PUBLIC SUMMARY DOCUMENT

Product: Risedronate Sodium, tablets, 5 mg and 35 mg, Actonel®, Risedronate Sodium And Calcium Carbonate, tablets, 35 mg and 1.25 g, Actonel Combi®

Sponsor: Sanofi-aventis australia pty ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

The submission requested an extension to the PBS-listing of risedronate sodium tablets 5 mg and 35 mg (Actonel®) and risedronate sodium tablet 35 mg with calcium carbonate 1.25 g (Actonel Combi®) to include patients aged 75 years or more with a bone mineral density (BMD) of –3.0 or less and without prevalent fracture.

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.

PBAC has considered previous requests which sought to extend the listing of this drug for use prior to first fracture.

The most recent consideration was a joint submission to the March 2005 meeting, for the treatment of osteoporosis in patients aged 60 years and older and with a BMD T-score of –2.5 or less.

The Committee considered the joint submission did not clearly provide an analysis of clinical benefits and cost-effectiveness in terms of an absolute risk model. In particular, it did not provide a basis to address the key request of the PBAC to identify the group of patients without minimal trauma fracture but with a combination of other risk factors generating an absolute risk of fracture equivalent to those for whom cost-effectiveness has been already established as being acceptable on the basis of a prior minimal trauma fracture.

The PBAC rejected the application because of uncertain but over-estimated extent of long-term clinical benefit and resulting uncertain cost-effectiveness which does not provide a sufficiently confident basis to conclude that the cost-effectiveness is acceptable.

3. Registration Status:

Risedronate 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

Authority required
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.
(b) a bone mineral density (BMD) T-score of –3.0 or less in a patient aged 75 years or older. The initial authority application must state patient's age and date of birth and the date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement. The radiological and/or laboratory reports supporting eligibility must be available for auditing purposes by the HIC.
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.

For the PBAC's view, see Recommendations and Reasons.

5. Clinical place for the proposed therapy

If risedronate were listed on the PBS as requested it would provide a treatment for the prevention of fracture in osteoporotic patients aged 75 years or older with a BMD T score of ≤ -3.0.

6. Comparator

The appropriate comparator was placebo or 'watchful waiting' (patient monitoring and standard management with calcium and vitamin D).

7. Clinical Trials

No changes were made to the trial data presented in the previous submissions. All four trials (and two of the three meta-analyses based upon them) had been published at the time of submission, as follows:

Trial/First author	Protocol/Publication title	Publication citation
BMD (North America) RON McClung et al.	Risedronate increases bone mineral density at the hip, spine and radius in post menopausal women with low bone mass.	American Society for Bone and Mineral Research 19th Annual Meeting, 1997; Abstract P269.

Trial/First author	Protocol/Publication title	Publication citation
BMD (Multinational) ROE/Fogelman et al.	Risedronate reverses bone loss in post menopausal women with low bone mass.	Journal of Clinical Endocrinology and Metabolism 2000; 85(5):1895-1900.
HIP (RHN, RHE)/McClung et al	Effect of risedronate on the risk of hip fracture in elderly women.	New England Journal of Medicine 2001; 344(5):333-340.
VERT (North America) RVN. Harris et al.	Effect of risedronate treatment on vertebral and non-vertebral fracture in women with postmenopausal osteoporosis.	JAMA 1999; 282(14):1344-1352.
Meta-analyses		
Harrington et al.	Risedronate rapidly reduces the risk of non-vertebral fractures in women with postmenopausal osteoporosis.	Calcified Tissue International 2004; 74(2):129-135. (includes: BMD North America, BMD Multinational, VERT North America, and VERT Multinational trials).
Heaney et al	Risedronate reduces the risk of first vertebral fracture in osteoporotic women.	Osteoporosis International 2002; 13(6):501-505. (includes: BMD North America, BMD Multinational, VERT North America, and HIP trials. Based on: Barton and Cline, 2001.)

8. Results of Trials

The key results were presented for the entire trial populations and the post hoc subgroup of patients without prevalent baseline vertebral fractures and a BMD T-score ≤-2.5. The vertebral and non-vertebral fracture results were based on a meta-analysis of four risedronate trials (BMD-ROE Multinational, BMD-RON North America, VERT-RVN North America and HIP). The hip fracture results were based on the HIP trial only. No trial data were presented for patients who would become eligible under the requested expansion to the listing, ie patients with no prevalent fracture, aged 75 years or older and with a BMD T score ≤-3.0. However, in the sponsor's pre-subcommittee response analyses were provided for this specific population.

The results were reported as differences in event rates as opposed to differences in patients with events.

From the results, risedronate may be associated with a greater reduction in vertebral fractures in the *post hoc* subgroup of patients with low BMD (-2.5 or less) and no baseline vertebral fractures, compared to the total trial population. For non-vertebral fractures and for hip fractures, the results in the *post hoc* subgroup were not statistically significant, whereas the results in the total population indicated that risedronate treatment significantly reduced the incidence of hip fractures compared to placebo.

No new toxicity data were presented in the re-submission. The toxicity data from the previous re-submission indicated similar rates of adverse events, including upper gastrointestinal adverse events in risedronate- and placebo-treated patients.

9. Clinical Claim

The submission claimed risedronate had significant advantages in effectiveness over placebo and had similar or less toxicity.

For PBAC's view see Recommendation and Reasons

10. Economic Analysis

The costs included in the preliminary economic evaluation were the costs of risedronate and the costs of vertebral, hip and other fractures. The outcome of the preliminary economic evaluation was the incidence of vertebral, hip and other fractures. The incidence of hip and other fractures was included despite the absence of a statistically significant treatment effect in the subgroup of patients aged 75 years or older, with a BMD T-score of –3.0 or less and without a prevalent fracture.

The trial-based incremental cost per extra patient avoiding vertebral fracture was estimated to be in the range of $15,000 - $45,000. The trial-based incremental cost per extra patient avoiding hip fracture was estimated to be > $200,000 per extra patient avoiding other fracture.

The base case modelled incremental discounted cost per extra discounted QALY gained was estimated to be < $15,000 for males and in the range of $15,000 - $45,000 for females aged 75-79 with a BMD T-score ≤-3.0. Incremental costs per QALY gained decreased as age increased.

The ESC requested that the PES undertake additional calibration exercises in order to establish the most reliable estimate for baseline fracture rates for the Australian population and take into account all fracture types not only hip fractures. The model was re-run:

- with recalibrated baseline fractures for all fractures including hip and vertebral fractures;
- for the age groups 70-74, 75-79 and 80+

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be in the range of 100,000 – 200,000 in Year 4, while the financial cost per year to the PBS was estimated to be in the range of $60 – 100 million in Year 4.

12. Recommendation and Reasons

The PBAC considered that the evidence presented for the treatment effect of risedronate for the prevention of first fracture compared with placebo is unclear in the sub-group of patients without prevalent fractures aged 75 years or older and with a BMD T-score of < -3.0. The results for non-vertebral and hip fractures were not significantly different from placebo in this sub-group of patients. A test for interaction presented in the Pre-PBAC Response showed that there was no treatment effect modification between the higher risk group and the ITT population. Therefore, the submission argued that on balance, the evidence suggests that risedronate is statistically significantly superior to placebo in patients with or without prior vertebral fractures, and thus is no worse than other bisphosphonates.

The PBAC noted that there were a number of uncertainties with the economic model leading to uncertainty in the comparison of risedronate with placebo in the sub-group of patients without prevalent fractures aged 75 years or older and with a BMD T-score of ≤ -3.0 . The model overestimated the baseline risk of fractures as shown by the calibration exercises undertaken during the evaluation. The relative risks applied in the model were applied for hip and other fractures for which there is no statistically significant difference from placebo in the sub-group of patients without a prevalent fracture aged 75 years or older and with a BMD T-score of < -3.0. The sensitivity analysis in which the relative risks of hip and other fractures were set to 1 resulted in an incremental cost per QALY gained of between 75,000 and $105,000 for females (compared to $15,000 - $45,000 in the base case), and an incremental cost per QALY gained between $15,000 and $45,000 for males (compared to < $15,000 in the base case).

The PBAC therefore rejected the submission because of uncertain benefit in the clinically relevant outcomes of non-vertebral fracture and hip fracture and uncertain cost-effectiveness in the sub-group of patients without prevalent fractures aged 75 years or older and with a BMD T-score of < -3.0.

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

Following the PBAC's request to find a population with the greatest clinical need; sanofi-aventis identified it as those patients without a fracture, aged 75 years or older and with a BMD T-score of –3.0 or less, who showed to be at a higher absolute risk than the currently reimbursed population.

That subgroup from the total population resulted in small patient numbers on the trials, which were not originally powered for that subgroup. Therefore, the statistically insignificant results in hip and non-vertebral fractures may be due to under powering and not lack of treatment effect, which risedronate has shown for all types of fractures (including hip and non-vertebral) on the total population (with and without prevalent fractures).

Nevertheless, sanofi-aventis is committed to ensuring the access of all Australians at high risk of fracture to risedronate and we are working with the PBAC to ensure the listing of risedronate for this population at the earliest time possible.