

An addendum to this Public Summary Document has been included at the end of the document.

**6.07 RISEDRONIC ACID,
Tablet (enteric coated) containing risedronate sodium
35 mg,
Actonel® EC,
THERAMEX AUSTRALIA PTY LTD.**

1 Purpose of submission

- 1.1 The Category 2 submission requested an expansion of the current General Schedule, Restricted Benefit listing of the risedronate 35 mg enteric coated once a week tablet (Actonel EC) for primary prevention of fractures in patients with osteoporosis/treatment of osteoporosis, to include patients below 70 years of age with a BMD T-score of -2.5 or less.
- 1.2 The submission requested that for commercial reasons, the expansion of the current listing be formulation-specific and should apply to the risedronate 35 mg enteric coated once a week tablet (Actonel EC brand, PBS item 8972F) only. There are potential policy implications related to the requested formulation-specific listing given the long history of PBAC considerations for osteoporosis medications, with considerable overlap in terms of clinical evidence, cost-effectiveness, and interchangeability. In particular, the clinical evidence and cost-effectiveness of alendronate versus placebo formed the basis of current listings for all therapies for the primary prevention of osteoporosis.
- 1.3 The submission refers to the risedronate 35 mg once weekly enteric coated formulation as risedronate delayed release (DR). The evaluation refers to this formulation as risedronate enteric coated (EC) to maintain consistency with descriptions used on the PBS and in the product information.
- 1.4 Listing was requested on the basis of a cost-effectiveness analysis of early treatment with risedronate EC versus delayed treatment with standard of care therapies (based on age threshold and fracture history).

Table 1: Key components of the clinical issue addressed in the submission (as stated in the submission)

Component	Description
Population	Patients aged less than 70 years with osteoporosis (defined as those with a BMD T-score of -2.5 or less) and without a history of minimal trauma fracture
Intervention	Risedronate 35 mg once weekly enteric coated tablet (risedronate EC)
Comparator	Placebo or 'watchful waiting' (patient monitoring and standard management with calcium and vitamin D)
Outcomes	Prevention of osteoporosis-related fractures that leads to reduced morbidity and mortality
Clinical claim	Risedronate EC is superior in terms of efficacy and non-inferior in terms of safety compared to placebo

Source: Table 1, p18 of the submission

2 Background

Registration status

- 2.1 Risedronate EC was first approved by the TGA in March 2011 and is currently approved for the following indications:
- Treatment of osteoporosis.
 - Treatment of glucocorticoid-induced osteoporosis.
 - Preservation of bone mineral density in patients on long term corticosteroid therapy.
- 2.2 No TGA documentation was included in the submission apart from the product information. The submission noted that risedronate EC has been subject to multiple sponsor transfers since the initial approval and the current sponsor faced challenges sourcing historical data for this product.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

- 3.1 The requested expansion of the current listing of risedronate EC for primary prevention of osteoporosis was based on a proposed removal of the existing age criterion, which limits PBS-subsidised therapy to patients aged 70 years or over. This amendment was presented in a simple format with no other changes requested in the submission. Full details of the requested restriction were not presented in the submission but were assumed during the evaluation based on the existing PBS listing of risedronate EC. The requested listing is presented below with proposed deletions in strikethrough.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
RISEDRONATE					
risedronate sodium 35 mg enteric tablet	\$36.09 ^a	1	4	5	actonel EC
Category / Program: General Schedule					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners					
Restriction type: <input checked="" type="checkbox"/> Restricted benefit					
Condition: Osteoporosis					
Population criteria:					
Patient must be aged 70 years or older					
Clinical criteria:					
Patient must have a Bone Mineral Density (BMD) T-score of -2.5 or less,					
AND					
Clinical criteria:					
Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this condition					
Prescribing 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					
Note: Anti-resorptive agents in osteoporosis include alendronate sodium, risedronate sodium, denosumab, raloxifene hydrochloride and zoledronic acid.					

^a PBS April 2022 Schedule. The price in the PBS July 2022 schedule was \$36.15.

- 3.2 The requested restriction is consistent with the TGA indication (treatment of osteoporosis). This was defined as patients with a BMD T-score of -2.5 or less, which is consistent with the diagnostic threshold recommended in Australian guidelines.
- 3.3 The submission noted that the requested restriction was age agnostic, while the economic model and budget impact were based on the 50–69-year-old population. The submission claimed that the inclusion of patients younger than 50 years would have minimal impact on the overall cost-effectiveness and financial estimates, as the size of the treated population in this age group is likely to be relatively small. The evaluation considered this claim was reasonable given the use of BMD scanning in patients less than 50 years for the detection of primary osteoporosis in the absence of a prior fracture is likely to be minimal.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Osteoporosis is a condition that occurs when the bones lose minerals more quickly than the body can replace them, leading to enhanced bone fragility (due to reduced bone mass and micro-architectural deterioration of bone tissue) and a consequent increase in fracture risk. Loss of bone strength occurs gradually over many years and usually shows no symptoms. The most common fractures occur at the hip, spine and wrist and can lead to increased mortality, long-lasting pain, reduced mobility and disability.
- 4.2 The submission positioned risedronate EC for the treatment of patients aged less than

70 years with a BMD T-score of -2.5 or less who are without fracture, as an alternative to watchful waiting (ongoing monitoring and/or use of calcium and vitamin D supplements). The submission noted that there are no currently subsidised treatments for the targeted group, however, there is potential for patients to access a wide range of osteoporosis treatments (e.g. bisphosphonates and denosumab) on the private market. The degree of utilisation of osteoporosis treatments outside of PBS restrictions is currently unknown.

- 4.3 The submission noted that in patients without fracture, MBS-subsidised BMD testing is currently limited to patients aged 70 years or older or patients with secondary osteoporosis. However, the submission claimed no expected changes to assessment and monitoring associated with the proposed listing of risedronate EC as these patients would likely be monitored in the same way as those currently receiving standard of care. The availability of risedronate EC for younger patients with a specified BMD threshold may increase the use of BMD tests in clinical practice. However, the additional population are not eligible for MBS-subsidised testing and therefore patients would be subject to out-of-pocket costs.
- 4.4 During the evaluation, the MSAC ESC Secretariat advised that there were no active applications seeking to amend the existing MBS items for BMD testing. The MSAC ESC Secretariat noted that MSAC application 1665 (seeking to use radiofrequency echographic multi spectrometry for bone density measurement) was considered at the July 2022 MSAC meeting, however, the application did not request changes to patient eligibility/use in a broader population. The evaluation considered there may be equity issues if subsidised BMD testing is not uniformly available to all patients eligible for PBS-subsidised osteoporosis treatment.
- 4.5 The PBAC previously considered that the logistics and funding of BMD testing requires resolution prior to any PBS listing of osteoporosis medications (alendronate Public Summary Document (PSD), July 2006 PBAC meeting). The existing PBS restrictions for primary prevention of osteoporosis are co-dependent on MBS items for BMD testing, in particular, items 12320 (screening of patients aged 70 years or older) and 12322 (monitoring of patients aged 70 years and above with osteopenia).
- 4.6 The Pre-Sub-Committee Response (PSCR) agreed with the evaluation that there may be equity issues if subsidised BMD testing is not uniformly available to all patients eligible for PBS-subsidised osteoporosis treatment. The PSCR stated it supported collaboration between the PBAC and MSAC to optimise access to and prudent utilisation of subsidised BMD testing. The ESC noted the existing PBS restrictions for primary prevention of osteoporosis are co-dependent on MBS items for BMD testing. The ESC advised that any submission requesting changes to the existing PBS restrictions should also consider the consequences of parallel changes to the MBS items for prerequisite BMD testing. The ESC noted that the submission did not consider the costs associated with BMD testing in the additional population in either the economic evaluation or the financial estimates.

4.7 The submission claimed the removal of the age criterion is appropriate as each individual’s risk profile should be assessed according to a broad range of risk factors including parental fracture history, co-morbidities, other medications and lifestyle factors. The evaluation considered this claim was reasonable, however, the submission did not clearly characterise specific risk profiles within the younger requested population who would meet the intervention thresholds specified in published Australian guidelines (Healthy Bones Australia May 2022 Position Statement). During the evaluation, a summary of age and BMD T-score thresholds that would meet the recommended treatment thresholds based on the Garvan risk calculator (10-year risk of any fragility fracture >20% or hip fracture >3%) was presented in Table 2 below.

Table 2: 10-year fracture risk based on Garvan risk calculator without fracture or recent fall

Gender	BMD T-score	Age, years			
		50	55	60	65
10-year risk of hip fracture					
Female	-2.5	2%	3%	3%	4%
	-3.0	3%	4%	5%	7%
Male	-2.5	0.6%	1%	2%	3%
	-3.0	1%	2%	3%	5%
10-year risk of any fragility fracture					
Female	-2.5	12%	14%	16%	18%
	-3.0	14%	16%	19%	22%
Male	-2.5	3%	4%	6%	9%
	-3.0	3%	5%	7%	11%

Source: estimated during the evaluation using the Garvan risk calculator (<https://www.garvan.org.au/promotions/bone-fracture-risk/calculator/>)

Note: Estimates highlighted in orange represent absolute fracture risk that met or exceed recommended treatment thresholds (10-year risk of any fragility fracture >20% or hip fracture >3%)

4.8 The calculated risk estimates suggest that the following patients would meet recommended treatment thresholds based on absolute fracture risk, which is narrower than the population requested in the submission:

- Females aged 55 years and above with a BMD T-score of -3.0 or less.
- Females aged 65 years and above with a BMD T-score of -2.5 or less.
- Males aged 65 years and above with a BMD T-score of -3.0 or less.

The PSCR stated that the sponsor supported management of an expanded restriction to incorporate subgroups of patients most at risk of fracture due to minimal trauma and those most likely to clinically benefit from anti-resorptive treatment. The ESC advised that consideration should be given to more clearly specifying who in the expanded population would meet the threshold for treatment as per current Australian guidelines.

4.9 The optimal duration of therapy is uncertain, with the most recent guidelines stating that treatment should be lifelong (Healthy Bones Australia May 2022) while older guidelines (RACGP Osteoporosis Guidelines 2017) suggest that treatment breaks may be considered after 5 to 10 years of treatment with bisphosphonates. Treatment breaks are not recommended in patients initiated on denosumab due to the rapid

decline of treatment benefit after cessation of therapy and increased risk of fracture.

- 4.10 The PBAC recalled that in September 2021 the Committee had deferred the consideration of alendronate, risedronate, and zoledronic acid for the treatment of osteoporosis in patients aged under 70 who have not had a prior fracture due to minimal trauma. At that time, the PBAC was of a mind to recommend alendronate and zoledronic acid, but deferred consideration pending a review of the Medical Benefits Scheme (MBS) implications, to ensure that the bone densitometry MBS items could be aligned with the PBAC recommendations. At that time, the PBAC was also of a mind to recommend risedronate for both populations on a cost-minimisation basis to alendronate. In September 2021, the PBAC did not recommend denosumab for either population (PBAC Meeting Outcomes, September 2021 PBAC meeting). The PSD for the September 2021 meeting were ratified and published post the lodgement of the risedronate submission for the November 2021 meeting.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated placebo or 'watchful waiting' (patient monitoring and standard management with calcium and vitamin D) as the main comparator. The submission claimed there are currently no available treatments for the requested subgroup aged less than 70 years with BMD T-score of -2.5 or less and no prior fracture. Available osteoporosis treatments have broader TGA-approved indications for the treatment of osteoporosis, however, utilisation of these treatments outside of PBS restrictions is unknown.
- 5.2 The submission also claimed the PBAC has previously accepted placebo/watchful waiting as appropriate in previous considerations of osteoporosis treatments for primary prevention populations. The nominated comparator was appropriate.
- 5.3 The submission claimed that the proposed listing of risedronate EC will reduce the risk of, and delay the time to, first fracture in the requested PBS population, therefore, it is expected that usage of standard of care therapies typically prescribed following the first fracture will be reduced. The impact of risedronate EC on the usage of standard of care therapies (predominantly denosumab) was included in the economic model and budget impact estimates of the submission. The submission did not consider the potential impact of risedronate on the use of later-line therapies such as romosozumab and teriparatide.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The Sponsor requested a hearing for this item. The clinician described the prevalence of osteoporosis in Australia and stated women aged between 60 -70 years old were a group of high need for subsidised treatment options. Further, the clinician noted bone loss accelerates as patients get older and bone remodelling increases, further highlighting the need for earlier intervention than current restrictions.

Consumer comments

6.2 The PBAC noted the advice received from specialist medical organisations including the Australian and New Zealand Bone and Mineral Society (ANZBMS), the Endocrine Society of Australia (ESA), and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), and advice from the consumer organisation Healthy Bones Australia. A summary of the advice is provided below:

- The ANZBMS advised it was open to expanded PBS criteria for risedronate for patients aged 50 years and over at increased risk of fracture, however was not supportive of expanding the listing to patients aged under 50 years, due to the lack of clear evidence of benefit and risk of adverse events.
- The ESA advised it was of the view that removing the age restriction entirely would create a risk of inappropriate use of risedronate in premenopausal women or younger individuals without specialist consideration, which may lead to adverse outcomes. Instead, ESA was supportive of amending the age restriction, such as subsidising therapy in patients over the age of 50 with low BMD T-scores and at risk of fracture.
- RANZCOG advised it was of the view there is a potential for harm with widespread prescribing of risedronate, particularly to reproductive age women, as bisphosphonates are long acting and there is a paucity of evidence of the effects of these agents on the foetal skeleton. RANZCOG noted fracture risks calculators were readily available and considered it was challenging to set a fracture risk threshold at which risedronate should be PBS subsidised and considered a fracture risk between 5-10% over the next 10 years may be a reasonable approach. On that basis, RANZCOG advised it was supportive of amending the lower age limit of risedronate in women to 50-55 years old.
- Healthy Bones Australia advised it was supportive of expanded access to risedronate, for both patients in the primary and secondary prevention settings. A second input from the Chair of the Healthy Bones Australia Board reiterated the benefit that more patients would be eligible for risedronate if the listing were expanded, which they stated would reduce the public health care burden of fractures in society and the individual.

Clinical trials

- 6.3 The following trials and analyses were previously considered by the PBAC in risedronate submissions for primary prevention of osteoporosis (PBAC meetings held between June 2003 and March 2013):
- Direct comparison of BMD outcomes with risedronate versus placebo in postmenopausal women with BMD T-score of -2 or less (BMD-MN).
 - Direct comparison of BMD outcomes with risedronate versus placebo in postmenopausal women with BMD T-score of -2 or less (BMD-NA).
 - Direct comparison of hip fracture outcomes with risedronate versus placebo in postmenopausal women aged 70 years or older, with very low BMD (T-score <-3 or <-4) and/or risk factors for hip fracture (HIP).
 - Direct comparison of vertebral fracture outcomes with risedronate versus placebo in postmenopausal women with multiple prior vertebral fractures (VERT-MN).
 - Direct comparison of vertebral fracture outcomes with risedronate versus placebo in postmenopausal women with at least one prior vertebral fracture (VERT-NA).
 - Post hoc subgroup analysis of nonvertebral fracture outcomes in postmenopausal women with or without vertebral fracture, with BMD T-score of less than -2.5 using data from the BMD-MN, BMD-NA, VERT-MN and VERT-NA trials (Harrington 2004).
 - Post hoc subgroup analysis of vertebral fracture outcomes in postmenopausal women without vertebral fracture, with BMD T-score of less than -2.5 using data from the BMD-MN, BMD-NA, HIP and VERT-NA trials (Heaney 2002).
 - Indirect comparison of vertebral, nonvertebral and hip fracture outcomes in postmenopausal women without vertebral fracture, with BMD T-score of less than -2.5, between risedronate (BMD-MN, BMD-NA, VERT-NA, HIP trials) and alendronate (FIT-CFA trial) (risedronate PSD, March 2013 PBAC meeting).
- 6.4 The submission was based on direct comparisons of risedronate versus placebo in the BMD-MN, BMD-NA, VERT-MN and VERT-NA trials. The submission excluded the HIP trial as it was conducted in the wrong population. The applicability of results from the HIP trial to the requested PBS population may be limited as it was conducted in older patients with very low BMD, however, this appears to be the only trial of risedronate that included hip fracture outcomes.
- 6.5 The submission included a post hoc pooled analysis of four trials of risedronate (BMD-MN, BMD-NA, VERT-MN and VERT-NA) that assessed the relationship between age and treatment effect (Boonen 2010). This analysis has not previously been considered by the PBAC.
- 6.6 The submission provided supportive evidence based on BMD outcomes from a non-inferiority trial of risedronate EC versus risedronate immediate release in postmenopausal women with osteoporosis (Fantasia). This trial has not been

previously considered by the PBAC, however, risedronate EC was recommended by the PBAC on a cost-minimisation basis against other immediate release formulations of risedronate (PBAC Outcomes Statement, March 2011 PBAC meeting).

- 6.7 During the evaluation, summaries of the HIP trial and post hoc subgroup analyses (Harrington 2004 and Heaney 2002) that were previously considered by the PBAC were included. Data from the indirect comparison of risedronate and alendronate previously considered by the PBAC were also included as supportive evidence during the evaluation, as modelled treatment benefits for risedronate in the economic model were derived from data for alendronate (assuming equivalence between treatments).
- 6.8 Details of the trials presented in the submission and included during the evaluation are provided in Table 3.

Table 3: Trials and associated reports presented in the submission and included during the evaluation

Study ID	Protocol title/Publication title	Publication citation
Randomised trials of risedronate vs placebo		
BMD-MN	Fogelman I et al (2000). Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial.	The Journal of Clinical Endocrinology & Metabolism 85(5):1895-1900
BMD-NA	McClung MR et al (1998). Risedronate increases bone mineral density at the hip, spine and radius in postmenopausal women with low bone mass.	Osteoporosis International 8(suppl 3):111, Abstract P349
HIP	McClung MR et al (2001). Effect of risedronate on the risk of hip fracture in elderly women.	New England Journal of Medicine 344(5):333-340
VERT-MN	Reginster JY et al (2000). Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis.	Osteoporosis International 11:83-91
VERT-NA	Harris et al (1999). Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis.	The Journal of the American Medical Association 282(14):1344-1352
Meta-analyses of risedronate vs placebo		
Boonen 2010	Boonen S et al (2010). Assessment of the relationship between age and the effect of risedronate treatment in women with postmenopausal osteoporosis: a pooled analysis of four studies.	The Journal of the American Geriatrics Society 58:658-663
Harrington 2004	Harrington JT et al (2004). Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis.	Calcified Tissue International 74:129-135
Heaney 2002	Heaney RP et al (2002). Risedronate reduces the risk of first vertebral fracture in osteoporotic women.	Osteoporosis International 13:501-505

Source: Table 14, p55; Table 38, p106 and Attachment 3 of the submission

- 6.9 The key features of the included trials and studies are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Risedronate versus placebo						
BMD-MN	541	MC, R, DB, 2 years	Unclear	Postmenopausal women with low BMD	BMD	Not used
BMD-NA	648	MC, R, DB, 18 months	Unclear	Postmenopausal women with low BMD	BMD	Not used
HIP	9,331	MC, R, DB, 3 years	Unclear	Postmenopausal women aged ≥ 70 years with very low BMD and/or risk factors	Hip fracture	Not used
VERT-MN	1,226	MC, R, DB, 3 years	Unclear	Postmenopausal women with multiple vertebral fractures	Vertebral fracture	Not used
VERT-NA	2,458	MC, R, DB, 3 years	Low	Postmenopausal women with ≥ 1 vertebral fracture	Vertebral fracture	Not used
Boonen 2010	3,229	Included BMD-MN, BMD-NA, VERT-MN and VERT-NA trials; post hoc pooled analysis; assessed the relationship between age and treatment effect				Risedronate fracture risk reductions used in sensitivity analyses
Harrington 2004	1,172	Included BMD-MN, BMD-NA, VERT-MN and VERT-NA trials; post hoc subgroup analysis of patients with/without vertebral fracture with BMD T-score ≤ -2.5 ; assessed nonvertebral fracture outcomes				Not used
Heaney 2002	640	Included BMD-MN, BMD-NA, HIP and VERT-NA trials; post hoc subgroup analysis of patients without vertebral fracture with BMD T-score ≤ -2.5 ; assessed vertebral fracture outcomes				Not used

Source: Section 2A.3.3, pp59-61 of the submission and study publications

Abbreviations: BMD, bone mineral density; DB, double-blind; MC, multi-centre; R, randomised

- 6.10 There was insufficient information reported in the trial publications for the BMD-MN, BMD-NA, HIP and VERT-MN trials to determine the risk of bias. None of the publications reported adequate details regarding random sequence generation and allocation concealment, and blinding of outcome assessment. There was limited reporting for the BMD-NA trial that was only published in an abstract.
- 6.11 Following protocol amendment, the risedronate 2.5 mg arms of the BMD-MN, VERT-MN and VERT-NA trials were discontinued prematurely. This was due to data from other trials suggesting the 2.5 mg dose was less effective and had a similar safety profile to the 5 mg dose. Any further discussions in the PSD regarding these trials will be focussed on the 5 mg dose regimen only, which is the recommended dose in the product information.

Comparative effectiveness

- 6.12 Table 5 below presents the key fracture outcomes reported in the included trials. No fracture outcomes were available in the published abstract of the BMD-NA trial.

Table 5: Key fracture outcomes reported in the included trials

Outcome	Trial	Risedronate 5 mg ^a	Placebo	Relative risk (95% CI)	NNT ^b
Incidence of new vertebral fracture (radiographic), n/N (%)					
Cumulative to 1 year	VERT-MN	19/333 (5.6)	45/334 (13.0)	0.39 (0.22, 0.68)	14
	VERT-NA	16/669 (2.4)	42/660 (6.4)	0.35 (0.19, 0.62)	25
Cumulative to 2 years	BMD-MN ^c	8/112 (7)	17/125 (14)	NE	15
Cumulative to 3 years	VERT-MN	53/344 (18.1)	89/346 (29.0)	0.51 (0.36, 0.73)	10
	VERT-NA	61/696 (11.3)	93/678 (16.3)	0.59 (0.43, 0.82)	20
Incidence of nonvertebral fracture (radiographically confirmed clinical fractures of the clavicle, humerus, wrist, pelvis, hip or leg), n/N (%)					
Cumulative to 2 years	BMD-MN ^c	7/140 (5)	13/145 (9)	NE	25
Cumulative to 3 years	HIP ^d	9.4%	11.2%	0.8 (0.7, 1.0)	56
	VERT-MN	36/406 (10.9)	51/406 (16.0)	0.67 (0.44, 1.04)	20
	VERT-NA	33/812 (5.2)	52/815 (8.4)	0.60 (0.39, 0.94)	32
Incidence of hip fracture, n/N (%)					
Cumulative to 3 years	HIP	137/6,197 (2.8)	95/3,134 (3.9)	0.7 (0.6, 0.9)	91

Source: Sections 2A.5.1.1 and 2A.5.1.2, pp78-82 of the submission and the McClung 2001 publication

Abbreviations: CI, confidence interval; NE, not estimated; NNT, number needed to treat

^a Results from the BMD-MN, BMD-NA, VERT-MN and VERT-NA trials were from the risedronate 5 mg arm only. Efficacy analyses for the HIP trial were based on pooled risedronate 2.5 mg and 5 mg groups.

^b Estimates were calculated during the evaluation using crude risk difference. Estimates were rounded up to the nearest integer.

^c Safety outcome reported in a subset of patients with known fracture status only. Limited reporting in the trial publication.

^d Secondary endpoint; limited reporting in the trial publication.

Note: Bolding indicates results that were statistically significant and were the primary endpoints of the trials. It was unclear whether the results for other outcomes were adjusted for multiplicity.

- 6.13 Treatment with risedronate 5 mg was associated with a statistically significant decrease in the incidence of new vertebral fractures compared to placebo, over planned trial durations of 3 years. Treatment with risedronate 5 mg was also associated with decreases in the incidence of nonvertebral fractures over the 3-year duration.
- 6.14 Treatment with risedronate 2.5 mg and 5 mg (pooled) was associated with a statistically significant decrease in the incidence of hip fracture compared to placebo, over a planned trial duration of 3 years (mean 2.3 years follow-up).
- 6.15 The assessment and results for fracture outcomes at each site were not documented consistently across the available trial publications. The VERT trials were designed to detect morphometric vertebral fractures (radiographic based on annual scans) while the BMD-MN trial captured fractures detected as adverse events only. The detection of nonvertebral fractures appeared to be based on clinical (symptomatic) fractures that were radiographically confirmed, however, there was limited documentation available for adequate verification.
- 6.16 The statistical significance of secondary/exploratory fracture outcomes was uncertain due to limited documentation. It was unclear whether the results were adjusted for multiplicity.
- 6.17 No quality of life outcomes were captured in the included trials.

- 6.18 No subgroup analyses were presented in the submission. There was limited reporting in the available trial publications, with no pre-specified subgroup analyses reported for the BMD-MN, BMD-NA, VERT-MN and VERT-NA trials.
- 6.19 Results from pre-specified and post hoc subgroup analyses reported in the HIP trial publication indicated that treatment with risedronate (pooled 2.5 mg and 5 mg arms) was associated with a reduction in hip fracture compared to placebo, in younger patients aged between 70-79 years but no apparent effect in patients aged 80 years and above. In patients aged 70-79 years, risedronate was associated with a reduction in hip fracture in patients with a prior fracture but no apparent effect in those without fracture. These results should be interpreted with caution due to limited reporting of patient characteristics in addition to missing baseline data for some patients including BMD measures and fracture status.
- 6.20 The submission acknowledged that the populations in the included trials were not representative of the target PBS population in terms of patient demographics (age, gender) and disease severity/fracture risk (mixed primary and secondary prevention populations).
- 6.21 The submission presented a post hoc pooled analysis of four trials of risedronate (BMD-MN, BMD-NA, VERT-MN and VERT-NA) that assessed the effect of age on the incidence of fractures and of risedronate treatment on fracture risk in different age groups in postmenopausal women with osteoporosis (Boonen 2010). On average, patients in each treatment group were 68 years old (placebo: 67.7 ± 7.6 (range 38-85) years, risedronate: 67.9 ± 7.9 (range 39-85) years) and had a mean lumbar spine T-score of -2.6. Pooled 3-year fracture risk data from the Boonen study indicated lower fracture risks across all fracture types (any fracture, clinical fracture, nonvertebral fracture and morphometric vertebral fracture) in the risedronate group compared to the placebo group. Results from a Cox regression model indicate that fracture risks were statistically significantly greater in older patients. On average, for every 1-year increase in age, a patient's risk for any fracture increased by 3.6% (95% CI: 2.3%, 5.0%). The findings were similar for clinical fractures, nonvertebral fractures and morphometric vertebral fractures. The results also indicate that irrespective of age, risedronate reduced fracture risk by 41% to 46% across the four fracture types. The results from this study should be interpreted with caution as the data were analysed retrospectively, with differences in the assessment of fracture outcomes across the included trials. The PSCR noted that 28% of patients included in Boonen 2010 were assessed for primary prevention and argued that the study represents the best available evidence that demonstrates age is not a treatment effect modifier and so the relative risk benefits with oral bisphosphonate therapies should be observed in younger age groups as with older age groups. The ESC considered that while Boonen 2010 may represent the best available evidence, the primary prevention patients (28%) were not separated from the secondary prevention patients. The ESC considered there are no data to suggest that age has an impact on the relative treatment benefit with risedronate, however, the Boonen study also showed that

there is an increasing fracture risk with age. The ESC considered the absolute benefit associated with risedronate in a younger population without fracture is likely to be smaller than observed in the trials. The ESC noted the included trials were also relatively old, conducted more than 20 years ago. Fracture risks in the trial populations may not represent contemporary risks in the current setting given improvements in the diagnosis and management of osteoporosis over time. The pre-PBAC Response acknowledged the view of the ESC that the Boonen 2010 study likely represents the best publicly available evidence for risedronate in the proposed population and reiterated it was not possible to separate the primary and secondary prevention populations within the data, therefore absolute risk reductions for these sub-populations could not be derived.

- 6.22 The submission claimed that the key trials of risedronate have previously been considered by the PBAC and current listings are not restricted to women only. Therefore, the submission claimed it is reasonable to consider that the PBAC has historically considered risedronate to be effective in males. No data were presented in the submission to support the treatment benefit of risedronate in males. During the evaluation, data were identified supporting improvements in BMD with risedronate treatment in men, while fracture outcomes were limited and exploratory only (Boonen 2009; placebo-controlled trial of risedronate in males with prevalent vertebral fracture).
- 6.23 The submission noted that the included trials consisted of mixed primary and secondary prevention populations. However, the submission considered that the benefits observed in the trials would be applicable to the primary prevention population. No data were presented in the submission in support of this claim.
- 6.24 The PBAC has previously considered results from post hoc subgroup analyses of patients without prevalent vertebral fractures and a BMD T-score of less than -2.5 from the BMD-MN, BMD-NA, HIP and VERT-NA trials (Heaney 2002) and in patients with BMD T-score of less than -2.5 from the BMD-MN, BMD-NA, VERT-MN and VERT-NA trials (Harrington 2004). Based on this body of evidence, the PBAC considered that there was uncertain benefit associated with risedronate versus placebo for the clinically relevant outcomes of nonvertebral fracture and hip fracture in patients with BMD T-scores of ≤ -2.5 (risedronate PSD, July 2006 PBAC meeting).
- 6.25 None of the included trials administered the risedronate EC once weekly formulation, however, the submission provided supportive data from a comparison of risedronate EC and risedronate 5 mg immediate release, suggesting non-inferiority between these formulations in terms of efficacy and safety. The results were consistent with the PBAC's previous consideration, recommending the listing of various risedronate enteric coated formulations on a cost-minimisation basis against risedronate immediate release formulations (PBAC Outcomes Statement, March 2011 PBAC meeting).
- 6.26 The included trials had planned treatment durations of up to 3 years only, with no

reported treatment adherence or persistence data. No long-term data were provided in the submission to support longer term treatment benefit with risedronate, which is reliant on persistence to treatment.

- 6.27 The submission claimed that the treatment effect of risedronate on hip and non-hip fracture (modelled health states in the economic evaluation) in the target population could not be sourced from the clinical evidence presented based on the BMD and VERT trials that were not powered to detect differences in the incidence of hip and non-hip fracture. The submission claimed that the PBAC previously considered risedronate to be non-inferior to alendronate in terms of efficacy and safety, therefore it was reasonable to use treatment effect estimates for alendronate in the economic model as a proxy for treatment benefit associated with risedronate. Treatment effect estimates were derived from a published indirect comparison of denosumab and alendronate (denosumab PSD, March 2012 PBAC meeting) and assumptions. No justification was provided for the selected source, given potentially relevant results were available from an indirect comparison of risedronate and alendronate in the subgroup of patients without prevalent vertebral fracture and BMD T-score ≤ -2.5 (risedronate PSD, March 2013 PBAC meeting).
- 6.28 The indirect comparison was presented in the risedronate submission to support the expansion of the primary prevention listing (patients aged ≥ 70 years, with BMD T-score < -3.0 who are without fracture) to include matching patients with BMD T-scores between -3.0 and -2.5 (risedronate PSD, March 2013 PBAC meeting). In March 2013, the PBAC noted that the presented trial data did not match the target patient population. However, the PBAC recalled that it had previously accepted that risedronate was non-inferior to alendronate in the primary prevention setting for osteoporosis. At that time, 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 (risedronate PSD, March 2013 PBAC meeting).
- 6.29 The ESC considered that the rationale for using alendronate as a proxy for the treatment benefit for risedronate was inadequately justified. The ESC advised the use of these data added to the uncertainty associated with estimating the treatment effects of risedronate in the proposed PBS population.

Comparative harms

- 6.30 The submission noted that the safety profile of risedronate has previously been considered by the PBAC. Therefore, a high-level summary of adverse events in the included trials was provided in the submission. The included trials were conducted in older patients (mean ages of 65 years and above) in mixed primary and secondary prevention populations and may not be representative of the safety profile of risedronate in the requested population. While acknowledging the uncertainty around the risk-benefit profile in younger patients, the PSCR argued post-marketing safety surveillance data captures usage in patients of all ages with no age-related safety

issues identified.

- 6.31 No safety data were reported in the published abstract of the BMD-NA trial. A summary of adverse event data from the trials (including the HIP trial) was presented during the evaluation (see Table 6 below).

Table 6: Summary of key adverse events in the randomised trials

Trial ID	Patients with events, n/N (%)				
	Any adverse event	Treatment-related adverse event	Serious adverse event	Withdrawal due to adverse events	Any upper GI event
BMD-MN (1 year)					
- Risedronate 2.5 mg	172/185 (93)	NR	21/185 (11)	18/185 (10)	55/185 (30)
- Risedronate 5 mg	169/178 (95)	NR	26/178 (15)	19/178 (11)	40/178 (23)
- Placebo	172/179 (96)	NR	27/179 (15)	14/179 (8)	47/179 (26)
HIP (3 years)					
- Risedronate 2.5 mg	2,762/3,093 (89)	NR	946/3,093 (31)	548/3,093 (18)	690/3,093 (22)
- Risedronate 5 mg	2,786/3,104 (90)	NR	943/3,104 (30)	550/3,104 (18)	564/3,134 (18)
- Placebo	2,805/3,134 (90)	NR	973/3,134 (31)	564/3,134 (18)	684/3,134 (22)
VERT-MN (3 years)					
- Risedronate 2.5 mg	374/408 (92)	109/408 (27)	124/408 (30)	51/408 (13)	94/408 (23)
- Risedronate 5 mg	374/407 (92)	116/407 (28)	151/407 (37)	63/407 (15)	109/407 (27)
- Placebo	370/407 (91)	129/407 (32)	135/407 (33)	81/407 (20)	104/407 (26)
VERT-NA (3 years)					
- Risedronate 5 mg	785/813 (97)	273/813 (34)	237/813 (29)	138/813 (17)	245/813 (30)
- Placebo	774/815 (95)	236/815 (29)	219/815 (27)	136/815 (17)	219/815 (27)

Source: Table 27, p90 of the submission and the McClung 2001 publication

Abbreviation: GI, gastrointestinal

- 6.32 The submission claimed the adverse event profiles of the risedronate and placebo groups across the studies were similar. Overall, the reporting of adverse events was brief and limited to summaries available in trial publications only.
- 6.33 The use of risedronate (all formulations and combination products) for the treatment of osteoporosis is well established. The adverse event profile is also well known, with the product information for risedronate including special warnings and precautions for use. The product information notes that bisphosphonates have been associated with oesophagitis, gastritis, oesophageal ulcerations and gastroduodenal ulcerations. Caution is recommended should treatment be considered in patients with a history of gastroesophageal disorders and/or are unable to take the tablet as recommended.
- 6.34 The submission provided supportive safety data from the three treatment groups in the Fantasia trial (risedronate EC before breakfast, risedronate EC after breakfast and risedronate immediate release). The incidence of upper and lower gastrointestinal adverse events was similar across groups. However, the incidence of events related to upper abdominal pain was higher in the risedronate EC before breakfast group than in the other two groups; most of these events were judged to be mild to moderate. Overall, the tolerability of weekly risedronate EC was similar to that observed with daily risedronate immediate release.
- 6.35 The submission provided data on potential safety concerns beyond those identified in

the included trials, based on the Fantasia trial and the Periodic Safety Update Report (PSUR) for all strengths and formulations of risedronate covering the April 2016 to March 2021 reporting period.

- 6.36 Important identified risks in the PSUR were osteonecrosis of the jaw, iritis/uveitis, hypersensitivity and skin reactions, hypocalcaemia and interaction with medicinal products containing polyvalent cations (e.g. calcium, magnesium, iron, aluminium) that affect the absorption of risedronate. Important potential risks were atypical femoral fracture, osteonecrosis of external auditory canal, serious upper gastrointestinal irritation, severe musculoskeletal pain and serious hepatic disorders. Missing information included use in children, use in pregnant women, effect in lactating women, effect on fertility and use in patients with severe renal impairment. No new safety signals were identified during the most recent reporting interval. The Pre-PBAC Response reiterated the safety profile of risedronate was well characterised, with well-defined mitigation strategies.

Benefits/harms

- 6.37 The clinical evidence included in the submission was based on the broader population with osteoporosis that may not be representative of the absolute treatment benefit and safety profile of risedronate EC in the younger subgroup of patients who are without fracture. The risk-benefit profile of risedronate EC in the requested population is unknown.

Clinical claim

- 6.38 The submission described risedronate EC as superior in terms of efficacy and non-inferior in terms of safety compared to placebo.
- 6.39 The clinical evidence included in the submission was based on the risedronate 5 mg daily immediate release formulation only, however, the supportive data suggests non-inferiority in terms of efficacy between the risedronate EC once weekly and risedronate 5 mg immediate release formulations which is consistent with prior PBAC considerations of various risedronate formulations.
- 6.40 The submission claimed that risedronate EC was superior in terms of safety compared to risedronate immediate release due to the unique formulation (consisting of a chelating agent and enteric-coating) which theoretically provides protection from food interactions. This claim was inadequately supported by the data presented, which suggest similar safety profiles between risedronate EC and risedronate immediate release formulations. The PSCR stated that the claim was made in error and acknowledged there no robust clinical evidence to support such a claim.
- 6.41 The submission acknowledged that the pivotal trial evidence has previously been considered by the PBAC. Based on broader evidence than presented in the submission, the PBAC previously considered that there was uncertain benefit associated with risedronate for the clinically relevant outcomes of nonvertebral fracture and hip fracture in patients with BMD T-scores of ≤ -2.5 (risedronate PSD, July 2006 PBAC

- meeting).
- 6.42 The current listings of risedronate for primary prevention were recommended on a cost-minimisation basis with alendronate. The initial primary prevention listing for alendronate was supported by evidence indicating that alendronate reduces morphometric vertebral, hip, nonvertebral and other fractures, but not clinical vertebral fractures, in patients with a BMD T-score ≤ -2.5 (alendronate PSD, July 2006 PBAC meeting). There was also trial evidence of both absolute and relative fracture risk reduction, supporting the hypothesis that the benefit of alendronate depends on the baseline risk of patients and that there would be greater benefit in the requested subgroup. In recommending the extension to the primary prevention listing for alendronate (BMD T-score threshold of -2.5 instead of -3.0), the PBAC noted the provision of tests for interaction suggesting that age, BMD T-score and falls history were not treatment effect modifiers (alendronate PSD, July 2011 PBAC meeting).
- 6.43 Overall, the body of evidence for risedronate for clinically relevant fracture outcomes remains weak. The submission did not provide evidence supporting absolute or relative risk reductions for clinically relevant outcomes in the requested population. The PSCR argued that Boonen 2010 represents the best available evidence that demonstrates age is not a treatment effect modifier and so the relative risk benefits with oral bisphosphonate therapies should be observed in younger age groups as with older age groups. The ESC considered there are no data to suggest that age has an impact on the relative treatment benefit with risedronate, however, the Boonen study also showed that there is an increasing fracture risk with age. The ESC considered the absolute magnitude of benefit associated with risedronate in a younger population without fracture is likely to be smaller than observed in the trials.
- 6.44 The PBAC has not previously considered risedronate to have non-inferior safety compared to placebo. The submission noted that the PBAC considered risedronate to have non-inferior safety to alendronate, however, the PBAC has not previously accepted that alendronate was of comparable safety and tolerability compared to placebo. The risk-benefit assessment of alendronate was an outstanding issue for the PBAC when considering the extension of the primary prevention listing (i.e. patients aged ≥ 70 years with a BMD T-score between -3.0 and -2.5) (alendronate PSD, July 2011 PBAC meeting). In July 2011, the PBAC considered that the additional patients would have a lower risk of fracture but were likely to be at a similar risk of adverse events as patients already eligible at the time. At that time, the PBAC was concerned as to the likely extent to which adverse events would offset gains in terms of fracture risk reduction but noted the inclusion of sensitivity analyses (in the cost-effectiveness analysis) to assess the impact of rare safety events of concern (osteonecrosis of the jaw, atypical femoral fractures, and oesophageal cancer).
- 6.45 The submission only provided high-level summaries of adverse events from the included trials based on the premise that the PBAC had already considered the safety profile of risedronate in prior submissions. The included trials were conducted in older patients (mean ages of 65 years and above) in mixed primary and secondary

prevention populations and may not be representative of the safety profile of risedronate in the requested population. The PSCR argued post-marketing safety surveillance data captures usage in patients of all ages with no age-related safety issues identified.

- 6.46 Overall, the ESC agreed with the evaluation that the risk-benefit profile in the additional population is uncertain given the absolute fracture risk would be lower than the currently eligible population.
- 6.47 The PBAC considered that the claim of superior comparative effectiveness versus placebo was uncertain but likely reasonable, with the absolute magnitude of benefit in a younger population without fracture likely to be smaller than observed in the trials. To reduce the uncertainty associated with the clinical claim the PBAC considered the listing should be restricted to patients aged 60 years and above.
- 6.48 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

- 6.49 The economic evaluation was based on early initiation of treatment with risedronate EC in eligible patients aged less than 70 years, versus delayed treatment with standard of care therapies (predominantly denosumab) in patients who fracture or reach the age of 70 years. The modelled population was synthesised using epidemiological data, with fracture risks estimated using the Garvan risk calculator, treatment effects derived from subgroups of the alendronate (FIT-CFA) and denosumab (FREEDOM) placebo-controlled trials as well as other modelled variables. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

Table 7: Key components of the economic evaluation

Component	Description
Treatments	Early treatment with risedronate EC versus delayed standard of care therapies (oral bisphosphonates, zoledronic acid, denosumab)
Outcomes	Fracture avoidance, life years and quality-adjusted life years (QALYs)
Time horizon	20 years
Methods used to generate results	Markov cohort state transition model (half-cycle corrected costs and outcomes)
Health states	6 health states including a no fracture health state (baseline), 2 acute fracture health states (new hip and new non-hip), 2 post-fracture health states (prior hip and prior non-hip) and dead
Cycle length	Annual
Transition probabilities	<p>Fracture risks were estimated using the Garvan risk calculator using modelled patient characteristics and assumptions.</p> <p>Treatment effect estimates for standard of care were based on estimated treatment effects for alendronate, denosumab, risedronate and zoledronic acid. Individual treatment effects were derived from published results of an indirect comparison of alendronate (FIT-CFA) and denosumab (FREEDOM) placebo-controlled trials in subgroups with BMD T-scores <-2.5 who are without fracture (denosumab PSD, March 2012 PBAC meeting). Treatment effects for risedronate and zoledronic acid were assumed to be equivalent to alendronate. A weighted treatment effect was calculated using PBS utilisation data.</p> <p>Treatment effect estimates for risedronate EC were based on estimated treatment effects for alendronate (same source as for standard of care, see above), as a proxy for risedronate EC.</p> <p>Mortality estimates were based on Australian life tables, adjusted using fracture-related mortality multipliers derived from the Dubbo Osteoporosis Epidemiology Study.</p>
Health related quality of life	Baseline utility estimates from the general Australian population (Clemens 2014). Utility values for fracture health states were based on utility multipliers used in a published cost-effectiveness study for osteoporosis (Karnon 2016; sourced from the Peasgood 2009 utility study and Chau 2012 cost-effectiveness analysis) applied to baseline utility estimates.
Costs	Drug acquisition costs were estimated using the published DPMQs for risedronate and alendronate (all formulations and combination products), zoledronic acid and denosumab. A weighted cost for standard of care was calculated using PBS utilisation data. Administration costs for denosumab and zoledronic acid were based on MBS costs for GP and specialist visits. Monitoring costs were based on MBS costs for BMD testing. Acute fracture costs were derived from the AusICUROS study, inflated to 2022 estimates using the CPI. Ongoing fracture costs were based on costs of nursing home care published in an Australian osteoporosis burden of disease study (Watts 2013).
Software package	Excel

Source: Table 50, p126 of the submission

Abbreviations: BMD, bone mineral density; CPI, consumer price index

- 6.50 The ESC noted that economic model did not incorporate costs associated with the determination of treatment eligibility with risedronate EC, which would require screening a potentially large population for low BMD.
- 6.51 All patients start in the baseline health state of no fracture. In each annual cycle, patients can have no event or experience a hip fracture, non-hip fracture or death. Patients experiencing a hip or non-hip fracture enter corresponding new hip or non-hip fracture health states. After a year, patients in the new hip or non-hip fracture health states can have no event, or experience another hip fracture, or non-hip fracture or death. Patients who have no event transition to corresponding prior hip or non-hip fracture health states, while patients who experience another fracture

transition to the relevant new hip or non-hip fracture health state. Patients in all fracture states are attributed elevated mortality risks due to fracture.

- 6.52 The ESC noted concerns surrounding the likely extent to which adverse events would offset gains in terms of fracture risk reduction in patients with lower underlying fracture risk (see paragraph 6.44). The ESC noted that the impact of rare safety events of concern (osteonecrosis of the jaw, atypical femoral fractures, and oesophageal cancer) was not explored in the model.
- 6.53 The submission acknowledged that the structure of the model limited the ability to track events occurring in patients over time. This constraint necessitated the use of simplifying assumptions with regards to fracture risks, mortality risks and the attribution of fracture-related costs and consequences in the model (fixed, based on one prior fracture/fall only). The model structure also had unreasonable impacts on patient flow, for example, a patient with multiple fractures (e.g. hip fracture then non-hip fracture) could accrue lower ongoing costs and have better quality of life than patients with a single hip fracture.
- 6.54 All patients are assumed to be continually persistent to treatment over the 20-year model duration, with patients in the risedronate arm switching to standard of care therapy (predominantly denosumab) upon experiencing a fracture; and patients in the delayed standard of care arm initiating standard of care therapy upon experiencing a fracture or at age 70 years, whichever occurs first. All patients are attributed lifelong treatment costs and benefits (either risedronate or standard of care). This assumption was inappropriate, inconsistent with utilisation estimates (based on 1 year of risedronate EC treatment) and is unlikely to reflect clinical practice. The PBAC has previously considered the assumption of continuing treatment benefits to be of significant concern for osteoporosis medications given the less than ideal rates of persistence in practice (para 7.13, romosozumab PSD, November 2018 PBAC meeting). The most optimistic results from a DUSC review suggest approximately 50% of patients remain on oral bisphosphonates at 1 year and approximately 50% of patients remain on denosumab at 4 years (DUSC review of denosumab, October 2020 report). The PSCR argued that as the persistence of the antiresorptive agents considered in the analysis are similar, the relative persistence is expected to have an immaterial impact on the cost-effectiveness of the proposed scenario. The ESC disagreed with the PSCR and considered the assumption that all patients in the standard of care arm aged 70 years and over would commence and continue therapy was not consistent with clinical practice and noted that it increased costs in that arm. In addition, the ESC agreed with the evaluation that the assumption of lifelong treatment costs and benefits was not appropriate and was not reflective of clinical practice. The ESC considered that modelled estimates over the 20 year time horizon are highly uncertain given the lack of long-term efficacy data which is also dependent on persistence to treatment. As such, the ESC considered a shorter time horizon of 10 years would be more appropriate.
- 6.55 The model structure was primarily based on a published Australian economic

evaluation of denosumab versus alendronate, representative of the population in the denosumab placebo-controlled FREEDOM trial (mean age 72 years, mean femoral neck BMD T-score -2.15, mixed primary/secondary prevention population) (Karnon 2016). Compared to the model in the submission, the Karnon 2016 model used a shorter time horizon of 10 years, applied estimates of non-persistence over 5-year durations of treatment, did not include use of later line therapies and used trial-based sources to model fracture risk.

- 6.56 Many published economic models, including those previously considered by the PBAC for osteoporosis, have used a microsimulation rather than the cohort approach used in the submission. A microsimulation would have greater ability to track patients over time, particularly when the occurrence of events influences both treatment decisions and long-term consequences such as the risk of subsequent events and mortality.
- 6.57 Key drivers of the economic model are summarised in Table 8 below.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Patient characteristics	Baseline fracture risks were based on an 85% female population with a mean age of 62 years and BMD T-score of -2.5, with no prior fracture or falls history. These characteristics were based on data from the Geelong Osteoporosis Study (GOS) (Henry 2011), ABS Australian population estimates, the DUSC review of denosumab (October 2020 report) and assumptions. The ESC considered that data from the GOS may not be representative of the contemporary setting given the data are approximately 30 years old, derived from the general population rather than people who would be actively screened, with prevalence estimates based on a relatively small sample of patients aged less than 70 years. Overall, characteristics of the younger population who are not already eligible for treatment are uncertain and likely dependent on the uptake of BMD screening in practice. The cost-effectiveness of early risedronate EC treatment is dependent on absolute benefit, which is reliant on underlying fracture risks determined by the characteristics of the target population. The pre-PBAC response (p4) stated the GOS was the most up to date estimated of osteoporosis prevalence in Australia and was used to inform the model start age of 62 years. The pre-PBAC response (p3) noted baseline fracture risks applied to the proposed patient population in the economic evaluation were derived from the Dubbo Osteoporosis Epidemiology Study.	High, direction unclear
Risedronate EC treatment effects	Calculated relative risk reductions for risedronate EC (hip: 56%; non-hip: 35%) were based on treatment effect estimates for alendronate versus placebo, published in an indirect comparison of alendronate (FIT-CFA) and denosumab (FREEDOM) placebo-controlled trials in subgroups with BMD T-scores <-2.5 without prevalent vertebral fracture (denosumab PSD, March 2012 PBAC meeting). These estimates were highly uncertain based on an inadequately justified source, calculations that produced anomalous results and were optimistic compared to treatment effect estimates published in wider systematic reviews of risedronate (see detail in paragraphs following this table).	High, favours risedronate EC
Treatment persistence	100% persistence to all treatments was assumed. The modelled extent of treatment benefit associated with early risedronate EC treatment was reliant on continuing treatment for up to 20 years in patients without fracture.	High, favours risedronate EC
Cost of standard of care therapies	Drug costs were based on published DPMQs for risedronate, alendronate, denosumab and zoledronic acid and weighted based on a utilisation analysis from the DUSC review of denosumab for osteoporosis 2020 report (80% denosumab, 10% alendronate, 7% risedronate, 3% zoledronic acid). Costs were adjusted using adherence rates of 75% for risedronate and alendronate (based on the Fantasia trial) and were assumed as 100% for zoledronic acid and 85% for denosumab. Adherence estimates only affected drug costs and not treatment effect. The use of lower adherence estimates for risedronate EC compared to standard of care (predominantly denosumab) was in favour of risedronate EC given similar treatment efficacies applied. Administration costs were estimated for denosumab assuming 2 GP visits per year (no adjustments for adherence), and for zoledronic acid assuming 1 specialist visit per year. The estimated costs were inadequately justified for denosumab as a proportion of administration is likely to be given by nurses, and the costs were not adjusted for imperfect adherence. The cost of zoledronic acid IV infusions is unknown as there is no specific MBS item, however, the impact of alternative costs is minimal given the relatively low utilisation.	High, favours risedronate EC

Source: constructed during the evaluation

Abbreviations: BMD, bone mineral density; GP, general practitioner

6.58 The submission used the Garvan risk calculator to estimate the background risk of fracture based on modelled population characteristics. Data informing the Garvan risk calculator are relatively old and may not represent more contemporary fracture risks. There have been several independent studies and systematic reviews examining the prognostic performance of the Garvan risk calculator, suggesting the calculator

provides reasonable estimates of major osteoporotic fractures (any site) but overestimates hip fractures. The PSCR stated that the Garvan Fracture Risk Calculator is routinely used in Australian practice and recommended in Australian clinical practice guidelines (RACGP, 2017). Predicted risks using the Garvan calculator may not be reasonable estimates of fracture risk in the target PBS population who are younger and without fracture.

- 6.59 The submission derived treatment effect estimates for hip and non-hip fracture for risedronate EC and standard of care therapies based on treatment effect estimates for alendronate and denosumab from an indirect comparison of alendronate (FIT-CFA) and denosumab (FREEDOM) placebo-controlled trials in subgroups with BMD T-scores <-2.5 without prevalent vertebral fracture (denosumab PSD, March 2012 PBAC meeting). No justification was provided for the use of data from the selected source, given uncertainties with the robustness of point estimates from the post hoc subgroup analyses. The PSCR stated that the treatment effect of risedronate was modelled using alendronate data to align with the clinical evidence presented and evidence previously evaluated by the PBAC.
- 6.60 Treatment effect estimates for risedronate and zoledronic acid were assumed, based on equivalent efficacy to alendronate. The submission used point estimates of treatment effects for hip fracture. The derivation of treatment effects for non-hip fracture was complex, based on the sum of the incidence of morphometric/clinical vertebral fracture and nonvertebral fracture minus the incidence of hip fracture. The submission used different vertebral fracture outcomes in the calculated non-hip fracture estimates for alendronate and denosumab. For alendronate, the incidence of morphometric vertebral fracture was used while the calculations for denosumab included the incidence of clinical vertebral fracture. The approach used to estimate the treatment effect for non-hip fractures was crude and yielded anomalous results based on the choice of clinical versus morphometric vertebral fracture. The ESC agreed with the evaluation that risedronate treatment effects using alendronate as a proxy were highly uncertain.
- 6.61 The calculated estimates yielded slightly higher relative risk reductions for risedronate EC (hip: 56%; non-hip: 35%) compared to standard of care therapies (hip: 55%, non-hip: 34%). The use of improved treatment effects for risedronate EC versus other treatments was inadequately justified. The calculated estimates were optimistic compared to the broader evidence base for risedronate, which suggests an approximately 30% relative risk reduction for hip fracture. The treatment effect of risedronate on non-hip fractures (excluding morphometric vertebral fracture, as per Garvan risk estimates) is unknown. A recently published systematic review of risedronate trials noted that the treatment effect of risedronate was unknown for wrist fractures and not estimable for clinical vertebral fractures (Wells 2022). The PSCR argued that to test the impact of using the alendronate data as a proxy for risedronate treatment effect, multiple sensitivity analyses were conducted in the submission, including using the results from the risedronate meta-analysis (Boonen 2010). The ESC

agreed with the evaluation that the calculated estimates were optimistic compared to the broader evidence base for risedronate. The ESC considered that use of the relative risk reductions (hip: 41%; non-hip: 46%) reported in the Boonen 2010 meta-analysis may be a more appropriate reflection of risedronate treatment effect.

- 6.62 During the evaluation, errors were identified in the calculation of non-hip fracture risks. The impact of these errors was tested in sensitivity analyses.
- 6.63 The submission used mortality multipliers based on the Dubbo Osteoporosis Epidemiology Study. The results from the Dubbo Osteoporosis Epidemiology Study indicate an association between osteoporotic fracture and increased mortality but do not demonstrate causation. Additionally, the ESC noted the submission assumed ongoing increased mortality which was inconsistent with the source data.
- 6.64 The submission used the same utility multipliers applied in the Karnon 2016 study to the fracture health states of the model. The submission noted that the utility multipliers applied in the Karnon 2016 study could not be recreated from the reported sources. However, the submission claimed the methodology appears appropriate and the utility multipliers meet face validity. The estimates used in the Karnon study may be appropriate for the conducted analysis that was based on a mixed primary/secondary prevention population that was older (mean age 72 years). However, the ESC considered the estimates may not be applicable to a younger population without prior fracture, who may experience less severe consequences after fracture. The ESC noted that ongoing fracture disutilities do not reflect the recovery patterns of patients observed in the AusICUROS study that was identified as a potential source in the submission.
- 6.65 New hip and non-hip fracture costs were weighted by the incidence of fractures by gender and age bands in the general Australian population, with most fractures occurring in those age 70 years and older. The ESC agreed with the evaluation that this approach is likely to overestimate the costs of fractures occurring in the younger population, with the Tatangelo 2019 study reporting lower costs for younger patients (e.g. hip fracture cost of \$23,893 for women aged 50-69 years versus \$39,192 for women aged 70+ years). The ESC considered a reduction in hip and non-hip fracture costs in line with the approximately 40% decrease reported in the Tatangelo 2019 study would likely be appropriate in the proposed PBS population.
- 6.66 Ongoing costs applied to the prior hip and non-hip fracture states were based on post-fracture nursing home costs identified from the Karnon 2016 publication. The ESC agreed with the evaluation that the inclusion of these costs was inadequately justified as these costs were applied to the older population in the Karnon study and are unlikely to represent all patients experiencing a fracture. In addition, the burden of disease study (Watts 2013) identified as the source of the cost estimates did not include nursing home costs for patients aged less than 70 years.
- 6.67 The submission presented disaggregated costs for the economic model based on discounted costs only (5% discount rate). During the evaluation, disaggregated costs

based on undiscounted costs were calculated (summarised in Table 9 below).

Table 9: Health care resource items: disaggregated summary of cost impacts in the economic evaluation

Resource item	Risedronate EC	Delayed SoC	Incremental cost
Risedronate EC drug costs in patients without fracture	\$5,768	\$0	\$5,768
Standard of care drug and administration costs in patients without fracture	\$0	\$3,992	-\$3,992
Standard of care drug and administration costs in patients with fracture	\$822	\$1,058	-\$236
No fracture monitoring costs	\$580	\$314	\$267
New hip fracture management costs	\$2,425	\$3,151	-\$726
Prior hip fracture management costs	\$1,075	\$1,663	-\$589
New non-hip fracture management costs	\$2,481	\$2,842	-\$361
Prior non-hip fracture management costs	\$360	\$450	-\$90
Total costs	\$13,510	\$13,469	\$41

Source: Estimates calculated during the evaluation based on 'Attachment 5 Risedronate DR_economic evaluation' Excel workbook of the submission

Abbreviation: SoC, standard of care

6.68 The difference in total cost between treatment arms was largely driven by risedronate drug costs, which was largely offset by standard of care drug costs in the delayed standard of care arm, in patients who never experience a fracture but become eligible for treatment at age 70 years.

6.69 The submission presented disaggregated outcomes for the economic model based on discounted outcomes only (5% discount rate). During the evaluation, disaggregated outcomes based on discounted and undiscounted outcomes were calculated (summarised in Table 10 below).

Table 10: Disaggregated summary of health outcomes included in the economic evaluation

Outcome	Risedronate EC	Delayed SoC	Incremental outcome
Incident hip fractures	0.061	0.078	-0.018
Incident non-hip fractures	0.230	0.263	-0.032
LYs excluding mortality multipliers for incident fractures (undiscounted) ^a	18.269	18.268	0
LYs including mortality multipliers for incident fractures (undiscounted) ^a	18.156	18.114	0.042
- Years in no fracture state ^a	16.336	15.773	0.563
- Years in new/prior hip and non-hip fracture states ^a	1.819	2.341	-0.522
QALYs including mortality multipliers for incident fractures (undiscounted) ^a	14.565	14.487	0.078
- QALYs in no fracture state ^a	13.231	12.777	0.455
- QALYs in new/prior hip and non-hip fracture states ^a	1.333	1.711	-0.378
Total QALYs (discounted)^a	9.547	9.503	0.044

Source: Table 86, p162 and the 'Attachment 5 Risedronate DR_economic evaluation' Excel workbook of the submission

Abbreviation: LYs, life years; QALYs, quality adjusted life years; SoC, standard of care

^a Estimates calculated during the evaluation

6.70 The difference in health outcomes between the risedronate EC and delayed standard of care arms was driven by additional time spent in the no fracture health state in the risedronate EC arm, due to reduced incidence of hip and non-hip fractures (with associated quality of life and survival gains).

6.71 A summary of base case results is presented in Table 11 below.

Table 11: Results of the economic evaluation

	Risedronate EC	Delayed SoC	Increment
Costs	\$8,263	\$7,724	\$539
QALYs	9.547	9.503	0.044
Incremental cost per QALY gained			\$¹

Source: Table 84, p161 of the submission

Abbreviation: QALY, quality adjusted life year; SoC, standard of care

The redacted values correspond to the following ranges:

¹ \$5,000 to < \$15,000

6.72 Based on the economic model, early risedronate EC was associated with a cost per QALY gained of \$5,000 to < \$15,000 compared to delayed standard of care for the treatment of osteoporosis in patients aged less than 70 years with a BMD of -2.5. The evaluation stated the results should not be considered reliable given identified limitations with the model structure and uncertainties with multiple inputs including patient characteristics, treatment effects, circumstances of use (adherence and persistence) and costs associated with standard of care therapies.

6.73 Prior PBAC considerations of primary prevention listings for osteoporosis treatments were based on the identification of a group of patients with an absolute risk of fracture equivalent to those for whom cost-effectiveness had been already established as being acceptable. No comparisons with currently eligible populations were presented in the submission.

6.74 The submission provided estimated numbers needed to treat (NNT) to prevent one hip fracture and one non-hip fracture over one year of early risedronate EC treatment compared to delayed standard of care. These estimates could not be validated during the evaluation and were also inconsistent with estimates presented in the economic model workbook provided in the submission. During the evaluation, the number of fractures avoided and NNTs were estimated for early risedronate EC versus delayed standard of care over 20 years as per the base case. Additional estimates were also calculated assuming 1 year of treatment with risedronate EC, which is consistent with the duration of treatment used in the financial estimates (see Table 12 below).

Table 12: Fractures avoided and number needed to treat (NNT) by treatment duration and baseline age

Baseline age, years	Hip fractures avoided	Non-hip fractures avoided	Total fractures avoided	NNT		
				Hip	Non-hip	All
Time horizon 20 years						
62	0.0175	0.0324	0.0500	57	31	20
Time horizon 1 year						
50-59	0.0010	0.0033	0.0043	993	303	232
60-64	0.0018	0.0043	0.0061	547	234	164
65-69	0.0024	0.0039	0.0063	415	257	159

Source: constructed during the evaluation based on 'Attachment 5 Risedronate DR_economic evaluation' Excel workbook of the submission

6.75 As expected, the magnitude of fractures avoided was substantially lower with 1 year of treatment, yielding higher NNTs compared to the base case assuming 20 years of treatment. The NNT in younger patients was higher compared to older patients, which

is expected given differences in underlying fracture risk.

6.76 For every 1,000 patients treated with early risedronate EC versus delayed standard of care therapies (based on age or fracture status, whichever occurs first) and followed up for 20 years, the economic evaluation (using undiscounted costs and outcomes) estimates that there would be:

- additional early risedronate EC treatment costs of \$0 to < \$10 million, comprising risedronate EC drug costs of \$0 to < \$10 million that were largely offset by savings in the delayed use of standard of care treatments of \$4.23 million.
- 50 fractures avoided, comprising 18 hip fractures and 32 non-hip fractures; which would result in additional \$266,508 in monitoring costs (not including BMD screening costs for eligibility), save \$1.77 million in acute and chronic fracture costs, be associated with improved quality of life and result in an average of 20.6 life years gained.

6.77 The results of key sensitivity analyses presented in the submission and conducted during the evaluation are summarised in Table 13 below.

Table 13: Sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER	% change to ICER
Base case		0.044	1	-
Background non-hip fracture risk calculation for treated patients (base case calculation used any fracture risk minus hip fracture risk that was adjusted for treatment effect)				
Calculation using unadjusted hip fracture risk ^a		0.045	1	-2%
Time horizon (base case 20 years)				
10 years ^a		0.020	2	351%
15 years		0.033	3	92%
25 years		0.055	1	-36%
Discount rate (base case 5%)				
0% ^a		0.078	4	-96%
3.5%		0.052	1	-31%
Baseline age and BMD T-score (base case mean age 62 years, BMD T-score -2.5)^b				
50 years, BMD T-score -2.5 ^a		0.041	5	442%
55 years, BMD T-score -2.5 ^a		0.046	6	228%
60 years, BMD T-score -2.5		0.049	3	45%
65 years, BMD T-score -2.5		0.032	4	-92%
50 years, BMD T-score -3.0 ^a		0.046	2	327%
55 years, BMD T-score -3.0 ^a		0.057	3	96%
60 years, BMD T-score -3.0 ^a		0.065	4	-70%
62 years, BMD T-score -3.0		0.059	4	-98%
65 years, BMD T-score -3.0 ^a		0.046	Dominant	-
Risedronate EC and SoC treatment effects (base case relative risk reductions for risedronate: 56% hip fracture and 35% non-hip fracture; SoC: 55% hip fracture and 34% non-hip fracture)				
Risedronate EC hip fracture RRR 41% and non-hip fracture RRR 46% ^c		0.046	3	26%
SoC assumed equivalent to risedronate EC base case ^a		0.045	1	0%
Risedronate EC and SoC hip fracture RRR 30% ^{a d}		0.033	7	130%
Risedronate EC and SoC hip fracture RRR 40% ^{a e}		0.037	3	70%
Risedronate EC and SoC non-hip fracture RRR 15% ^{a f}		0.033	3	94%

Analyses	Incremental cost (\$)	Incremental QALY	ICER	% change to ICER
SoC drug costs (base case weighted costs of \$386.76 based on 10% alendronate, 7% risedronate, 80% denosumab and 3% risedronate)				
Alendronate only		0.044	6	257%
Risedronate only		0.044	3	91%
Denosumab only		0.044	1	-48%
Zoledronic acid only		0.044	6	257%
Treatment adherence (base case risedronate EC: 75%, SoC: 75% alendronate and risedronate, 85% denosumab and 100% zoledronic acid)				
Perfect adherence for all treatments ^a		0.044	7	168%
85% for all treatments ^a		0.044	3	90%
75% for all treatments ^a		0.044	3	38%
Risedronate EC adherence 90% ^a		0.044	7	142%
Risedronate EC adherence 70% ^a		0.044	1	-47%
First year fracture costs (base case hip fracture: \$41,626, non-hip fracture: \$11,170)				
20% decrease in hip fracture costs		0.044	1	21%
20% increase in hip fracture costs		0.044	1	-21%
20% decrease in non-hip fracture costs		0.044	1	11%
20% increase in non-hip fracture costs		0.044	1	-11%
40% decrease in hip and non-hip fracture costs based on younger patients in Tatangelo 2019 study		0.044	3	63%
Multivariate analyses				
10 year time horizon, risedronate EC treatment effects based on hip fracture RRR 41% and non-hip fracture RRR 46%, 40% decrease in hip and non-hip fracture costs ^g		0.019	8	540%
10 year time horizon, equivalent risedronate EC and SoC treatment effects based on hip fracture RRR 41% and non-hip fracture RRR 46%, 40% decrease in hip and non-hip fracture costs ^g		0.020	8	532%

Source: Table 89, p165 and the 'Attachment 5 Risedronate DR_economic evaluation' Excel workbook of the submission

Abbreviations: QALY, quality adjusted life year; SoC, standard of care

^a Sensitivity analyses conducted during the evaluation

^b There was an error in the fracture risk probabilities for age 50-59 years in the model, with non-hip fracture risks based on any fracture risks. These estimates were corrected during the evaluation, with non-hip fracture risks based on any fracture risks minus hip fracture risks.

^c Based on vertebral and non-vertebral fracture effects, Boonen 2010 meta-analysis

^d Based on risedronate HIP trial data

^e Based on denosumab trial data (FREEDOM)

^f Based on alternative calculation for alendronate (counting clinical instead of morphometric vertebral fracture from FIT-CFA subgroup)

^g Conducted during the development of the ESC Advice

The redacted values correspond to the following ranges:

¹ \$5,000 to < \$15,000

² \$45,000 to < \$55,000

³ \$15,000 to < \$25,000

⁴ \$0 to < \$5,000

⁵ \$55,000 to < \$75,000

⁶ \$35,000 to < \$45,000

⁷ \$25,000 to < \$35,000

⁸ \$75,000 to < \$95,000

6.78 The model was most sensitive to baseline age and BMD T-score, time horizon, standard of care drug costs (dependent on the distribution of included therapies and treatment adherence), and risedronate EC treatment effects.

- 6.79 The impact of baseline age and BMD on cost-effectiveness estimates was explored during the evaluation. Improvements in cost-effectiveness with increasing age were largely driven by decreases in the incremental cost associated with early treatment with risedronate EC. Any additional costs associated with the initiation of risedronate EC from age 66 years onwards were exceeded by increased standard of care therapy costs in the placebo arm from age 70 years onwards.
- 6.80 Sensitivity analyses using alternative adherence estimates should be interpreted with caution as changes to these estimates only affect drug costs and not treatment effect. The impact of imperfect persistence could not be assessed due to limitations with the model structure.
- 6.81 The model was only sensitive to changes in risedronate EC treatment effects but not standard of care. This appears to be due to the impact on amount of time spent in the no fracture state of the risedronate EC arm versus the placebo arm.
- 6.82 The ESC noted concerns regarding persistence assumptions over the 20 year time horizon (see paragraph 6.54), use of alendronate as a proxy to determine risedronate treatment effects (see paragraph 6.61) and overestimating the costs of fractures occurring in the younger population (see paragraph 6.65). The ESC noted that the multivariate sensitivity analysis that reduced the time horizon to 10 years, used the risedronate treatment effects reported in Boonen 2010 and decreased hip and non-hip fracture costs increased the ICER from a base case of \$5,000 to < \$15,000 per QALY gained to \$75,000 to < \$95,000 per QALY gained. The ESC considered that the resulting ICER of \$75,000 to < \$95,000 per QALY gained was more reliable than the base case ICER proposed in the submission. However, the ESC remained concerned that the costs associated with BMD testing in the proposed population were not included in the economic evaluation. The ESC noted that any submission requesting changes to the existing risedronate PBS restrictions should also consider the consequences of parallel changes to the MBS items for prerequisite BMD testing.
- 6.83 The pre-PBAC Response disagreed with the ESC that a 10 year time horizon was appropriate, and stated that Karnon 2016 specified a base case of 10 years in a model with a starting age of 72 years. Given the model has a base case starting age of 62 years, the response argued a 10 year horizon would significantly overestimate the cost of risedronate relative to the comparator arm and stated that a 15 year time horizon was more reasonable. In addition, the pre-PBAC response disagreed with the ESC that a reduction in hip and non-hip fracture costs in line with the Tatangelo 2019 study would likely be appropriate. The pre-PBAC response argued that fracture costs be weighted based on the proportion of fractures occurring in the model prior to or after age 70. The response stated this resulted in a 6% reduction in hip and non-hip fracture costs. The pre-PBAC response provided a respecified base case which used equivalent risedronate EC and standard of care treatment effects based on hip fracture RRR 41% and non-hip fracture RRR 46%, a 15 year time horizon and a 6% reduction in hip and non-hip fracture costs, with a resultant ICER of \$25,000 to < \$35,000 per QALY gained.

Drug cost/patient/year

Table 14: Drug cost per patient for risedronate EC

	Risedronate IR trials (BMD-MN, BMD-NA, VERT-MN, VERT-NA, HIP)	Risedronate EC trial (FANTASIA)	Economic model	Financial estimates
Treatment adherence	NR	94% of patients took at least 80% of study tablets	75.2% ^a	75.2% ^a
Treatment duration	Up to 3 years	Up to 2 years	Up to 20 years, fully persistent with therapy ^b	1 year ^c
Cost per script	-	-	\$36.09 ^d	\$36.09 ^d
Scripts per patient per year	-	-	9.81 ^e	9.78 ^f
Cost per patient	-	-	\$354.00 per year	\$352.96 for 1 year

Source: Trial publications; Section 3.6.1, pp146-147 and Attachment 6 Risedronate DR Utilisation and Cost workbook of the submission
Abbreviations: IR, immediate release

^a The submission calculated adherence rates for risedronate EC (75.2%) based on the proportion of patients categorised as adherent (94%, > 80% adherent) or non-adherent (6%, < 80% adherent) in the FANTASIA trial and assuming that patients in each category had the lowest possible usage value (adherent: 80%, non-adherent: 0%).

^b Assumed

^c Assumed

^d Proposed DPMQ, based on published DPMQ in June 2022

^e Calculated as 0.752 x 13.04 scripts per year (365.25 days per year)

^f Calculated as 0.752 x 13 scripts per year (52 weeks per year)

Estimated PBS usage & financial implications

6.84 The submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impact of removing the age criterion from the current PBS restriction for risedronate EC.

6.85 Key inputs for the financial estimates are summarised in Table 15.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Osteoporosis prevalence	Males aged 50-69 years: 1.9-5.7% Females aged 50-69 years: 4.7-24.0% Based on the proportion of patients with osteoporosis (BMD < -2.5) in each 5-year age band from the Geelong Osteoporosis Study (Henry 2011). The submission identified other potential Australian epidemiology studies but indicated that the Geelong study was the preferred source as estimates were from the general population, included both diagnosed and undiagnosed osteoporosis using BMD measurements and was not limited by participant age.	DUSC considered applying the proportion of patients with (BMD < -2.5) in each 5-year age band from the Geelong Osteoporosis Study was reasonable. DUSC commented that the estimated eligible annual prevalent population is around 500,000 persons and that the estimates are very sensitive to changing diagnostic rates.
Diagnosed cases	Males: 10%, Females: 25% Based on a statement that "More than 75% of women and about 90% of men with a high likelihood of osteoporosis are not investigated" from the abstract of a published review of osteoporosis in Australia (Nguyen 2004).	Estimates could not be validated during the evaluation due to a lack of documentation in the publication but did not appear to relate to the use of BMD scans in patients younger than 70 years of age. Additionally, the data included in the review were relatively old, with more recent studies indicating

Parameter	Value applied and source	Comment
		<p>substantial changes in osteoporosis diagnosis and management over time in Australia (Smith 2022).</p> <p>During the evaluation no useful estimates were identified on the utilisation of BMD scans for the detection of primary osteoporosis in patients aged <70 years with and without prior fracture.</p> <p>DUSC commented that clinicians may be more likely to pursue diagnosis of osteoporosis in younger patients if treatment options were PBS listed. DUSC considered that there could be programs run to target and increase diagnosis and that patients could be encouraged to undertake private BMD testing.</p> <p>DUSC agreed with the commentary that the source of the diagnosis rate was uncertain and likely out of date.</p> <p>DUSC considered there is a risk that utilisation may be substantially higher than predicted if diagnosis rates are targeted.</p>
Proportion without prior fracture	<p>Males: 93.8%, Females: 84.2%</p> <p>Based on the estimated 10-year risk of any fracture using the Garvan risk calculator for individuals 60 years of age with a BMD of -2.5 and no prior fracture or history of falls (males: 6.2%, females: 15.8%). The complement of this estimate was then used as the proportion of patients without fracture.</p>	<p>The submission did not adequately justify the use of a single estimate of fracture risk for males and females for all patients aged less than 70 years particularly given that age is one of the key determinants of fracture risk.</p> <p>Additionally, it should be noted that the Garvan risk calculator predicts future fracture risk for a particular individual and therefore risk estimates for a 60 year old represent fractures over the next 10 years rather than fractures occurring in the previous 10 years.</p> <p>By independently estimating the proportion of cases diagnosed and the proportion of patients without a prior fracture, the submission implicitly assumed that the presence of a prior fracture does not affect the likelihood of diagnosis. DUSC agreed with the evaluation that this assumption was not reasonable.</p>
Uptake of risedronate EC	<p>Males 50-59 years: 44.9%, 60-69 years: 54.1% Females 50-59 years: 36.7%, 60-69 years: 52.3%</p> <p>DUSC review of denosumab for osteoporosis (October 2020). Analysis of MedicineInsight data on the proportion of patients who regularly attended GP practices (3 visits between 2018-2019) who were diagnosed with osteoporosis and who had ever received at least one osteoporosis medication.</p>	<p>The estimated uptake rates included patients with and without prior fracture (proportions were not reported but likely to be biased towards patients with prior fracture due to the availability of PBS subsidised therapy). It was unclear whether these rates would be representative of the target population given the lower fracture risk in patients without a prior fracture. DUSC agreed with the evaluation that the patients included in the October 2020 review likely included a majority of patients who had a prior fracture. DUSC considered that the intended population may be more likely and capable</p>

Parameter	Value applied and source	Comment
		<p>than older patients to increase regular physical activity and delay initiation of medicine.</p> <p>Additionally, DUSC estimates were based on the use of any osteoporosis medication (with various dosing frequencies, methods of administration, adverse events) while the submission is limited to risedronate EC only. DUSC commented that eligible patients may already be treated with osteoporosis medicines, either outside of the PBS restrictions or through private prescriptions, and that the degree of this utilisation is unknown. DUSC noted the most commonly used PBS listed osteoporosis medicine is denosumab, and that an early summary of the PBAC consumer comments appeared to indicate a preference for medicines other than risedronate EC to treat this group of patients. DUSC considered that if patients are already treated with other osteoporosis medicines through private prescriptions they would be unlikely to switch to PBS listed risedronate EC, and considered the uptake rates were overestimated</p> <p>The assumption of constant uptake rates over time was not justified in the submission and was inconsistent with the gradual uptake pattern typically seen with the introduction of a medication in a new population.</p>
Persistence to risedronate EC	<p>Assumption of one year treatment persistence.</p> <p>Based on analyses from the DUSC review of denosumab for osteoporosis, a sponsor-commissioned 10% PBS sample analysis and a published French utilisation analysis (Hilgsmann 2019) which indicated low persistence to oral bisphosphonate therapy beyond one year for existing indications</p>	<p>This assumption was inconsistent with the available utilisation data (which indicated that a substantial minority of patients may continue treatment beyond one year), with the clinical trial data used to support fracture outcomes (18 months to 3 years of treatment) and the economic analysis (which assumed perfect persistence for up to 20 years in the absence of fracture).</p> <p>Persistence to oral bisphosphonates for existing indications may not be representative of the use of risedronate EC in patients younger than 70 years without prior fracture.</p> <p>DUSC considered it was likely that patients would be treated for longer than one year, but commented the duration did not need to be changed in the budget impact model. DUSC advised that while the optimal duration of therapy is uncertain the prevalence approach applied in the submission accounts for all eligible patients in each year and considered that treatment durations longer than one year should not be applied in the prevalence estimates.</p>
Adherence to risedronate EC	<p>9.78 scripts/patient/year.</p> <p>Calculated based on total script coverage for one year of treatment x estimated treatment adherence. The submission calculated adherence rates for risedronate EC (75.2%) based on the proportion of</p>	<p>DUSC noted that the October 2020 DUSC report suggested patients were supplied 10 prescriptions per year, which accounts for a number of patients initiating and ceasing treatment during the year, and considered this assumption reasonable.</p>

Parameter	Value applied and source	Comment
	patients categorised as adherent (94%, > 80% adherent) or non-adherent (6%, < 80% adherent) in the FANTASIA trial and assuming that patients in each category had the lowest possible usage value (adherent: 80%, non-adherent: 0%).	

Source: Table 90, p168; Table 91, p169 of the submission

Abbreviations: BMD, bone mineral density; DUSC, Drug Utilisation Sub-Committee; EC, enteric-coated; GP, general practitioner; PBS, Pharmaceutical Benefits Scheme

6.86 The estimated use and financial impact of risedronate to the PBS/RPBS for the treatment of osteoporosis in patients younger than 70 years of age and without prior fracture is presented in Table 16.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Total treated patients	1	1	1	1	1	1
Risedronate EC scripts ^a	2	2	2	2	2	2
Cost to PBS/RPBS less copayments	3	3	3	3	3	3
Cost offsets from reduced use of other osteoporosis medications ^b	4	4	4	4	4	4
Net cost to PBS/RPBS	3	3	3	3	3	3

Source: Source: Table 97, p179; Table 114, p189 of the submission

Abbreviations: EC, enteric-coated; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

^a Assuming 9.78 scripts/patient/year as estimated in the submission.

^b Due to prevention of fractures with early risedronate EC treatment using outputs from the economic model

The redacted values correspond to the following ranges:

¹ 50,000 to < 60,000

² 500,000 to < 600,000

³ \$10 million to < \$20 million

⁴ net cost saving

6.87 The estimated net cost to the PBS/RPBS for risedronate EC was \$10 million to < \$20 million in Year 1, increasing to \$10 million to < \$20 million in Year 6, with a cumulative total of \$90 million to < \$100 million over the first 6 years of listing.

6.88 DUSC considers the estimates presented in the submission to be uncertain. The main issues are:

- The financial estimates were highly uncertain given the lack of any credible estimates of the use of BMD screening in patients <70 years of age without prior fracture, which is currently not subsidised through the MBS. The expected utilisation of risedronate EC in younger patients is difficult to quantify without this information.
- The eligible population based on prevalence data in those aged 50-69 years would be 500,000 persons. There is a risk that the utilisation of risedronate EC may be substantially higher than predicted if diagnosis rates are targeted, and it is likely that if other preferred osteoporosis medicines are listed the market would also be larger than predicted for risedronate EC.

- Circumstances of use in the budget impact model were based on an assumed one-year duration of risedronate EC treatment. Although this reflects treatment durations in the key fracture outcome trials, persistence estimates from available utilisation data show longer durations than this, and there was assumed perfect persistence of up to 20 years in the economic analysis which suggest patients may be treated for longer than one year. Treatment durations longer than one year should not be applied to prevalence estimates.
- The treatment uptake rates were likely overestimated as:
 - They were based on the uptake of osteoporosis medicines in PBS patients, the majority of who likely had prior fracture. Younger patients who haven't experienced a prior fracture may be more likely and capable of increasing their regular exercise to delay initiation of medication.
 - Patients who do decide to initiate treatment may have a preference for medicines other than risedronate EC as private prescriptions.

6.89 The Pre-PBAC Response acknowledged the view of the evaluation and DUSC of the challenges in developing financial estimates for the proposed population due to the lack of information on the use of BMD screening in patients younger than 70 years of age. The response acknowledged the view of the DUSC that diagnosis and uptake will depend on the MBS and PBS criteria to target potentially osteoporotic patients at high risk of a first fracture, and advised it was willing to work with the Department to develop revised utilisation and financial estimates.

6.90 The PBAC noted the financial estimates presented in the submission were based on the 50–69-year-old population. The PBAC noted the submission did not consider the costs associated with BMD testing in the additional population in the financial estimates.

Quality Use of Medicines

6.91 The submission stated the sponsor is actively involved in a range of quality use of medicines activities to improve the diagnosis and treatment of osteoporosis in Australia.

Financial Management – Risk Sharing Arrangements

6.92 The submission did not propose a risk-sharing arrangement. The submission claimed that the sponsor is willing to discuss management options but considered that financial caps based on utilisation would not be consistent with the objective of increasing the rates of diagnosis and treatment for osteoporosis as outlined in the National Strategy on Osteoporosis (Australian Department of Health, 2019).

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation to amend the current age restriction

on the PBS listing of risedronic acid (risedronate) for primary prevention of fracture in patients with a bone mineral density (BMD) T-score of -2.5 or less. The PBAC advised it was of a mind to support amending the current age restriction of risedronate from patients aged 70 years and older, to patients aged 60 years based on the fracture risk in these patients. However, the PBAC deferred consideration pending a review of the Medical Benefits Scheme (MBS) implications, to ensure that the bone densitometry MBS items could be aligned with the PBAC recommendations. The PBAC noted the cost-effectiveness of risedronate for the expanded population needs to be assessed considering the absolute fracture risk in these patients, the cost of alternative therapies and the impact of BMD screening.

- 7.2 The PBAC noted that while input from specialist medical organisations including the Australian and New Zealand Bone and Mineral Society, the Endocrine Society of Australia, and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists supported amending the lower age restriction of the current risedronate listing they did not support the total removal of an age restriction (see paragraph 6.2). The PBAC also noted the advice in the sponsor hearing supported access to risedronate for women with osteoporosis aged 60 years and over (see paragraph 6.1). The PBAC agreed with the specialist medical organisations that it was not appropriate to remove the current risedronate age restriction entirely.
- 7.3 The PBAC considered the nominated comparator of placebo or watchful waiting was appropriate.
- 7.4 The PBAC noted that the pivotal trial evidence has previously been considered by the Committee (see paragraph 6.41). The submission primarily relied on the Boonen 2010 meta-analysis which included four of the five randomised controlled trials (RCTs) presented in the submission (see Table 4). The PBAC acknowledged the Boonen 2010 results should be interpreted with caution as the data were analysed retrospectively, with differences in the assessment of fracture outcomes across the included trials. In addition, the PBAC noted that the mean age of patients in each treatment arm was 68 years (although patients as young as 38 were included in the meta-analysis) and that the study included both primary and secondary prevention populations. However, the PBAC agreed with the Pre-Sub-Committee Response that the Boonen 2010 meta-analysis likely represented the best available evidence that demonstrates irrespective of age risedronate reduced fracture risk by 41% to 46% across the four fracture types (see paragraph 6.21). The PBAC also considered that while there were no data to suggest age is a treatment effect modifier, the Boonen 2010 study showed there is a reduced fracture risk in younger people.
- 7.5 The PBAC noted that current Australian guidelines recommend treatment thresholds based on the use of a validated absolute fracture risk algorithm. Using the Garvan risk calculator, patients with a 10-year risk of hip fracture of >3% or any fragility fracture >20% would meet recommended treatment thresholds. The PBAC noted these thresholds would be met for hip fracture in females with a BMD T-score of -2.5 aged 65 years and above. The PBAC noted that females with a BMD T-score of -3.0 would

- meet the threshold for treatment for hip fracture when aged 55 years and above (see Table 2). The PBAC noted support from the clinician from the sponsor hearing for expanding the listing to women aged 60 years and over. The PBAC noted the submissions argument that it was reasonable to consider that the PBAC has historically considered risedronate to be effective in males (see paragraph 6.22). On balance, the PBAC considered that the claim of superior comparative effectiveness versus placebo was uncertain but likely reasonable, with the absolute magnitude of benefit in a younger population without fracture likely to be smaller than observed in the trials. To reduce the uncertainty associated with the clinical claim the PBAC considered the listing should be restricted to patients aged 60 years and above (regardless of gender).
- 7.6 The PBAC considered the safety of risedronate was generally well understood from a long history of use and noted that while many patients tolerate it acceptably, there are risks in patients who are of childbearing age and rare cases of osteonecrosis of the jaw which are serious safety concerns. Overall, the PBAC did not accept the claim of non-inferior safety to placebo and considered a claim of inferior safety was reasonable; however, the PBAC considered that the benefits of risedronate treatment outweigh the risks in its proposed extended population (i.e. patients aged 60 years and over with a BMD T-score of -2.5 or less).
- 7.7 The economic evaluation was based on early initiation of treatment with risedronate EC in eligible patients aged less than 70 years, versus delayed treatment with standard of care therapies (predominantly denosumab) in patients who fracture or reach the age of 70 years. The PBAC agreed with ESC concerns regarding persistence assumptions over the 20 year time horizon, use of alendronate as a proxy to determine risedronate treatment effects and overestimating the costs of fractures occurring in the younger population. The PBAC noted the ESC favoured a multivariate sensitivity analysis addressing these concerns which increased the ICER from a base case of \$5,000 to < \$15,000 per QALY gained to \$75,000 to < \$95,000 per QALY gained (see paragraph 6.82). The PBAC acknowledged the pre-PBAC response provided a respecified base case that included a longer time horizon (15 years) and a different method for costing fractures in younger patients than the approach favoured by ESC (see paragraph 6.83). However, like the ESC, the PBAC remained concerned that the costs associated with BMD testing in the proposed population were not included in the economic evaluation. Overall, the PBAC considered the economic model to be problematic and may not be reliable for decision making.
- 7.8 The PBAC noted that on average the fracture risk in patients aged 60 years and over with a BMD T-score of -2.5 or less will be lower than that for patients meeting the current PBS listing criteria (patients aged 70 years and over with a BMD T-score of -2.5 or less). However, the PBAC further noted that for patients aged 60-70 years with a BMD T-score of -3.0 or less the fracture risk approaches that based on the current PBS criteria (Table 2). On this basis, the PBAC considered risedronate may be cost-effective for the expanded population at a price similar to that for the PBS listed bisphosphonates, however the PBAC also noted that a price higher than that for the

least costly PBS listed bisphosphonate has not been justified and any differences in extent of BMD screening needs to be accounted for.

- 7.9 The PBAC noted DUSC considered the utilisation and financial estimates in the submission to be uncertain. DUSC considered the lack of credible estimates of the use of BMD screening in patients <70 years of age without prior fracture and the likely overestimation of uptake rates as key sources of uncertainty (see paragraph 6.88). The PBAC acknowledged the difficulty of estimating BMD screening in the proposed expanded population. The PBAC noted the financial estimates presented in the submission were based on the 50–69-year-old population and advised revised estimates for the population aged 60–69 years would be required to progress a listing. The Committee considered the revised estimates should address concerns regarding overestimation of uptake rates and the uncertainty regarding BMD screening in patients <70 years without prior fracture.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.

Addendum to the November 2022 PBAC PSD:

**4.03 RISEDRONIC ACID,
Tablet (enteric coated) containing risedronate sodium
35 mg,
Actonel[®] EC,
THERAMEX AUSTRALIA PTY LTD.**

10 Background

- 10.1 The current PBS restrictions for risedronic acid (risedronate) for primary prevention of osteoporosis are co-dependent on MBS items for bone mineral density (BMD) testing. The November 2022 risedronate submission was not submitted as a co-dependent application and the submission did not consider the costs associated with BMD testing in the expanded population in either the economic evaluation or the financial estimates.
- 10.2 At its November 2022 meeting, the PBAC deferred making a recommendation to amend the current age restriction on the PBS listing of risedronate for primary prevention of fracture in patients with a BMD T-score of -2.5 or less. Overall, the PBAC advised it was of a mind to support amending the current age restriction of risedronate from patients aged 70 years and older, to patients aged 60 years and older based on the fracture risk in these patients. However, the PBAC deferred consideration pending a review of the Medical Benefits Scheme (MBS) implications, to ensure that the bone densitometry MBS items could be aligned with the PBAC recommendations.
- 10.3 The advice of the Medical Services Advisory Committee (MSAC) Executive was sought regarding the appropriate process for MSAC to consider amending age requirements for specific bone densitometry MBS items.

11 Additional information

Advice from the MSAC Executive

- 11.1 The MSAC Executive considered the PBAC request for advice in December 2022. The MSAC Executive considered expanding the MBS listing of bone densitometry to include people aged 60-69 years of age may have a substantial net cost to the MBS. The MSAC Executive advised the MSAC assessment of BMD testing can be achieved either through a resubmission of the risedronate PBAC submission as a co-dependent application or through the department independently progressing the September 2021 PBAC advice (see paragraph 4.10).

Follow-up advice from the Sponsor

- 11.2 The sponsor advised in early March 2023, following receipt of the MSAC Executive advice, that it was not in a position to prepare a co-dependent application exploring expanded access to BMD testing to address the concerns raised by the MSAC Executive.

12 PBAC Outcome

- 12.1 The PBAC did not recommend an amendment to the current age restriction on the PBS listing of risedronic acid (risedronate) for the primary prevention of fracture in patients with a bone mineral density (BMD) T-score of -2.5 or less, on the basis the MSAC Executive advised that resubmission as a co-dependent application would be required to assess the cost-effectiveness and financial implications of expanded bone mineral density (BMD) testing on the MBS to support such a listing.
- 12.2 The PBAC noted the advice from the sponsor that they were not in a position to prepare a co-dependent application for risedronate (see paragraph 11.2). The PBAC noted the MSAC Executive advice that an alternative approach to achieving MSAC assessment of BMD testing would involve the department independently progressing the September 2021 PBAC advice (see paragraph 4.10) and considered that this approach should be explored.
- 12.3 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

13 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

14 Sponsor's Comment

Theramex wishes to thank the PBAC, clinicians, medical organisations (ANZBMS, ESA, RANZCOG) and Healthy Bones Australia for their advice and support to broaden access to anti-resorptive therapy for those, mainly older female Australians, in medical need.