg and 35 mg) and risedronate sodium with calcium carbonate (Actonel Combi) to include the treatment of corticosteroid-induced osteoporosis 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. Listing was effective 1 February 2009.

At the March 2009 meeting, the PBAC recommended listing risedronate 150 mg tablets under the same listing conditions as those for currently listed risedronate products and be priced on a comparable annual cost with the lower strength tablets.

Therapeutic Groups:

In June 2009, the PBAC gave advice that it was of the opinion that two new therapeutic groups should be formed - one comprising alendronate, combination drugs containing alendronate, risedronate and combination drugs containing risedronate (osteoporosis therapeutic group) and one comprising alendronate, tiludronate and risedronate (Paget disease of bone therapeutic group). It also advised that the relevant drugs were, within their groups, interchangeable on an individual patient basis.

In January 2010 the PBAC reaffirmed its opinion that the Minister should form a therapeutic group containing risedronate and alendronate (together with the combination drugs containing alendronate and risedronate with calcium and/or Vitamin D) in the prevention of fracture in patients with osteoporosis and a therapeutic group containing risedronate, alendronate and tiludronate in the management of Paget disease of bone. These drugs should be treated as interchangeable on an individual patient basis (re-affirming the specific items of risedronate and alendronate previously identified for this purpose).

On 21 January 2010 the Delegate formed the new therapeutic groups for osteoporosis and Paget Disease. On 11 March 2010, the Senate disallowed part of the therapeutic groups instrument. Disallowance meant that the new groups ceased to exist from 11 March 2010.

3. Registration Status

Risedronate 5 mg, 35 mg and 150 mg tablets and Actonel Combi and Actonel Combi D are registered for:

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

Risedronate 30 mg tablet is registered for treatment of Paget disease of bone.

4. Listing Requested and PBAC's View

Current Listing:

No changes to the current PBS listings (available at www.pbs.gov.au) were made in the submission.

5. Clinical Place for the Proposed Therapy

Risedronate provides a treatment option for osteoporosis and Paget disease.

6. Comparator

The submission nominated alendronate as the comparator. The PBAC considered this was appropriate.

7. Clinical Trials

The submission presented clinical evidence to address the claim that risedronate and alendronate are not interchangeable on an individual patient basis based on the following eight areas:

1. Bone turnover suppression
2. Fracture data
3. Onset of anti-fracture efficacy
4. Speed of reversal of effect
5. Gastrointestinal adverse events
6. Osteonecrosis of the jaw
7. Vitamin D and calcium supplementation
8. Pharmacovigilance

The key trials published at the time of submission are in the table below:

Trial ID / First author	Protocol title / Publication title	Publication citation
Bone Turnover Suppression		
FACTS-International & 12-month extension		
Reid, DM.	Alendronic acid produces greater effects than risedronic acid on bone density and turnover in postmenopausal women with osteoporosis: Results of FACTS International.	Clinical Drug Investigation. 2006; 26(2):63-74.
Reid, DM.	A comparison of the effect of alendronate and risedronate on bone mineral density in postmenopausal women with osteoporosis: 24-month results from FACTS-International.	International Journal of Clinical Practice. 2008; 62(4):575-584.
FACT-USA & 12-month extension		
Rosen CJ, et al.	Treatment with once-weekly alendronate 70mg compared with once-weekly risedronate 35mg in women with postmenopausal osteoporosis: a randomised double-blind study.	Journal of Bone and Mineral Research: the Official Journal of the American Society for Bone and Mineral Research. 2005;20(1):141-151
Bonnick S.	Comparison of weekly treatment of postmenopausal osteoporosis with alendronate versus risedronate over two years.	Journal of Clinical Endocrinology and Metabolism. 2006; 91(7): 2631-2637.
Sarioglu M, et al.	Comparison of the effects of alendronate and risedronate on bone mineral density and bone	Rheumatology International. 2006; 26(30):195-200).

	turnover markers in postmenopausal osteoporosis.	
Fracture Data		
REAL Silverman SL.	Effectiveness of bisphosphonates on nonvertebral and hip fractures in the first year of therapy: The risedronate and alendronate (REAL) cohort study.	Osteoporosis International 2007; 18:25-34.
Sato Y (2005c)	Risedronate therapy for prevention of hip fracture after stroke in elderly women.	Neurology 2005; 64(5):811-816.
Sato Y (2005b)	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 (2007)	Risedronate and ergocalciferol prevent hip fracture in elderly men with Parkinson disease.	Neurology 2007; 68(12):911-915.
Sato Y (2005c)	The Prevention of Hip Fracture With Risedronate and Ergocalciferol Plus Calcium Supplementation in Elderly Women With Alzheimer Disease: A Randomized Controlled Trial.	Arch Intern Med. 2005;165(15):1737-1742.
Sato Y (2006)	Alendronate and vitamin D2 for prevention of hip fracture in Parkinson's disease. A randomized controlled trial.	Mov Disord 2006;21:924-929.
Onset of Anti-fracture Efficacy		
FIT Trial Hochberg MC.	Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. Fracture Intervention Trial Research Group.	Arthritis & Rheumatism 1999; 42(6):1246-1254.
FIT-VFA Black DM.	Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures.	Lancet 1996;348:1535-41.
FIT-CFA Cummings SR.	Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures.	JAMA 1998;280:2077-82
Roux C.	Efficacy of risedronate on clinical vertebral fractures within six months.	Current Medical Research & Opinion 2004; 20(4):433-439.
VERT-NA Harrington JT.	Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis.	Calcified tissue international 2004; 74(2):129-135.
Watts NB.	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.
Harris ST.	Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group.	JAMA 1999; 282(14):1344-1352.
VERT-MN Reginster J-Y.	Randomized trial of the effects of risedronate on	Osteoporosis International 2000;

	vertebral fractures in women with established postmenopausal osteoporosis.	11(1):83-91.
Site and patient specific data - Efficacy of bisphosphonates at vertebral and nonvertebral sites.		
Liberman UA.	Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group.	The New England Journal of Medicine 1995; 333(22):1437-1443.
VERT-NA Harris ST.	Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group.	As above.
HIP Trial McClung MR.	Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group.	New England Journal of Medicine 2001; 344(5):333-340.
FOSIT Pols HA.	Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Fosamax International Trial Study Group.	Osteoporosis International 1999; 9(5):461-468.
VERT-MN Reginster J-Y.	Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis.	As above.
Speed of reversal of effect		
Bone HG.	Ten years' experience with alendronate for osteoporosis in postmenopausal women.	New England Journal of Medicine 2004, 350:1189-1199.
Rossini M.	Long-term effects of a treatment course with oral alendronate of postmenopausal osteoporosis.	Journal of Bone and Mineral Research 1994, 9(11):1833-1837.
Watts NB.	Fracture risk remains reduced one year after discontinuation of risedronate.	Osteoporosis International 2008, 19:365-372.
Gastrointestinal Tolerability		
Adachi, JD.	Tolerability of risedronate in postmenopausal women intolerant of alendronate.	Aging Clin Exp Res 2001 Pct;13(5):347-354
FACT-USA extrn. Bonnick S.	Comparison of Weekly Treatment of Postmenopausal Osteoporosis with Alendronate versus risedronate over two years.	J Clin Endocrinol Metab (2006) 91:2631-2637
Cadarette SM.	Comparative gastrointestinal safety of weekly oral bisphosphonates.	Osteoporosis Int (2009) 20:1735-1747
Hosking D.	Comparison of change in bone resorption and bone mineral density with once-weekly alendronate and daily risedronate: a randomised, placebo-controlled study.	Current Medical Research and Opinion 2009; 19, 383-394
Kane SB.	Pharmacoeconomic evaluation of gastrointestinal tract events during treatment with risedronate or alendronate: A retrospective cohort study.	American Journal of Managed Care 2004; 10(SUPPL. 7):S216-S226.

Lanza F.	An endoscopic comparison of the effects of alendronate and risedronate on upper gastrointestinal mucosae.	Am J Gastroenterol 2000;95:3112-3117.
Miller RD.	Incidence of Gastrointestinal Events Among Bisphosphonates Patients in an Observational setting.	Am J Manag Care. 2004;10:S207-S215.
Rosen CJ.	Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study.	J Bone Miner Res. 2005 Jan; 20(1):141-51. Epub 2004 Sep 29.
Thomson AB.	14 day endoscopy study comparing risedronate and alendronate in postmenopausal women stratified by Helicobacter pylori status.	J Rheumatol. 2002 Sep; 29(9):1965-74.
Osteonecrosis of the jaw		
Mavrokokki T. et al.	Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia.	J Oral Maxillofac Surg. 2007 Mar; 65(3):415-23.
Vitamin D and calcium supplementation		
Adami S. I.	Fracture incidence and characterization in patients on osteoporosis treatment: The ICARO study.	Journal of Bone and Mineral Research 2006; 21(10):1565-1570.
Adami S. I.	Osteoporosis treatment and fracture incidence: The ICARO longitudinal study.	Osteoporosis International 2008; 19(8):1219-1223.
Adami S. I.	Vitamin D status and response to treatment in postmenopausal osteoporosis.	Osteoporosis International 2009; 20(2):239-244.

8. Results of Trials

Bone turnover suppression

The results from the bone turnover suppression trials indicated that there were statistically significantly larger reductions in bone turnover markers in alendronate-treated patients in the two FACTS studies. There were statistically significantly greater increases in hip trochanter BMD in the alendronate groups compared with risedronate at both 12 and 24 months. There were no statistically significant differences in bone turnover markers or BMD between the risedronate and alendronate groups in the much smaller (N=50) Sarioglu 2006 study.

Fracture data

Key fracture data in the submission was sourced from Silverman 2007 (REAL study). The submission did not include two further cohort studies, Cadarette (2008) and Curtis 2009 (REALITY study) which reported no statistically significant differences in fracture rates between risedronate and alendronate. These later studies were added during the evaluation.

The submission also presented the results of randomised trials reporting fracture outcomes for patients treated with alendronate or risedronate compared with placebo, or alendronate versus risedronate (FACTS-International and FACTS-USA trial extensions).

With the exception of the FACTS-International and FACTS-USA trial extension studies, which reported all clinical fractures as adverse events, there were no head-to-head trials of risedronate and alendronate comparing risks of fractures.

For vertebral fracture, the relative risk estimates were similar for risedronate and alendronate, despite differences in prevalent fracture at baseline in the study populations and differences in the assessment of outcomes (15% reduction in vertebral height in the risedronate trials, 20% reduction in vertebral height in the alendronate trials).

For non-vertebral fracture, there were statistically significant reductions in risks of non-vertebral fractures in one risedronate (VERT-NA) and one alendronate trial (FOSIT) compared to placebo.

For hip fracture, there were similar, statistically significant reductions in hip fracture in both the risedronate (HIP) and alendronate (FIT-VFA) trials conducted in patients with baseline vertebral fractures, despite differences in study populations (older age range in HIP, BMD T-scores in HIP ≤ -3.0 compared with FIT-VFA ≤ -1.6). There were no statistically significant reductions in the risk of hip fracture with either risedronate or alendronate in patients without baseline vertebral fracture.

There were statistically significant reductions in risk of hip fracture for risedronate compared to placebo in three of the Sato trials (Sato 2005a, 2005b, 2005c) and for alendronate compared to placebo in Sato 2006. There was no statistically significant reduction in hip fracture with risedronate treatment compared with placebo in Sato 2007 (conducted in men with Parkinson disease).

For all clinical fractures, there were no statistically significant differences in rates of clinical fractures of all types between alendronate and risedronate in the head-to-head FACTS-International and FACT-USA trial extensions.

Overall, the relative risk estimates were similar for risedronate and alendronate for vertebral, non-vertebral and hip fractures.

The results of two meta-analyses by Wells et al (Cochrane Database of Systematic Reviews 2008, Issue 1. Art. Nos.: CD004523 and CD001155) (Wells 2008a, 2008b) of placebo controlled trials of risedronate and alendronate in women with and without prevalent fractures at baseline showed there were statistically significant reductions in the risk of vertebral, non-vertebral, hip and wrist fractures for both risedronate and alendronate compared to placebo in women with prevalent fractures at baseline. There was no consistent pattern that the magnitude of the risk reduction is larger with risedronate than alendronate.

Site-specific data

Results of an indirect comparison of risedronate and alendronate for the subgroup of patients with no prior vertebral fracture and a BMD T-score of ≤ -2.5 have been previously reported in the March 2007 Public Summary Document.

The submission presented the BMD results of three risedronate trials (VERT-NA, VERT-MN and HIP) and one alendronate trial (FOSIT) as evidence to support the claim risedronate demonstrates a larger increase in BMD in non-vertebral sites than alendronate:

Percentage change (95% CI) in BMD in VERT-NA, VERT-MN, HIP and FOSIT trials

Trial	Hip	Femoral neck	Femoral trochanter	Midshaft radius	Vertebral
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Trial	Hip	Femoral neck	Femoral trochanter	Midshaft radius	Vertebral
Risedronate vs placebo					
VERT-NA	NR	2.80	4	1.60	4.30
VERT-MN	NR	3.1 (1.8, 4.5)	6.4 (4.9, 7.8)	2.1 (1.1, 3.2)	5.9 (4.5, 7.3)
HIP	NR	3.4*	4.8*	NR	NR
Alendronate vs placebo					
FOSIT	3 (2.6, 3.4)	2.4 (2.0, 2.8)	3.6 (3.2, 4.1)	NR	4.9 (4.6, 5.2)
Lieberman 1995 (10mg group)	NR	5.9 [†] (SE 0.5)	7.8 [†] (SE 0.6)	2.2 [†] (SE 0.4)	8.8 [†] (SE 0.4)
FIT-VFA	4.7 [†]	4.1 [†]	6.1 [†]	1.6 [†]	6.8 [†]
FIT-CFA	5.0 [†]	3.8 [†]	6.8	3.1	6.6 [†]

* 70-79 year old group only; data not presented for women 80 years and older

[†] p < 0.001

NR = not reported; BMD = bone mineral density; SE = standard error

The PBAC considered that the relationship between an increase in BMD and fracture reduction is uncertain.

Onset of anti-fracture efficacy

The results of analyses presented in the submission (Watts 2004) and identified during the evaluation (Levis 2002, Silverman 2007 and Cadarette 2008) of non-vertebral fractures at six and twelve months after initiation indicated that there were no statistically significant differences in risk of non-vertebral fractures between risedronate and alendronate at 6 months in any of three cohort studies (of borderline statistical significance in Silverman 2007).

Speed of reversal of effect

Data from Watts 2004, Bone 2004 and Rossini 1996 were used in the submission to demonstrate differences in the rates of change in bone turnover markers (BTMs) and BMD after the cessation of alendronate and risedronate. The data are consistent with reductions in bone turnover suppression (shown as increases in bone turnover markers such as bone alkaline phosphatase (BAP) and N-telopeptide to creatinine ratio (NTX/Cr)) after cessation of both alendronate and risedronate. There was partial resolution of BMD effect in the risedronate trial over 12 months (Watts 2004), no change in lumbar spine BMD 12 months after cessation of alendronate 20 mg in Rossini 2004, and no statistically significant changes in BMD at the spine during years 6-10 or 8-10 after cessation of alendronate in the study by Bone (2004).

The PBAC noted that interpretation of these data is difficult because the studies were conducted in different populations of women, with and without prevalent fractures at baseline, using different doses of alendronate and risedronate, and with different treatment and follow-up times.

Calcium and vitamin D supplements

The submission argued that as there is a greater risk of fracture in those with no supplementation of calcium and vitamin D, patients would be disadvantaged if they were switched from risedronate combination products with calcium and vitamin D supplements to alendronate combination products without these supplements.

For PBAC's view on these results, see Recommendation and Reasons

Gastrointestinal tolerability

The submission presented results from Hosking 2003, Thomson 2002, FACT USA and Extension, FACTS International and Extension, Lanza 2000 and Adachi 2001 randomised control trials to support the claim that patients treated with alendronate show a higher risk of gastrointestinal (GI) adverse events than patients treated with risedronate.

While there were statistically significantly more alendronate treated patients with gastric ulcers ≥ 3 mm (RD 6.1%; 95% CI: 0.7%, 11.8%) in Thomson 2002, the estimates were not adjusted for differences in baseline smoking levels in this study. There was no statistically significant difference in rates of discontinuations due to upper gastrointestinal adverse events between risedronate and placebo in Adachi 2001.

The submission also presented results of GI adverse events from the observational studies Cadarette 2009, Miller 2004 and Kane 2004. There were no statistically significant differences between alendronate 70 mg/week and risedronate 35 mg/week in Cadarette 2009. Miller 2004 reported higher rates of gastrointestinal events in alendronate-treated patients after adjustment for demographic variables and a previous history of gastrointestinal events (RR 1.44, 95% CI: 1.03, 2.00). Kane 2004 reported a statistically significantly higher rate of all GI events in the alendronate group compared with the risedronate group, (5.4% vs 3.4% respectively, $p=0.034$) although not for specific types of GI events.

Osteonecrosis of the jaw

The submission presented one survey of cases of osteonecrosis of the jaw (ONJ) up to the year 2005 in Australia (Mavrokokki 2007) in support of the claim that risedronate has a lower risk of ONJ. Of 26 patients taking bisphosphonates for osteoporosis and 3 for Paget disease, 2 patients had taken risedronate and 27 alendronate. The submission suggested that the risk of ONJ associated with risedronate appears to be lower than the risk associated with alendronate.

For PBAC's view, see Recommendation and Reasons

9. Clinical Claim

The submission claimed that due to the very significant scientific and clinical differences which have effects on efficacy (bone turnover markers, fracture, onset of fracture efficacy and speed of reversal effect) and safety (GI tolerability and ONJ) as well as strengths available and PBS listings, alendronate and risedronate cannot be considered to be interchangeable at the individual patient level.

For PBAC's view, see Recommendation and Reasons

10. Economic Analysis

The re-submission presented both a cost-effectiveness analysis and a cost-utility analysis, based on the results of the Silverman 2007 (REAL) study.

A Markov model was used to simulate three key health states and the movement of subjects over time, with two treatment arms, risedronate 35 mg once/week versus alendronate 70 mg once/week. The health states were alive with no previous fracture, alive with previous fracture and dead. The model time horizon was 10 years.

The results of the economic evaluation demonstrated that the incremental cost per quality adjusted life year was dominant for risedronate over alendronate (i.e less costly and more effective).

For PBAC's view, see Recommendation and Reasons

11. Estimated PBS Usage and Financial Implications

The re-submission did not present estimated PBS usage and financial implications.

The re-submission claimed that if the proposed osteoporosis therapeutic group was implemented and risedronate was considered interchangeable with alendronate, if 50% of the current risedronate patients switched to alendronate, there would be an increase over the 10 year horizon of the number of hip and non-vertebral fractures.

The re-submission estimated the economic impact of the increased number of fractures to be approximately \$30 million over the next 10 years, significantly more than the expected savings from the implementation of the proposed osteoporosis therapeutic group.

12. Recommendation and Reasons

The PBAC considered that the comparator for osteoporosis nominated by the submission of alendronate was appropriate.

The PBAC noted that the data presented indicated that there is less suppression of bone turnover markers with risedronate than with alendronate, and that the increase in bone mineral density (BMD) is less with risedronate than with alendronate. The PBAC however considered that the patient relevant outcomes are fractures and there is no supporting data that the differences either in bone turnover markers or BMD results in differences in fracture rate or risk. The PBAC noted the review by Russell et al. 2008 presented as evidence in the submission states in regard to the issue of difference in bone turnover that "the clinical relevance of these differences is unclear".

The PBAC considered the evidence of efficacy in fracture prevention presented in the submission was selective. The PBAC noted that the results from Silverman et al. 2007 (REAL) were presented as the basis of the submission, however that two further cohort studies, Cadarette 2008 and Curtis 2009 (REALITY), which showed no significant difference between risedronate and alendronate in regard to fracture rates, were omitted. The PBAC considered, on the basis of the evidence overall, the relative risk estimates were similar for risedronate and alendronate for vertebral, non-vertebral and hip fractures, and that the whole body of data from the literature failed to demonstrate a clear advantage in relative fracture rate for either alendronate or risedronate. The PBAC further noted that the indirect analysis presented for the listing of risedronate on the PBS for the primary treatment of osteoporosis in 2007 also showed no statistically significant differences in vertebral, non-vertebral or hip fractures between risedronate and alendronate.

(Refer to the March 2007 Public Summary Document for details)

The PBAC noted that the submission suggested that evidence from the VERT-NA, VERT-MN and HIP trials indicated greater increases in BMD for risedronate over alendronate (FOSIT). However, the PBAC considered the trial data presented in the submission for site-

specific activity were selective and noted that BMD data for alendronate versus placebo from the Liberman (1995) and the FIT trials (FIT-VFA and FIT-CFA) suggest increases in BMD compared to placebo are at least as large as those reported in the VERT-NA, VERT-NM and HIP trials for risedronate. The PBAC also noted this claim was at odds with the data presented in terms of bone turnover markers showing that alendronate was associated with greater gains in BMD than risedronate. The PBAC also noted that in the pre-PBAC response the sponsor agreed that the evidence is conflicting.

The PBAC noted the submission claimed that risedronate is the only bisphosphonate to have shown evidence of a reduction in fracture within 6 months; however the PBAC considered that the submission again did not include key studies, including Levis (2002), Silverman (2007) and Cadarette (2008). The PBAC noted that when analysis of the full dataset is undertaken, there is evidence that an onset of fracture prevention for alendronate is seen within 6 months. The PBAC hence considered that on the basis of the data presented in the submission and that added during the evaluation there was no evidence for an advantage of risedronate over alendronate in the speed of onset of fracture reduction rate.

The PBAC noted that the submission claimed that after stopping risedronate treatment, bone turnover recovers more quickly compared with when alendronate treatment is stopped, and more alendronate is retained in the skeleton than risedronate. The PBAC however also noted that the risk of fracture in most patients increases with time, and therefore it could be argued that a slower reversal of effect could be a clinical advantage, such as in patients who are non-compliant to treatment. Overall, the PBAC considered that there was no compelling evidence to support the contention, on a population basis, that the speed of reversal is clinically relevant.

The submission argued that as there is a greater risk of fracture in those with no supplementation of calcium and vitamin D, patients would be disadvantaged if they were switched from risedronate combination products with calcium and vitamin D supplements to alendronate combination products without these supplements. The PBAC noted that a combination product of alendronate with colecalciferol and calcium (Fosamax Plus D-Cal[®]) is now PBS listed.

The PBAC considered the data presented in the submission did not consistently identify lower risks of gastrointestinal events with risedronate compared to alendronate. The PBAC noted that there were no statistically significant differences between risedronate and alendronate in GI events in most of the studies presented in the submission including the FACTS head-to-head trials.

The submission presented one survey of cases of osteonecrosis of the jaw (ONJ) up to the year 2005 in Australia (Mavrokokki 2007) in support of the claim that risedronate has a lower risk of ONJ. The PBAC considered that the use of the Australian observational data is likely to be fundamentally flawed due to differences in the extent and duration of use of risedronate and alendronate during the period of observation (2 years versus 8 years, respectively). The PBAC also noted that systematic reviews and other literature have not shown a difference in ONJ incidence between alendronate and risedronate. The PBAC hence considered that there is no acceptable data which supports a lower risk of ONJ with risedronate.

The economic analysis was based on the data of Silverman 2007 (REAL) study only. The PBAC considered that in view of the overwhelming body of evidence which failed to show a clinical advantage in fracture reduction or tolerability of risedronate over alendronate there was no basis on which to support a cost effectiveness analysis and the original cost minimisation approach accepted by the PBAC was appropriate. The PBAC also considered the economic model presented was highly flawed.

The PBAC hence considered that the submission provided no basis on which to change its original recommendation that alendronate and its combinations are interchangeable on an individual patient basis with risedronate and its combinations.

The PBAC hence reaffirmed its previous decision to advise the Minister that, in accordance with Subsection 101(4AA) of the *National Health Act 1953*, an oral bisphosphonates osteoporosis therapeutic group could be formed, and reaffirmed its advice that alendronate and its combinations and risedronate and its combinations should be treated as interchangeable on an individual patient basis in the treatment of osteoporosis.

The PBAC also reaffirmed its previous decision to advise the Minister that in accordance with Subsection 101(4AA) of the *National Health Act 1953* an oral bisphosphonates Paget disease of bone therapeutic group could be formed, and reaffirmed that alendronate, risedronate and tiludronate should be treated as interchangeable on an individual patient basis in the treatment of Paget disease of bone.

In making this recommendation, the PBAC noted that the sponsor provided no new data in regard to Paget disease of bone. Under this circumstance the PBAC considered there was no basis on which it could alter its previous recommendation in regard to the interchangeability of the drugs and suitability for inclusion in a therapeutic group of oral bisphosphonates for the treatment of Paget disease of bone.

The PBAC noted it has interpreted the term “interchangeable on an individual patient basis” as meaning, that in the context of a clinical decision to commence treatment with a bisphosphonate, that for the vast majority of the population it would not make a difference which agent is commenced in terms of the patient relevant outcome(s), as the data does not demonstrate superiority of one drug over the other relevant to PBS subsidy.

Recommendation:

Reject

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 maintains that there are significant chemical, pharmacological and clinical differences between alendronate and risedronate which are taken into consideration by

physicians when deciding which treatment is most suitable for an individual patient. We contend that these drugs are therefore not interchangeable on an individual patient basis.

Sanofi-aventis also points out that at the time the PBAC made the decision that risedronate and alendronate are interchangeable on an individual basis, alendronate with colecalciferol and calcium (Fosamax Plus D-Cal[®]) was not PBS listed.