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Final protocol to  
guide the assessment  
of bone mineral  
density analyses  
using Dual Energy X-  
Ray Absorptiometry  
(DXA) in breast  
cancer patients  
receiving aromatase  
inhibitor treatment

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Final

## MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

### Purpose of this document

This document is intended to provide a draft decision analytic protocol that will be used to guide the assessment of an intervention for a particular population of patients. The draft protocol will be finalised after inviting relevant stakeholders to provide input to the protocol. The final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

- P**atients – specification of the characteristics of the patients in whom the intervention is to be considered for use;
- I**ntervention – specification of the proposed intervention
- C**omparator – specification of the therapy most likely to be replaced by the proposed intervention
- O**utcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

## Purpose of application

The Department of Health and Ageing received a proposal for the listing of dual energy X-ray absorptiometry (DXA) on the Medicare Benefits Schedule (MBS) in June 2011. This proposal is for the provision of an MBS item for bone densitometry by DXA to women with breast cancer who receive, or are being considered for, treatment with aromatase inhibitors. The Australian and New Zealand Bone and Mineral Society (ANZBMS) became involved with the preparation of a Decision Analytic Protocol (DAP) in March 2012.

This decision analytic protocol was drafted to guide the assessment of safety, effectiveness and cost-effectiveness of bone mineral density analysis using DXA for women with breast cancer who receive aromatase inhibitors in order to inform MSAC's decision-making regarding public funding of the intervention.

## Intervention

### Description

Osteoporosis (OP) is a 'skeletal disorder characterised by compromised bone strength predisposing a person to an increased risk of fracture', and is an established and well defined disease assessed on the basis of bone mineral densitometry (BMD). In terms of bone mineral density, osteoporosis can be defined as "a BMD that lies 2.5 standard deviations (SD) or more below the average value for young healthy women (a T-score of  $\leq -2.5$  SD)" (WHO 2007). According to the AIHW (2011) 692,000 Australians (3.4% of the total population) received a principle diagnosis of osteoporosis in 2007–08, of which women accounted for 82 per cent of cases.

Maintenance of bone mineral density relies upon equilibrium between the processes of bone formation and bone resorption. Bone formation refers to the deposition of bone matrix and the fixing of calcium in its mineral form. Bone resorption is the process of bone breakdown by osteoclasts and the release of minerals from bone. Coupled together, these processes are referred to as bone remodelling. The process of bone remodelling is mediated through the action of osteoblasts, osteocytes and osteoclasts (Santen et al, 2011).

- Osteoblasts are bone forming cells which produce organic bone matrix and aid its mineralisation.
- Osteoclasts are bone resorptive cells which digest bone mineral and degrade extracellular matrix proteins and form bone resorptive "pits".
- Osteocytes are osteoblasts which do not undergo apoptosis and become incorporated into the bone matrix and are important in the coupling mechanism of bone formation and resorption.

The processes underlying bone remodelling are complex and not completely understood.

Osteoporosis and low BMD are thought to occur as a result of increased numbers and activity of osteoclasts. Oestrogen promotes the apoptosis of osteoclasts and as a result women who are

oestrogen deficient, particularly post-menopausal women, experience higher rates of bone resorption due to the increased activity of osteoclasts (Santen et al 2011).

Bone formation exceeds bone resorption from birth until the age of approximately 20 years. At the end of this period, peak bone mass is achieved and between the ages of 20 and 40 is roughly maintained through equilibrium between bone formation and resorption (Marcus et al 2008). However, the rate of bone resorption exceeds that of formation for menopausal and post-menopausal women and men 60 years or older, resulting in net bone loss. The rate of decline in bone mass is most rapid in women within two years of menopause and averages two per cent to four per cent a year during the first five years after menopause and may exceed 5 per cent per annum (Elders et al 2008). Bone mineral content may decline by 25 per cent to 33 per cent during this period. Following this bone loss the rate slows to around one per cent per annum. The areas of greatest loss include the femoral neck and lumbar vertebrae, sites rich in trabecular bone and subject to future fracture. Cortical bone, comprising 80 per cent of skeletal bone, is lost less rapidly. This reduction in bone density frequently remains undiagnosed, and is most often clinically manifest as a skeletal fracture sustained with minimal trauma (WHO 2007).

Fractures are defined as minimal trauma fractures when the trauma is a result of a fall from standing height or less, and comprise a significant portion of the health burden caused by OP. Patients with minimal trauma fractures experience increased morbidity, complications, and mortality compared to age- and gender-matched peers (Center et al 2007) as they are more likely to immobilise patients and leave them vulnerable to diseases (e.g. pneumonia). Common sites of minimal trauma fracture are the hip, pelvis, the wrist and forearm and the spine.

**Table 1 Risk factors for developing osteoporosis**

Type of risk factor	Examples
Fixed (non-modifiable) risk factors	Age (increases with the age after 40-50) Sex (osteoporosis affects women at an earlier age) Menopause Family history of osteoporosis (genetic predisposition) Previous low trauma fracture (fragility fracture) particularly of the hip, spine or wrist.
Lifestyle (modifiable) risk factors	Physical inactivity Diet: low calcium intake Vitamin D deficiency Tobacco smoking Excessive alcohol consumption Low body mass index (BMI <18.5) Anorexia/exercise induced amenorrhoea Excessively high body mass index
Diseases implicated in OP	Rheumatoid arthritis Hyperthyroidism Hyperparathyroidism Hypogonadism, including early menopause Cushing's syndrome Chronic gut conditions including coeliac disease, and inflammatory bowel disease Chronic liver disease Chronic renal disease Some cancers (eg myeloma) Type 1 diabetes Gastrectomy Ankylosing spondylitis
Drug therapies implicated in OP	Chemotherapy Aromatase inhibitors for the treatment of breast cancer Long-term corticosteroid use Anti-androgenic treatments for prostate cancer

Source; AIHW (2008 and 2010), Osteoporosis Australia 2011, Smith 2006 and Bjarnason et al 2008

### **Aromatase inhibitors for hormone receptor positive breast cancer**

In hormone receptor-positive breast cancer the proliferation of mammary carcinoma cells is dependent on oestrogen. Oestrogen is biosynthesized from androgens by the enzyme complex aromatase and in premenopausal women the highest levels of aromatase are present in the ovaries whilst in postmenopausal women aromatase activity occurs primarily in the peripheral adipose tissues. In women with hormone receptor-positive breast cancer, expression of aromatase is also high at or near breast tumour sites. Common therapies for hormone receptor positive breast cancer include aromatase inhibitors (AIs) and tamoxifen. Aromatase inhibitors act by inactivating the aromatase enzyme complex and reduce circulating oestrogen whilst tamoxifen acts on oestrogen receptors as an oestrogen antagonist in breast tissue (Bjarnason et al 2008). Aromatase inhibitors have been shown to be effective in the treatment for hormone receptor-positive breast cancer in postmenopausal women and in women who have experienced failure of tamoxifen or failure of tamoxifen plus other hormonal therapy. In these patients, Bjarnason et al (2008) indicates that AIs produce higher cure rates and have a more favourable toxicity profile.

Several studies comparing the effects of AIs and tamoxifen on BMD have reported significantly higher rates of bone-turnover in patients treated with AIs (Perez et al 2006, Confavreux et al 2007 and Hadji et al 2009). In addition, several trials comparing treatment with AIs to tamoxifen have reported higher rates of fracture in patients treated with AIs. One trial (Cuzick et al 2010) had a median follow up of 120 months and found that fractures within the active treatment period were more frequent in patients receiving AIs than tamoxifen (odds ratio 1.33, 95% Confidence interval 1.15-1.55;  $p < 0.001$ ). A randomised controlled trial (Coleman et al 2007) involving 206 postmenopausal women (with 2-3 years of treatment with tamoxifen) who either continued treatment with tamoxifen or switched to AIs found that after a median of 58 months of follow-up the odds ratio for fractures in AI treated patients was significantly higher ( $p = 0.003$ ).

The negative impact of AIs on bone density is due to the inhibition of overall oestrogen production within the body. Tamoxifen, which acts as a local agonist/antagonist at oestrogen receptor sites, does not appear to have a detrimental effect on BMD. There are no Australian clinical practice guidelines specifically for the management of BMD in women being treated with aromatase inhibitors. Cancer Australia has published "Recommendations for Aromatase inhibitors as adjuvant endocrine therapy" (NBCC 2006) which state that "reduction of bone mineral density in women receiving an aromatase inhibitor should be managed according to existing guidelines for women in general. This includes the identification and treatment of women at high risk of osteoporosis". This statement refers to guidelines published in 2004 (O'Neil et al 2004). More recent Australian guidelines regarding the prevention and treatment of osteoporosis in postmenopausal women and older men are available (RACGP 2010b); however, these guidelines do not contain recommendations for the patient population of interest. Two relevant publications were identified, "Management of early breast cancer" from the New Zealand Guidelines Group (2009) and "Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group" (Reid et al 2008). The New Zealand Guidelines Group (2009) made the following recommendations regarding BMD monitoring in postmenopausal women receiving adjuvant therapy with an aromatase inhibitor:

- Patients should have bone density monitored at least every two years following a baseline DXA (dual energy X-ray absorptiometry).
- Frequency of bone mineral density monitoring should be tailored to the individual. If baseline T-score is greater than -1.0, further monitoring of bone density may not be necessary.

### **Methods for measuring BMD**

Dual energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT) can be used in measuring BMD. DXA is more widely used, has better reproducibility, and is considered more appropriate in general use than QCT which delivers higher doses of radiation. QCT may be preferred when measuring BMD in the presence of fractures, but has been excluded from this DAP (see Summary box below). Another tool for measuring BMD is quantitative ultrasound (QUS).

The DXA scan is used to generate T-scores which is a comparison of a patient's bone density to that of peak bone density for the patient's gender and is the number of standard deviations above or below the normal young adult mean BMD (WHO 2007).

DXA is currently reimbursed through the MBS to men and women aged 70+, for people who have previously experienced a minimal trauma fracture and for those with one of several risk factors including: prolonged corticosteroid use, hypogonadism, primary hyperparathyroidism, chronic liver disease, chronic renal disease, proven malabsorptive disorders, rheumatoid arthritis, or conditions associated with thyroxine excess (Table 3).

Bone mineral density in OP is defined by the WHO as a T-score that is less than or equal to 2.5 standard deviations below the young normal mean (a T-score of -2.5 or less) (WHO 2007). Bone mineral density reflects the bone strength, the amount of bone (i.e. mass), its spatial distribution (i.e. shape and microarchitecture) and the intrinsic properties of the materials that comprise it, such as density, matrix mineralization, collagen traits and micro-damage (Marcus et al 2008). "Osteopenia" (low bone density) is a precursor to OP and according to WHO is defined as a T-score is between -1.0 and -2.5 (**Error! Reference source not found.**). The Z-score is a comparison of a person's bone density with that of an average person of the same age and sex. Although the Z-score does not form a part of the diagnosis of osteoporosis according to WHO guidelines which quote T-scores, it may be used in premenopausal women and men <50 years to give the physician some idea of a patient's risk in relation to other patients of the same age (National Institutes of Health 2012).

Table 2 Diagnosis according to T-score and WHO classification of osteoporosis

T-score	Diagnosis
Equal or greater than -1.0	Normal bone density
Between -1.0 to -2.5	Low bone mass ("osteopenia": at risk for developing osteoporosis and increasing fracture risk)
Equal to or less than -2.5	Osteoporosis

Source: WHO 2007, RACGP 2010b

### Fracture risk

Ten-year fracture risk can be estimated through the use of on-line tools such as the FRAX tool developed by the University of Sheffield on behalf of the WHO (WHO 2007; WHO 2012). The assessment is likely to be less accurate for premenopausal women, young men (<50 years) and is not validated for children (Dasher et al 2010). A variation of FRAX supported with Australian data is available at: <http://www.shef.ac.uk/FRAX/tool.jsp?country=31>.

In terms of normative data, RACGP guidelines state: 'In Australia as a reference for fracture risk calculation in women, the T-scores calculated from the Geelong Osteoporosis Study database are used for the lumbar spine and the proximal femur. Normative data in Australian men are not currently available. Most BMD assessments currently report T-scores for men based on the US National Health and Nutrition Examination Survey (NHANES) normative data or reference ranges provided by densitometer manufacturers' (RACGP 2010b).

## Administration, dose, frequency of administration, duration of the intervention

Bone density scanning can be performed at any location which has both a DXA machine and qualified technician. A radiologist, nuclear medicine physician or other accredited specialist is required to perform the test and analyse the results. Communication of the results to the patient is facilitated through the patient's referring practitioner.

Diagnosis of low bone mineral density is dependent on the measurement site and number of sites measured. According to local guidelines, bone mineral density should be measured by DXA scanning performed on two sites, preferably anteroposterior spine and hip (RACGP 2010b).

Absorbed radiation doses from using DXA are negligible for first-generation pencil beam scanners (well below the estimated dose from natural background radiation of 7 uSv per day). Newer fan beam scanners produce slightly more radiation, with absorbed dose ranging from approximately 10 to 20 uSv per examination (Damilakis and Guglielmi 2010), and generating a combined dose from anterior-posterior spine, lateral spine, and hip scans of <30 uSv (SIGN 2003). The estimated dose of radiation is lower for DXA measurements than most diagnostic X-ray examinations including mammography; as such radiation is well tolerated and would not severely limit the safe use of DXA for BMD measurements. Bearing that in mind however, radiation dose can vary considerably between sites and DXA systems from different manufacturers based on scanning technique, x-ray tube filtration, efficiency of detection systems, exposure parameters, scan speed, scan size and patient body size (Damilakis and Guglielmi 2010).

Although the DXA device measures total density, the use of both high- and low-energy X-rays facilitates the separation of soft tissue and bone contributions to overall density (Dasher et al 2010). Scanning of the hip and spine usually takes up to a maximum of approximately 15-20 minutes (Dasher et al 2010). Several different MBS items provide services on a variety of indications with repeat scans dependent on the indication (Table 3).

Current guidelines suggest general practitioners to evaluate patients at increased risk for osteoporotic fractures who are not receiving specific preventive anti-osteoporotic therapy in regard to future fracture risk at intervals adequate to the risk in question. BMD measurement can identify some non-fragility causes of fracture, for example T-score above -1.5. If a decision is made to not recommend specific preventive anti-osteoporotic therapy following evaluation of BMD, this must be formally reviewed in relation to future fracture risk at intervals relevant to the risk in question. In most cases BMD testing is recommended for intervals of 2 years or longer (RACGP 2010b).

In patients with confirmed OP and receiving anti-osteoporotic treatment, repeat DXA scans are recommended to be considered at 1 year if there is a change to anti-osteoporotic therapy, and recommended at 2 year intervals when BMD is likely to be approaching -2.5 (average decrease in T-score is 0.1/ year) (RACGP 2010b). The BMD at the time of screening is the most important factor in determining treatment and the time to repeat scan. The rates of change between scans are not as important in overall management decisions.

Several MBS items cover a variety of indications for bone loss and reimbursement for scans every 12 or 24 months depending on the indication (see current arrangements for public reimbursement). Current guidance from a UK expert group (Reid et al 2008) for women taking AIs indicate that women with T-scores greater than -1.0 at baseline would not require repeat scans whilst women with T-scores falling within the osteopenic or osteoporotic range would require repeat scans at 24 months. Currently, the patient population of interest are not eligible for a DXA scan, baseline or otherwise unless they are over the age of 70, have risk factors specified in current MBS items or experience a minimal trauma fracture.

Treatment options are available for the prevention and treatment of OP; however, a number of pharmacological interventions exist and the treatment regime indicated varies according to the principal mechanism of bone loss and the comorbidities of each patient. A brief description of the different treatment modalities applicable to women with hormone receptor positive breast cancer taking AIs is presented in co-administered interventions and comes from the RACGP (The Royal Australian College of General Practitioners, 2010b) guidance on the management of osteoporosis as well as guidance from a UK expert group on the management of breast cancer treatment-induced bone loss (Reid et al 2008).

#### **Summary of the approach to assessment for the test**

The **proposed test** is DXA.

Bone density testing with QCT is excluded for the following reasons:

- QCT results are less reproducible than DXA
- There is less robust evidence currently available to support the use of QCT
- Although QCT radiation doses are reducing over time, currently the use of QCT involves a higher dose of radiation than DXA so exposes patients to a greater degree of harm.
- There are no standardised Australian normative data for QCT.
- QCT assessment of the spine may overestimate osteoporosis compared to DXA using the WHO standard definitions.
- PASC recognise that QCT may be considered an alternative to DXA in the future.

### **Co-administered interventions**

For people with OP, a variety of treatment options exist through which to reduce the rate of bone loss. In addition to maintenance of bone formation through supplementation (calcium and vitamin D), and reduction of bone resorption through lifestyle modification (exercise), pharmaceutical medications are available for the treatment of osteoporosis in certain patient groups (RACGP 2010b). Different preventive and treatment modalities include:

- Exercise - regular, progressive weight-bearing and resistance exercise aids in the preservation and increase of bone density
- Calcium and vitamin D – it is recommended that to optimise clinical efficacy, adequate calcium and vitamin D are required. If sufficient calcium cannot be obtained from diet, and adequate

Vitamin D levels are not achieved by sun exposure, supplements may be required. Total calcium intake of 1000-1300 mg/day (combination of food and supplement) is recommended (RACGP 2010b). Where sun exposure is not adequate to generate sufficient Vitamin D levels, supplementation of vitamin D 700-800 IU/day is recommended (Nowson et al 2012).

- Bisphosphonates–The bisphosphonates currently used in Australia include alendronate, disodium etidronate, risedronate, and zoledronic acid. These drugs reduce the risk of fractures by increasing bone density through the reduction of osteoclast activity. On average, these drugs lead to an increase in bone density by approximately 4-8 per cent at the spine and 1-3 per cent at the hip over the first 3-4 years of treatment.
- Monoclonal antibodies (Denosumab) – the RANK Ligand inhibitor, monoclonal antibody Denosumab binds to a specific ligand which is required for osteoclast formation. This inhibition of osteoclast formation, activity and viability results in decreased bone resorption and increased bone mass and strength in both cortical and trabecular bone.

Examples of anti-osteoporotic medication listed on the ARTG are shown in Appendix 1. Indications, contraindications and potential complications of anti-osteoporotic medication are presented in Appendix 2. PBS-listed anti-resorptive pharmaceuticals are listed by drug in Appendix 3 and by indication in Appendix 4.

Anti-osteoporotic medications on the ARTG are listed according to relatively broad indications. For example, alendronate is available to post-menopausal women and to men for the treatment of osteoporosis to help prevent fractures. Other medications are available if the finding of low bone mass is confirmed, for patients on long-term corticosteroid therapy, or in the presence or history of osteoporotic fracture.

#### **Clinical research questions for the assessment relating to the intervention:**

- What is the effect of anti-resorptive medication on the rate of bone mineral density loss and minimal trauma fracture in the defined population?
- What is the rate of bone loss over time in the population who are not provided test and therapy? What is the rate of bone loss over time in the population who are provided test and therapy? Evidence provided in response to these questions will inform the number and frequency of DXA re-testing and monitoring (respectively). The frequency of re-testing and monitoring should be justified by the submission of available evidence.
- What is the appropriate threshold for therapy in this population?
- What proportion of the population will reach the threshold T-score for therapy?
- The assessment phase should also consider patient who are already on aromatase inhibitors and who may have been taken them for some time at the time of introduction (i.e. effectiveness in people who enter the test-and-treat regime when they are already in treatment).

## Summary of the approach to assessment for the intervention

### Test

The **proposed test** is DXA. PASC consider that testing for serum vitamin D sufficiency would occur during standard clinical evaluation of a patient for low bone mineral density. Therefore the use of this resource would be the same in both the current and proposed scenario.

### Therapy

The **proposed therapy** is treatment with anti-resorptive agents. Women taking aromatase inhibitors would receive dietary and lifestyle advice as part of their ongoing management.

The proposed threshold is a T-score of less than/equal to -2.5. PASC considered that different BMD **thresholds** should be examined as the trigger for anti-resorptive treatment. The assessment phase should examine a T- score of -1.5 and -1.0 (the current triggers for PBS eligibility in patients taking glucocorticoid therapy) and sensitivity analyses around T-scores of -1, -2.0 and -2.5 should also be conducted. Any evidence identified to establish thresholds for therapy based on Z-scores in younger women should be presented.

The **timing and frequency of monitoring and re-testing** should be informed by evidence of change in BMD as a surrogate for the risk of minimal trauma fracture over time. The assessment phase will need to address the rate of bone loss in women taking aromatase inhibitors and anti-resorptives (who reach the threshold for treatment) as well as the rate of bone loss in women taking aromatase inhibitors and not anti-resorptives. This will inform questions around monitoring and re-testing. For sensitivity analyses the following options should be evaluated regarding re testing and monitoring of the proposed population:

- Re testing and monitoring of patients every 24 months
- Re testing and monitoring of patients every 12 months
- Re testing and monitoring of patients at frequencies advised by the evidence.

### Co-dependency

PASC noted that this application will be a **co-dependent application** involving prescription medicines not currently PBS subsidised for the patient population in question. However, at this stage there is **no concurrent co-dependent application**.

As the use of prescription medicines is essential to the overall cost-effectiveness of this proposal, the necessary co-dependencies will need to be addressed for PBS listing as well as MBS listing purposes.

Note that the final eligibility criteria, including the threshold T-score of the proposed population to access any co-dependent anti-resorptive drug would be defined by the Pharmaceutical Benefits Advisory Committee (PASC).

The assessment phase should address the efficacy of co-dependent medicines with respect to the

following populations in the proportion of women reaching the threshold for therapy:

- Post-menopausal women with breast cancer taking aromatase inhibitors.
- Women taking aromatase inhibitors who have previously been treated with tamoxifen.

## Background

### Current arrangements for public reimbursement

DXA scanning is not currently funded for men and women below the age of 70 unless they suffer from certain pre-defined conditions. Unconditional access to DXA scanning under the schedule is currently available to persons aged 70 years and over (MBS item number 12323). A variety of other patient populations are covered for DXA or QCT under the MBS (Table 3), including:

- Presumed low BMD following one or more fractures occurring after minimal trauma;
- Who have undergone prolonged glucocorticoid therapy and conditions associated with excess glucocorticoid secretion;
- Male (all) and female (lasting > 6 months before the age of 45) hypogonadism
- Primary hyperparathyroidism
- Chronic liver and/or renal disease
- Proven malabsorptive disorders;
- Rheumatoid arthritis; or
- Conditions associated with thyroxine excess

Table 3 lists the currently available MBS item numbers for DXA. Relevant explanatory notes are in Appendix 5.

Several different MBS items cover a variety of indications for repeat scans every 12 or 24 months depending on the indication (See Table 3). According to current Australian guidelines (RACGP 2010), for patients with low risk factors and T-scores above osteopenic values ( $\geq -1.0$  SD), repeat scans are not required unless substantial changes in circumstance (minimal trauma fracture or increased risk conditions). People diagnosed with osteoporosis ( $\leq -2.5$ ) would be eligible for repeat testing as required under MBS item 12306; however, patients with confirmed OP and receiving anti-osteoporotic treatment, repeat DXA scans are not generally required unless there is a change in, or cessation of, anti-osteoporotic therapy (RACGP 2010b).

Table 3 Current MBS item descriptors for Dual-energy X-ray absorptiometry

<p>Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS</p> <p><b>MBS 12306</b> Bone densitometry (performed by a specialist or consultant physician where the patient is referred by another medical practitioner), using dual energy X-ray absorptiometry, for:</p> <ul style="list-style-type: none"><li>• The confirmation of a presumptive diagnosis of low bone mineral density made on the basis of 1 or more fractures occurring after minimal trauma; or</li><li>• For the monitoring of low bone mineral density proven by bone densitometry at least 12 months previously.</li></ul> <p>Measurement of 2 or more sites – 1 service only in a period of 24 months – including interpretation and report; not being a service associated with a service to which item 12309, 12312, 12315, 12318 or 12321 applies (Ministerial Determination). Fee: \$102.40 Benefit: 75% = \$76.80 85% = \$87.05</p> <p><u>Relevant explanatory notes: See Note D1.27</u></p>
<p>Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS</p> <p><b>MBS 12312</b> Bone densitometry (performed by a specialist or consultant physician where the patient is referred by another medical practitioner), using dual energy X-ray absorptiometry, for the diagnosis and monitoring of bone loss associated with 1 or more of the following conditions:</p> <ul style="list-style-type: none"><li>• Prolonged glucocorticoid therapy;</li><li>• Conditions associated with excess glucocorticoid secretion;</li><li>• Male hypogonadism; or</li><li>• Female hypogonadism lasting more than 6 months before the age of 45</li></ul> <p>Where the bone density measurement will contribute to the management of a patient with any of the above conditions – measurement of 2 or more sites – 1 service only in a period of 12 consecutive months – including interpretation and report; not being a service associated with a service to which item 12306, 12309, 12315, 12318 or 12321 applies (Ministerial Determination)</p> <p>Fee: \$102.40 Benefit: 75% = \$76.80 85% = \$87.05</p> <p><u>Relevant explanatory notes: See Note D1.27</u></p>
<p>Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS</p> <p><b>MBS 12315</b> Bone densitometry (performed by a specialist or consultant physician where the patient is referred by another medical practitioner), using dual energy X-ray absorptiometry, for the diagnosis and monitoring of bone loss associated with 1 or more of the following conditions:</p> <ul style="list-style-type: none"><li>• Primary hyperparathyroidism;</li><li>• Chronic liver disease;</li><li>• Chronic renal disease;</li><li>• Proven malabsorptive disorders;</li><li>• Rheumatoid arthritis; or</li><li>• Conditions associated with thyroxine excess</li></ul> <p>Where the bone density measurement will contribute to the management of a patient with any of the above conditions – measurement of 2 or more sites – 1 service only in a period of 24 consecutive months – including interpretation and report; not being a service associated with a service to which items 12306, 12309, 12312, 12318 or 12321 applies (Ministerial Determination)</p> <p>Fee: \$102.40 Benefit: 75% = \$76.80 85% = \$87.05</p> <p><u>Relevant explanatory notes: See Note D1.27</u></p>

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS

**MBS 12321**

Bone densitometry (performed by a specialist or consultant physician where the patient is referred by another medical practitioner), using dual energy X-ray absorptiometry, for the measurement of bone density 12 months following a significant change in therapy for:

- Established low bone mineral density; or
- The confirmation of a presumptive diagnosis of low bone mineral density made on the basis of 1 or more fractures occurring after minimal trauma.

Measurement of 2 or more sites – 1 service only in a period of 12 consecutive months – including interpretation and report; not being a service associated with a service to which item 12306, 12309, 12312, 12315 or 12318 applies (Ministerial Determination)

Fee: \$102.40    Benefit: 75% = \$76.80    85% = \$87.05

*Relevant explanatory notes: See Note D1.27*

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS

**MBS 12323**

Bone densitometry (performed by a specialist or consultant physician where the patient is referred by another medical practitioner), using dual energy X-ray absorptiometry or quantitative computerised tomography, for the measurement of bone mineral density, for a person aged 70 years or over.

Measurement of 2 or more sites – including interpretation and report; not being a service associated with a service to which item 12306, 12309, 12312, 12315, 12318 or 12321 applies (Ministerial Determination)

Fee: \$102.40    Benefit: 75% = \$76.80    85% = \$87.05

*Relevant explanatory notes: See Note D1.27*

Taken from <http://www9.health.gov.au/mbs/search.cfm>, accessed 08 July 2013

A test for vitamin D sufficiency is available through MBS item 66608 (vitamin D or D fractions – 1 or more tests, Fee \$33.20). Anti-osteoporotic medication on the PBS is shown in Appendix 3 (by drug) and Appendix 4 (by indication). PBS eligibility is in general focused to specific indications. A T-score is required for most indications, other than where patients have a fracture due to minimal trauma, where the fracture has been established using radiology.

## Regulatory status

Four DXA devices are used in Australia – Hologic, Lunar, Norland and Medilink. All devices are listed in the ARTG as category IIb devices (medium-high level of risk; Table 4) (Global Medical Device Nomenclature (GMDN) code 37661).

Table 4 Regulatory status of the intervention

ARTG number	Approval date	manufacturer	Product	Approved indication
97975	10/11/2003	GE Medical Systems	GE Medical Systems Australia Pty Ltd - X-ray system, diagnostic, bone absorptiometer, dual-energy	x-ray imaging for bone densitometry
117461	16/03/2005	Norland Corp	Inderlec Medical Systems Pty Ltd - X-ray system, diagnostic, bone absorptiometer, dual-energy	For the estimation of bone density and other structural parameters using x-ray absorptiometry for the purpose of aiding in the diagnosis of osteoporosis including bone regeneration and loss.
119491	25/05/2005	Medlink	Inderlec Medical Systems Pty Ltd - X-ray system, diagnostic, bone absorptiometer, dual-energy	For the estimation of bone density and other structural parameters of bones using x-ray absorptiometry for the purpose of aiding in the diagnosis of osteoporosis including bone regeneration and loss.
158772	23/01/2009	Hologic Inc	Cytec Australia Pty Ltd - X-ray system, diagnostic, bone absorptiometer, dual-energy	Intended to be used to estimate bone density. The data can then be used to calculate bone mineral density.

Taken from <https://www.ebs.tga.gov.au/>, accessed 9 August 2012

## Patient population

DXA scanning is proposed for women with breast cancer who are being considered for, or are being treated with, aromatase inhibitors and who are not otherwise eligible for a DXA scan. PASC has identified the need to collect evidence around the rate of bone loss in patients who are treatment naïve, patients who are aromatase inhibitor naïve and patients who have been on aromatase

inhibitors for some time. Where available, the assessment phase should present evidence on these patient groups separately.

In the context of this DAP the patient population is women who are being treated with aromatase inhibitors. At the assessment phase this patient population should be further stratified to identify relevant outcomes for:

- Post-menopausal women with breast cancer currently taking aromatase inhibitors.
- Women taking aromatase inhibitors who have previously been treated with tamoxifen

#### Risk factors

The specific risk factors associated with this population are sex (female) and treatment with aromatase inhibitors.

#### Baseline population

The baseline population for this application is postmenopausal women.

#### Benchmark population

People on prolonged glucocorticoid therapy, a medication associated with rapid bone loss and currently eligible for DXA scanning through MBS item 12312. These patients are also eligible for PBS subsidy of bisphosphonates. The PBS eligibility threshold for patients taking glucocorticoid medications is a T-score of - 1.5 or less in the case of zoledronic acid and -1.0 or less in the case of risedronate.

#### Questions for the review relating to the population:

- What is the risk of minimal trauma fracture (possibly informed by the surrogate of rate of loss of bone mineral density) in the proposed population (with no intervention) compared to minimal trauma fracture in the baseline population (with no intervention)? This will confirm the clinical need for testing for bone mineral density in this population.
- What is the effect of previous treatment with tamoxifen on minimal trauma fracture or BMD?
- What is the rate of bone mineral density loss in the proposed population? What is the rate of bone mineral density loss in the benchmark population? This will provide information regarding the frequency of re-testing and monitoring for the proposed population in light of evidence pertaining to the benchmark population who are already eligible for BMD scanning through the MBS. For the benchmark population (patients taking glucocorticoid therapy) annual retesting is supported by MBS item 12312.
- Are there any other prognostic factors such as age or other medications which impact on the risk of this population to low BMD or MTF?

### Summary of the approach to assessment for the population

The **population** is women with breast cancer who are being treated with aromatase inhibitors and who are not otherwise eligible for a DXA scan. There is no age restriction.

Subpopulations within this population include:

- Women taking aromatase inhibitors who have previously been treated with tamoxifen

The **baseline population** for this DAP is postmenopausal women. The **benchmark population** for this DAP is people taking glucocorticoid therapy.

The assessment of evidence should provide evidence on:

- the rate of bone loss and minimal trauma fracture for women on aromatase inhibitors taking anti-resorptive agents;
- the rate of bone loss and minimal trauma fracture for women on aromatase inhibitors not taking anti-resorptive agents; and
- the rate of bone loss and minimal trauma fracture in women following menopause.

This will be used to identify the baseline risk levels of minimal trauma fracture in the proposed population as compared to the baseline and benchmark populations. In the context of this DAP PASC has accepted change in BMD as measured by DXA as an appropriate surrogate marker for risk.

**Note that** a comparison of the rate of bone loss in the target population to the baseline and benchmark populations will need to take into account the age of persons within those populations as age is also a risk factor for bone mineral density loss.

### Excluded populations

- All patients at age 70 and over are excluded, as these are eligible for current MBS items for DXA scanning.
- Patients presenting with a minimal trauma fracture are excluded, as these are eligible for current MBS items for DXA scanning (12306, 12309).
- Women taking aromatase inhibitors who have undergone premature menopause as a result of treatment for breast cancer (12312). Patients eligible for any other current MBS item for DXA scanning are excluded.

## Proposed MBS listing

The proposed MBS item is shown in **Error! Reference source not found..** For patients with T-scores  $\leq -2.5$  repeat scans would be available through the existing MBS item 12306.

The proposed item would be in addition to existing MBS items for DXA. At 70 all patients will be eligible for existing MBS item 12323.

Table 5 Proposed MBS item

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Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS, Bone Densitometry

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MBS XXXXX

Bone densitometry (performed by a specialist or consultant physician where the patient is referred by another medical practitioner), using dual energy X-ray absorptiometry, for the measurement of bone mineral density in patients with breast cancer who are currently being treated with or are about to commence treatment with aromatase inhibitors.

Measurement of 2 or more sites – 1 service only in a period of 12 consecutive months - including interpretation and report; not being a service associated with a service to which item 12306, 12309, 12312, 12315, 12318, 12321 or 12323 applies

Fee: \$102.40      Benefit: 75% = \$76.80    85% = \$87.05

[Relevant explanatory notes]

D1.27, Bone Densitometry – (Items 12306 to 12323)

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Currently, no specific PBS-listed medication is proposed for use in this population.

## Clinical place for the proposed intervention

The current diagnosis and management algorithm for suspected or proven low bone mineral density follows in Figure 1. The current and proposed clinical management algorithms for the defined patient population follows in Figure 2 and Figure 3. Note that treatment stratified according to T-score is in line with PBS restrictions for access to drug therapy and may not represent those patients who choose to have a DXA scan and subsequent anti-resorptive treatment despite not being eligible via the MBS and PBS.

Figure 1 : Current clinical management algorithm for eligibility to MBS and PBS items for osteoporosis

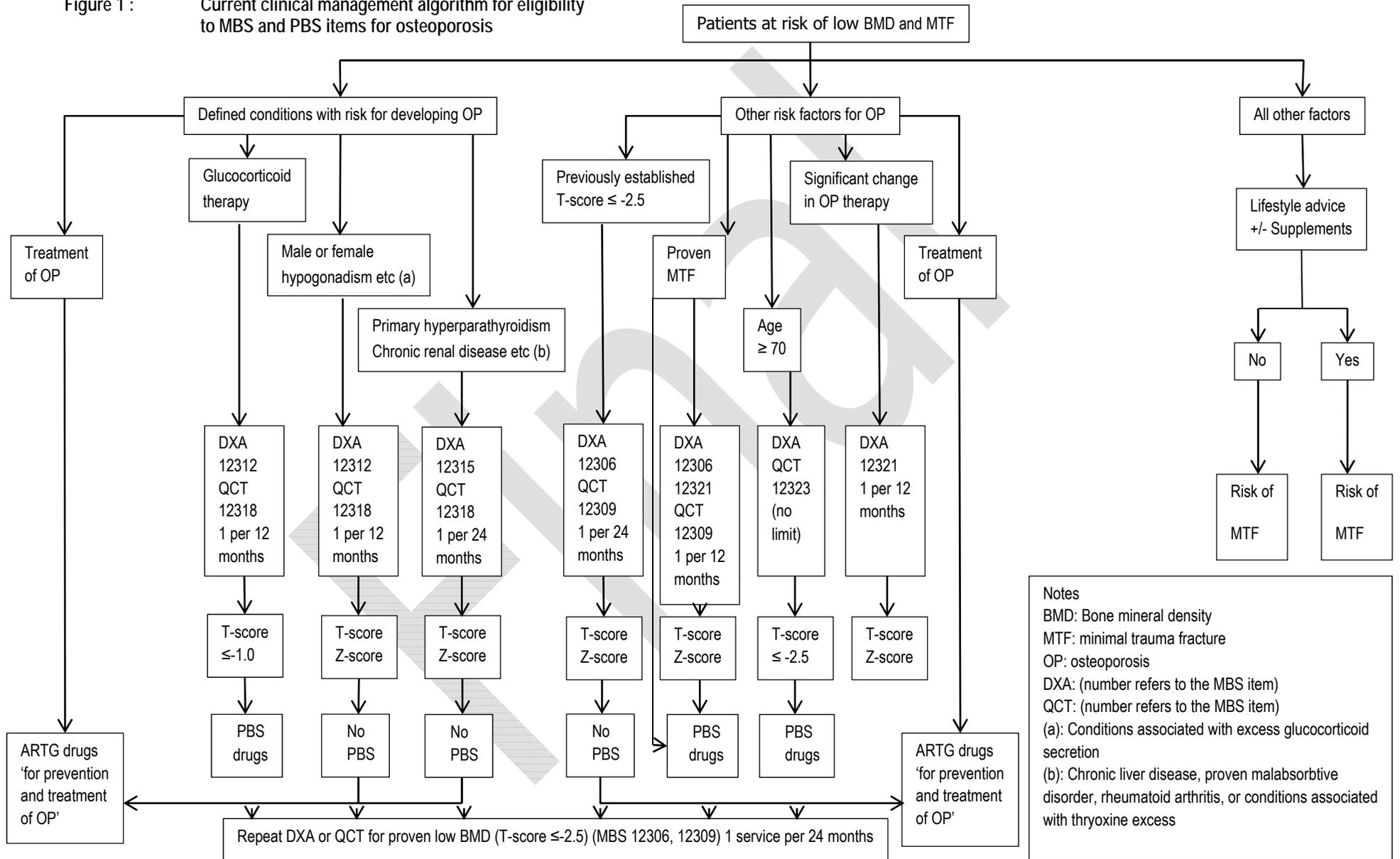


Figure 2 Current clinical management of breast cancer patients receiving aromatase inhibitor therapy

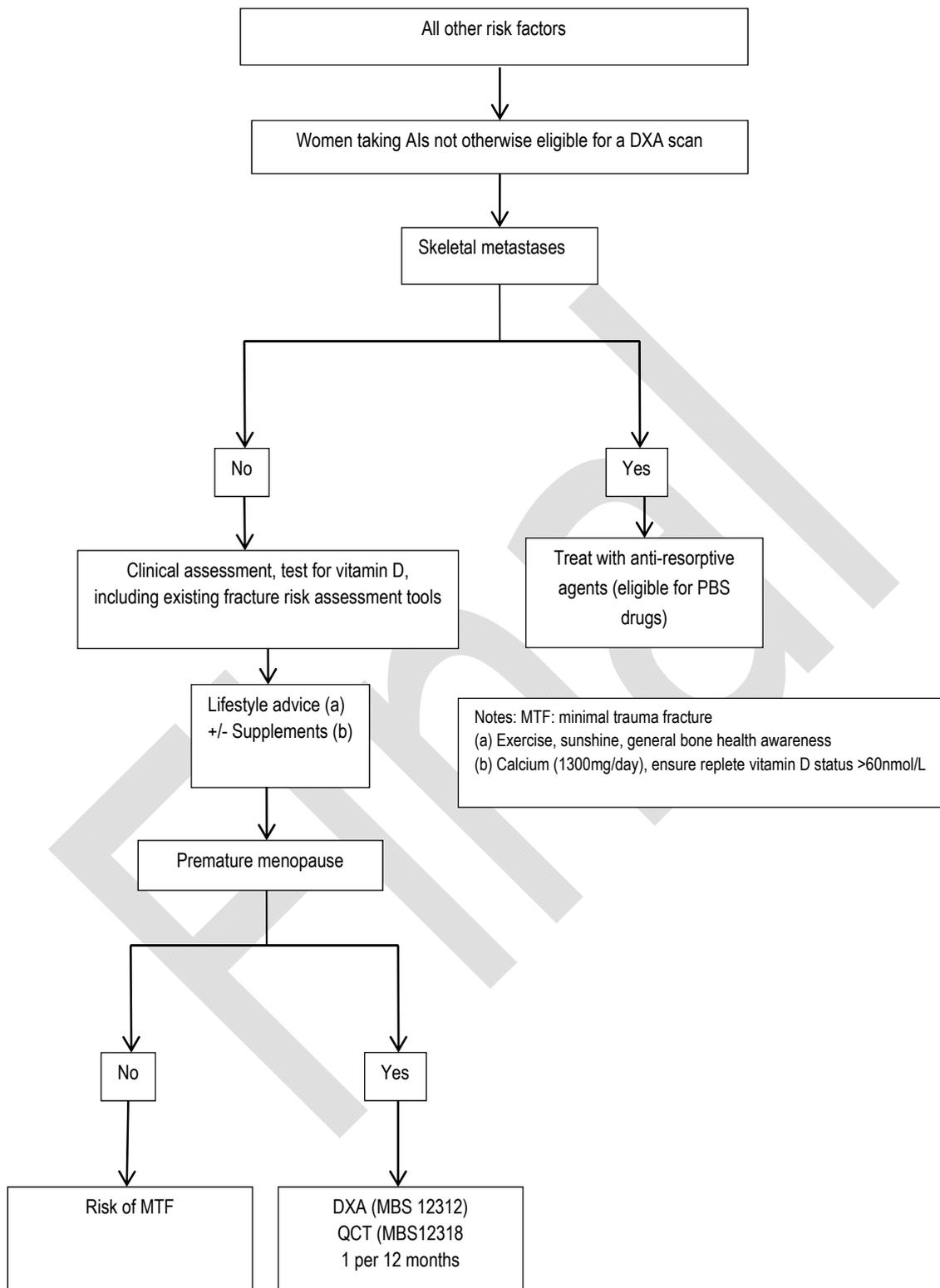
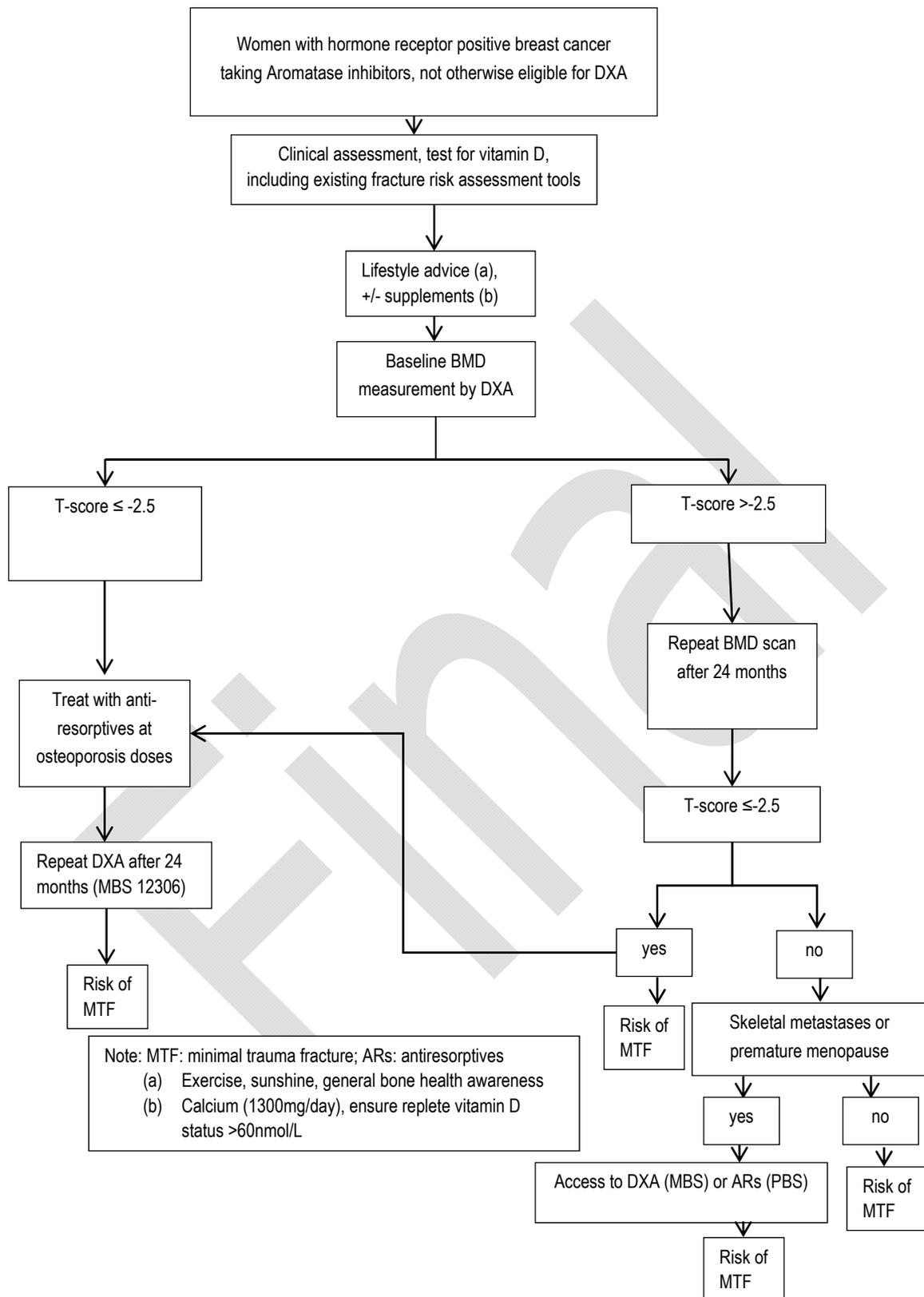


Figure 3 Proposed clinical management algorithm of breast cancer patients receiving aromatase inhibitor therapy



(Adapted from information provided by the applicant and Reid DM, Doughty J, Eastell R, Heys SD, Howell A, McCloskey EV, Powles T, Selby P, Coleman RE. Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group. Cancer Treat Rev 2008;34:S1–S18)

## Comparator

Currently patients on aromatase inhibitor therapy do not routinely receive DXA scanning covered by the MBS, unless they are 70 years of age or older. Vulnerability to the condition may be predicted through a clinical assessment, including a test for vitamin D sufficiency and the use of existing fracture determinant tools. Determining the probability of 10-year fracture risk can be assessed through use of the FRAX tool (WHO 2007). This tool can be used successfully in combination with DXA results, or without DXA as a predictor of risk of fracture.

Part of the population may take dietary and lifestyle measures to promote good bone health, including supplements (calcium and vitamin D), without a bone mineral density test. These supplements are available without prescription.

The comparator is:

- Lifestyle and dietary advice (calcium and vitamin D) based on a clinical assessment by a general practitioner using existing fracture risk assessment tools (for example the FRAX tool) without the results of a bone mineral density test. This clinical assessment would include a test for vitamin D sufficiency (MBS item 66608).

## Clinical claim

The applicant makes the clinical claim that the proposed intervention will reduce the incidence of fractures in patients taking aromatase inhibitors thereby reducing harm to patients and costs of treatment downstream.

PASC agreed that the assessment of evidence will need to report the effectiveness of the co-dependent medicines in the proportion of the target population for BMD testing who achieve a threshold result to trigger the initiation of prescribed medication.

Table 6 Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness (DXA scanning, AI) versus comparator				
		<u>Superior</u>		<u>Non-inferior</u>	<u>Inferior</u>	
Comparative safety versus comparator	<u>Superior</u>	CEA/CUA		CEA/CUA	<u>Net clinical benefit</u>	CEA/CUA
					<u>Neutral benefit</u>	CEA/CUA*
					<u>Net harms</u>	None <sup>^</sup>
	<u>Non-inferior</u>	CEA/CUA		CEA/CUA*	None <sup>^</sup>	
	<u>Inferior</u>	<u>Net clinical benefit</u>	CEA/CUA	None <sup>^</sup>	None <sup>^</sup>	
		<u>Neutral benefit</u>	CEA/CUA*			
		<u>Net harms</u>	None <sup>^</sup>			

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

\* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

<sup>^</sup> No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

#### Questions for the review relating to the economic evaluation

Cost effectiveness models should be undertaken:

- To establish the baseline scenario: What are the downstream costs and outcomes without the proposed intervention?
- To assess the proposed scenario: What are the downstream costs and outcomes with the proposed intervention?
- As noted throughout the DAP, sensitivity analyses should be undertaken around:
  - The factors, ages and eligibility criteria as specified in the proposal;
  - The variables as advised by the available evidence;
  - The variables as advised by PASC as being informative for sensitivity analyses to inform the final decision making.
  - Specifically, what impact does treatment with aromatase inhibitors have on bone mineral density as a surrogate for minimal trauma fracture? This should include a consideration of the effect of other possible prognostic factors including age and previous treatment with tamoxifen.
- The economic analysis should account for different thresholds for therapy as advised by the available evidence.

- The economic evaluation should account for all patients in the target population who become eligible for current MBS items (for example through age, minimal trauma fracture, skeletal metastases or premature menopause).

## Outcomes and health care resources affected by introduction of proposed intervention

### Outcomes

The body of evidence indicates that administration of AIs in postmenopausal women with hormone receptor positive breast cancer leads to significant decreases in bone mineral density. These side effects are unlikely to affect the use of AIs to treat breast cancer as they are presently considered the gold standard of endocrine therapy. The applicant claims that the proposed MBS item will facilitate the identification of patients with low BMD prior to AI treatment and result in the following:

- Quantify the rate of bone loss during and after treatment with AIs
- Potentially prevent fractures and thus the associated costs to the healthcare system and patient

Primary effectiveness outcomes:

- Incidence of minimal trauma fracture
- Incidence of all fractures
- Patient related quality of life

Secondary effectiveness:

- Change in morbidity/mortality
- Bone mineral density (as measured by T-score, or by Z-score in premenopausal women)

Safety outcomes and adverse events:

- Any adverse event related to scanning or treatments
- Any adverse event arising from exposure to ionising radiation

Please note:

- Incidence of minimal trauma fracture is the main primary outcome; however, for this DAP, PASC considers that bone mineral density loss is an appropriate surrogate for minimal trauma fracture.
- Where possible, the outcome of minimal trauma fracture should be disaggregated to type and location of fracture (eg hip vs non-hip) as this is important to translate to any possible effects on life-years and quality-adjusted life-years.

- The site of the DXA exam (for example, proximal femur, lumbar spine, hip, distal radius) should be reported for all studies where possible. This is to account for any variability related to the site of the body where the testing is conducted.
- Where women are re-tested or monitored, it should be noted whether subsequent tests are undertaken on the same machine, or a different machine but the same model, or at the same or different practice. This is to account for any variability of test results between machines.
- PASC acknowledges that DXA is associated with low radiation doses, but that increasing the availability of DXA may significantly increase the exposure of the proposed population to ionising radiation, especially when this population includes young women. This issue should be addressed in the assessment of evidence.

## Health care resources

In terms of healthcare resource information, all issues and data inputs will be examined and reported in full in the assessment report.

Table 7 List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					Total cost
					MBS	Safety net	Other govt budget	Private health insurer	Patient	
<u>Resources provided to identify eligible population</u>										
- Confirmation of age and risk factor status	GP	public	TBA							
<u>Resources provided to deliver comparator 1</u>										
- GP visit to assess risk and discuss lifestyle management	GP	public								
<u>Resources provided in association with comparator 1 (e.g., pre-treatments, co-administered interventions, resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions)</u>										
- Dietary supplements									Patient cost	
- Costs associated with a fracture	Public or private hospital									
- Costs associated with recovery from a fracture									Patient cost	
- Resource 2, etc										
<u>Resources provided to deliver proposed intervention</u>										
- Dual-Energy X-ray absorptiometry device	Technician	Mainly private, but there may be some public	TBA	1 per patient	MBS					
- GP visit for referral to DXA	GP				MBS					
- GP visit to discuss results and to provide advice	GP				MBS					
<u>Resources provided in association with proposed intervention</u>										
- Dietary supplements									Patient cost	
- Vitamin D test			TBA		Fee \$33.20					
- Treatment with anti-resorptive agents	Pharmacy	Private	Unknown	Variable**	\$37.38 to \$589.17	\$5.60 to \$34.20				
- Costs associated with a fracture	Public or private hospital									
- Costs associated with recovery from a fracture	-	-	-	-	-	-	-	-	- Patient cost	-

## Proposed structure of economic evaluation (decision-analytic)

Table 8 Summary of extended PICO to define research question that assessment will investigate

Patients	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered
<p>Post-menopausal women with breast cancer taking aromatase inhibitors.</p> <p>Women taking aromatase inhibitors who have previously been treated with tamoxifen.</p> <p>Exclude: Women at age 70 and over, with a previous minimal trauma fracture, or currently eligible for MBS items for DXA scanning (e.g. women who have undergone premature menopause).</p>	<p>DXA scan and treatment with a prescription drug at a T-score of <math>\leq -2.5</math>.</p> <p>Follow-up options:</p> <ul style="list-style-type: none"> <li>Sensitivity analyses should investigate options of repeat scanning as advised by the evidence.</li> </ul> <p>Threshold to therapy options for sensitivity analysis:</p> <ul style="list-style-type: none"> <li>T-scores of -1.0, -1.5, -2.0.</li> <li>Sensitivity analyses should investigate other options of threshold to therapy as advised by the evidence.</li> <li>QCT is excluded</li> <li>Different thresholds of access to therapy should be investigated</li> </ul>	<p>Clinical assessment including the use of existing fracture risk assessment tools (including vitamin D test) with lifestyle and dietary advice.</p> <ul style="list-style-type: none"> <li>DXA and QCT are excluded.</li> </ul>	<p>Primary effectiveness outcomes:</p> <ul style="list-style-type: none"> <li>Incidence of minimal trauma fracture</li> <li>Incidence of all fractures</li> <li>Patient related quality of life</li> </ul> <p>Secondary effectiveness:</p> <ul style="list-style-type: none"> <li>Change in morbidity/mortality</li> <li>Bone mineral density (as measured by T-score, or by Z-score in premenopausal women)</li> </ul> <p>Safety outcomes and adverse events:</p> <ul style="list-style-type: none"> <li>Any adverse event related to scanning or treatments</li> <li>Any adverse event arising from exposure to ionising radiation</li> </ul>	Refer to Table 7

Note that lifestyle modification and supplementation may also be recommended for these patients and may be considered a confounding factor at the assessment phase.

PASC has specified a range of questions which will need to be addressed during the assessment phase. These questions will guide the evaluation and have been raised throughout the DAP. The assessment should address the questions raised throughout the DAP in relation to the population and intervention in order to provide MSAC with the necessary information to make an informed decision.

PASC also identified a need to appropriately structure the assessment phase so as to inform on broad issues of testing thresholds and monitoring protocols. Given the number and complexity of the questions for the assessment phase the key components and requests from PASC are summarised in Table 9 below.

**Table 9 Summary of issues relating to the approach to assessment**

<b>Population</b>	Women with breast cancer taking aromatase inhibitors Sub-populations include patients previously treated with tamoxifen.
<b>Context</b>	DXA scanning is proposed for women with breast cancer who are being considered for, or are being treated with, aromatase inhibitors and who are not otherwise eligible for a DXA scan. PASC has identified the need to collect evidence around the rate of bone loss in patients who are treatment naïve, patients who are aromatase inhibitor naïve and patients who have been on aromatase inhibitors for some time. Where available, the assessment phase should present evidence on these patient groups separately. In the context of this DAP the patient population is women who are being treated with aromatase inhibitors. At the assessment phase this patient population should be further stratified to identify relevant outcomes for: <ul style="list-style-type: none"> <li>• Post-menopausal women with breast cancer currently taking aromatase inhibitors.</li> <li>• Women taking aromatase inhibitors who have previously been treated with.</li> </ul> PASC has also identified a need to compare the rate of bone mineral density loss in women taking aromatase inhibitors to a baseline as well as a benchmark population.
<b>Baseline population</b>	The baseline population is postmenopausal women. The baseline population should align in terms of age with the target population.
<b>Benchmark population</b>	The benchmark population is people being treated with long-term glucocorticoid therapy. The benchmark population should align in terms of age with the target population.
<b>Approach to assessment</b>	The assessment phase should present evidence to define: <ul style="list-style-type: none"> <li>• The rate of bone loss for women on aromatase inhibitors taking anti-resorptive agents</li> <li>• The rate of bone loss for women on aromatase inhibitors not taking anti-resorptives</li> <li>• The rate of bone loss in women following menopause.</li> </ul> The assessment phase should also present evidence to inform on the baseline risk of MTF in the proposed population as compared to the baseline and benchmark populations as well as in women taking aromatase inhibitors but not co-dependent medicines. This will be used to inform the cost effectiveness analysis.
<b>Intervention</b>	DXA test with therapy for women who meet the threshold (for women with T-scores $\leq -2.5$ )
<b>Context</b>	The proposed test is DXA The proposed therapy is anti-resorptive medications
<b>Co-dependency</b>	There is a co-dependency for this DAP and the assessment of evidence will be required to present evidence with regards to the efficacy of the co-dependent medicines in the proportion of the target population for BMD testing who achieve a threshold result to trigger the initiation of prescribed medication. At this stage no co-dependent submission has been received.
<b>Treatment threshold</b>	The proposed threshold for therapy is T-score of less than -2.5
<b>Context</b>	PASC has identified a need to assess various thresholds for therapy in an evidence based manner.
<b>Approach to assessment</b>	The assessment phase will be required to present evidence and conduct a sensitivity analysis to examine various thresholds for initiating therapy. The assessment should examine the following thresholds: <ul style="list-style-type: none"> <li>• T-score <math>\leq -1.5</math> (PBS eligibility for patients on glucocorticoid therapy)</li> <li>• T-score <math>\leq -2.0</math></li> <li>• T-score <math>\leq -2.5</math> (ARTG accessibility for bisphosphonates and denosumab)</li> </ul>
<b>Re-testing and monitoring</b>	Patients taking glucocorticoid therapy are currently eligible for annual retesting under MBS item 12312
<b>Context</b>	PASC noted that whilst patients are taking aromatase inhibitors with or without anti-resorptives they will remain at an elevated risk and thus will require monitoring.
<b>Approach to assessment</b>	The assessment phase is required to provide evidence to inform the question of with what frequency re-testing and monitoring should occur in the population of interest. This should include information on the: <ul style="list-style-type: none"> <li>• rate of bone loss in patients taking aromatase inhibitors but not anti-resorptives (re-testing)</li> <li>• rate of bone loss in patients taking aromatase inhibitors and anti-resorptives (monitoring)</li> </ul> This information will inform the appropriate rate of re-testing in the proportion of the population who do not reach the threshold for therapy at their initial test <i>and</i> the appropriate schedule of monitoring in the proportion of the population which has initiated therapy following their initial test.
<b>Comparator</b>	Lifestyle and dietary advice (calcium and vitamin D) based on a general clinical assessment by a general practitioner using existing fracture risk assessment tools (for example the FRAX tool) without the results of a bone mineral density test. This clinical assessment would include a test for vitamin D sufficiency (MBS item 66608).

Outcomes	<p>Outcomes include primary effectiveness, secondary effectiveness and safety outcomes.</p> <p>Primary effectiveness outcomes:</p> <ul style="list-style-type: none"> <li>• Incidence of minimal trauma fracture</li> <li>• Incidence of all fractures</li> <li>• Patient related quality of life</li> </ul> <p>Secondary effectiveness:</p> <ul style="list-style-type: none"> <li>• Change in morbidity/mortality</li> <li>• Bone mineral density (as measured by T-score, or by Z-score in premenopausal women)</li> </ul> <p>Safety outcomes and adverse events:</p> <ul style="list-style-type: none"> <li>• Any adverse event related to scanning or treatments</li> <li>• Any adverse event arising from exposure to ionising radiation</li> </ul> <p>Note that it will be important to report all outcomes according to patient age and time of treatment with aromatase inhibitors.</p>
Context	PASC has stated that change in BMD as measured by a T-score or Z-score is an acceptable surrogate marker for the risk of MTF.
Approach to assessment	<p>Where possible, the outcome of minimal trauma fracture should be disaggregated to type and location of fracture (e.g. hip vs non-hip) as this is important to translate to any possible effects on life-years and quality-adjusted life-years.</p> <p>The location of the DXA exam (for example, proximal femur, lumbar spine, hip, distal radius) should be reported for all studies where possible.</p> <p>Where women are re-tested, it should be noted whether subsequent tests are undertaken on the same machine, or a different machine but the same model, or at the same or different practice.</p> <p>PASC acknowledges that DXA is associated with low radiation doses, but that increasing the availability of DXA may significantly increase the exposure of the proposed population of otherwise healthy women to ionising radiation. This issue should be addressed in the assessment of evidence.</p> <p>Any evidence relating to the proportion of women in the target population who will have a T-score below the proposed threshold should be reported.</p> <p>Outcomes should be separated according to subpopulations if possible.</p>

## Clinical research questions for public funding

- Is the proposed population of women being treated with aromatase inhibitors, at greater risk of minimal trauma fracture than the baseline population?
- What is the safety of DXA and management of bone mineral density compared with no DXA and no bone loss management in women taking AIs? This question should be applied to each of the specified populations:
  - Post-menopausal women with breast cancer taking aromatase inhibitors
  - Women taking aromatase inhibitors who have previously been treated with tamoxifen.
- What is the effectiveness of DXA and management of bone mineral density compared with no DXA and no bone loss management in women taking AIs? What are the long term effects of treatment on the incidence of minimal trauma fracture? These questions should be applied to each of the specified populations:
  - Post-menopausal women with breast cancer taking aromatase inhibitors
  - Women taking aromatase inhibitors who have previously been treated with tamoxifen.

- What is the cost effectiveness of DXA and management of bone mineral density compared with no DXA and no bone loss management in women taking AIs? This question should be applied to each of the specified populations:
  - Post-menopausal women with breast cancer taking aromatase inhibitors
  - Women taking aromatase inhibitors who have previously been treated with tamoxifen.
  - Sensitivity analyses should be undertaken to provide information on the range of variables identified throughout this DAP.
- Secondary clinical research questions include:
- What is the appropriate threshold T-score to trigger anti-resorptive treatment in women taking aromatase inhibitors?
- For patients reaching the threshold T-score and subsequently being treated with anti-resorptive therapy, with what frequency should women receive a repeat DXA scan?
- For patients not reaching the threshold T-score for therapy at their initial test, with what frequency should women undergo repeat testing?

PASC is interested to define the baseline fracture rate and bone mineral density loss in the proposed population, how this differs from fracture rate and BMD loss in the broader population with age, and how a specific intervention (scanning and medication) can improve bone loss outcomes. Ideally the main outcome measure should be fracture rate. In the absence of this information change in BMD as measured by a T-score or Z-score is an acceptable surrogate marker for the risk of MTF.

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## Appendix 1 Examples of treatments currently listed on the ARTG for the treatment of osteoporosis

ARTG number	Product name	Approved indication
<b>Selective oestrogen receptor modulators (SERMs)</b>		
161797	Femarelle	Standard: For the symptomatic relief of menopause. Specific: Maintenance of bone health.
64709	Evista	Evista is indicated for the prevention and treatment of osteoporosis in post-menopausal women. Evista is indicated for the reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis. Evista is indicated for the reduction in the risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer.
<b>Bisphosphonates</b>		
ARTG number	Product name	Approved indication
113482,120028,136846,157805, 161137, 53158, 54380, 67262, 68428, 73520, 73772, 76851, 93333, 98944	Fosamax	Specific: Treatment of osteoporosis in postmenopausal women to prevent fractures, including those of the hip and spine (vertebral compression fractures) and to help ensure vitamin D adequacy and/or to reduce the risk of Vitamin D insufficiency. Treatment of osteoporosis in men to prevent fractures and to help ensure vitamin D adequacy and/or to reduce the risk of Vitamin D insufficiency indicated for the treatment of Paget's disease of bone in men & women.
46852	Didrocal	Specific: Treatment of osteoporosis. Osteoporosis must be confirmed by the finding of low bone mass (at least two standard deviations below the gender-specific mean for young adults) or by the presence or history of osteoporotic fracture. Prevention of bone loss in patients for whom long-term treatment with high-dose corticosteroids is either about to be commenced or has been recently initiated
117667, 138211, 141530, 150618, 166838, 166853, 166942,74135, 74136, 82746	Actonel	Specific: Treatment of osteoporosis. Treatment of glucocorticoid-induced osteoporosis. Preservation of bone mineral density in patients on long-term corticosteroid therapy.
134664	Aclasta	Specific: Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures. - Treatment of osteoporosis in patients over 50 years of age with a history of at least one low trauma hip fracture, to reduce the incidence of further fractures. - To increase bone mineral density in men with osteoporosis. - To increase bone mineral density in patients with osteoporosis associated with long term glucocorticoid use. To prevent glucocorticoid-induced bone mineral density loss. - Treatment of Paget's

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disease of bone.

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**Monoclonal antibodies**

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ARTG number	Product name	Approved indication
159322, 159323, 159324	Denosumab	The treatment of osteoporosis in postmenopausal women. Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.

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**Parathyroid hormone**

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ARTG number	Product name	Approved indication
80333	Teriparatide	indicated for the treatment of osteoporosis in postmenopausal women and the treatment of primary osteoporosis in men when other agents are considered unsuitable and when there is a high risk of fractures. Teriparatide is indicated for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at high risk for fracture.

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**Strontium ranelate**

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ARTG number	Product name	Approved indication
99978	Strontium ranelate (Protos)	Treatment of postmenopausal osteoporosis to reduce the risk of fracture. Treatment of osteoporosis in men at increased risk of fracture.

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Source: Australian Register of Therapeutic Goods (ARTG) searched on 01/08/2012 < <https://www.ebs.tga.gov.au/>>

## Appendix 2 Indications, contraindications and potential complications of the co-administered interventions

### Co-administered interventions

**Bisphosphonates; Alendronate (Fosamax), Disodium etidronate (Dirrocal), Risedronate (Actonel), Zoledronic Acid (Aclasta)**

*[prevention (Grade A), treatment (Grade A)]*

ARTG: Fosamax: 113482,120028,136846,157805, 161137, 53158, 54380, 67262, 68428, 73520, 73772, 76851, 93333, 98944; Dirrocal: 46852; Actonel: 117667, 138211, 141530, 150618, 166838, 166853, 166942,74135, 74136, 82746; Aclasta: 134664; Clodronate: 181921, 181922, 66703, 66704, 80125, 80130

Indication	Contraindication	Side effects
<p>Paget's disease of bone</p> <p>Prevention and treatment of osteoporosis (including postmenopausal and corticosteroid-induced)</p> <p>Hypercalcaemia of malignancy</p> <p>Prevention of skeletal-related events in patients with malignancies involving bone</p> <p>Prevention and treatment of heterotopic ossification due to spinal cord injury or complicating total hip replacement</p>	<p>Abnormalities of the oesophagus which delay oesophageal emptying, such as stricture or achalasia.</p> <p>Inability to stand or sit upright for at least 30 minutes.</p> <p>Hypersensitivity to any component of bisphosphonates.</p> <p>Hypocalcaemia.</p> <p>Severe hypercalciuria.</p>	<p><i>Common</i></p> <p>nausea, vomiting, diarrhoea, headache, hypocalcaemia, musculoskeletal pain (may rarely be severe and/or disabling)</p> <p>IV: fever, flu-like symptoms, injection site reaction, increased creatinine concentration, hypophosphataemia, myalgia, bone pain, hypertension</p> <p><i>Infrequent</i></p> <p>oesophagitis, oesophageal erosions and ulcers (mainly with alendronate), gastritis, duodenitis, glossitis, rash</p> <p>IV: hypotension, hypomagnesaemia, hypokalaemia</p> <p><i>Rare</i></p> <p>heart failure, renal impairment, ocular inflammation, osteonecrosis of the jaw, allergic reactions including angioedema</p> <p>IV: anaphylactic shock</p> <p><i>*Osteonecrosis of the jaw</i></p> <p>Risk appears to be associated with the potency, route and total dose of bisphosphonate and a history of dental surgery, trauma or disease.</p> <p><i>Possible associations</i></p> <p>Atypical low-energy femoral fractures have occurred rarely during long-term bisphosphonate treatment for osteoporosis. It is possible that bisphosphonates slightly increase the risk of AF, although this association was not found in all studies. Some epidemiological data suggest an association between long-term use of oral bisphosphonates and an increased risk of oesophageal cancer; further evidence is needed.</p>

### Hormone Replacement Therapy

*[prevention (Grade A), treatment (Grade A)]*

Indication	Contraindication	Side effects
Prevention of postmenopausal osteoporosis when there is a high risk of fractures and alternative treatment is inappropriate	Breast cancer or other oestrogen-dependent tumour. Unexplained vaginal bleeding. History of endometriosis Uterine fibroids Migraine—may be exacerbated or relieved. Diabetes—HRT may improve glycaemic control Epilepsy Treatment with enzyme-inducing drugs Smoking Systemic lupus erythematosus Hereditary angioedema	<i>Common</i> breast enlargement and tenderness, abnormal mammogram, headache, depression, change in libido, irregular or breakthrough bleeding, spotting, endometrial hyperplasia (oestrogen-only HRT; infrequent with combined HRT), leg cramps, dry eye syndrome (oestrogen-only HRT; infrequent with combined HRT)  <i>Infrequent</i> benign proliferative breast disease, breast cancer, premenstrual-like syndrome, dementia, migraine, cardiovascular events, fluid retention, oedema, increased BP, exacerbation or recurrence of endometriosis, acne, itch, nausea, increased triglycerides, gall stones  <i>Rare</i> cholestatic jaundice, pancreatitis, glucose intolerance, galactorrhoea, visual changes, chloasma, hypersensitivity (angioedema, urticaria), ovarian cancer, endometrial cancer, enlargement of uterine fibroids, enlargement of hepatic haemangiomas

**Selective oestrogen receptor modulators (SERMs); Raloxifene hydrochloride ( Evista)**  
**[treatment (Grade A)]**

ARTG: Evista: 64709; Femarelle: 161797

Indication	Contraindication	Side effects
For the symptomatic relief of menopause.  Maintenance of bone health, indicated for the prevention and treatment of osteoporosis.  Hormone receptor-positive breast cancer	Venous thromboembolism (VTE) — contraindicated in patients with a history of VTE or risk factors for VTE . Prolonged immobilisation—increases risk of VTE. Women with or at risk of coronary heart disease—increased risk of VTE or fatal stroke. History of hypertriglyceridaemia induced by oestrogens—increased risk of hypertriglyceridaemia. History of breast cancer—raloxifene is not indicated for treating, or reducing risk of recurrence of, breast cancer. hepatic impairment Surgery Pregnancy Breastfeeding Contraindicated.	<i>Common</i> hot flushes, sweating, leg cramps, peripheral oedema, sleep disorders  <i>Infrequent</i> VTE

**Monoclonal antibodies; Denosumab (Prolia)**

ARTG: 159322,159323, 159324

Indication	Contraindication	Side effects
Treatment of postmenopausal osteoporosis	Hypocalcaemia Renal increased risk of hypocalcaemia	<i>Common</i> eczema, hypercholesterolaemia

if CrCl <30 mL/minute.

*Infrequent*  
skin infections (mainly cellulitis)

*Rare*  
hypocalcaemia, osteonecrosis of the jaw

**Teriparatide (Forteo) (parathyroid hormone) [treatment – (Grade A)]**

ARTG: 80333

Indication	Contraindication	Side effects
Postmenopausal osteoporosis when there is a high risk of fractures and other agents are unsuitable	Paget's disease of bone Hyperparathyroidism Urolithiasis, hypercalcaemia Skeletal malignancies, history of skeletal radiation treatment, unexplained increases in ALP—manufacturer discourages use.	<i>Common</i> nausea, headache, dizziness, muscle cramp, arthralgia, hyperuricaemia, injection site reactions
Primary osteoporosis in men when there is a high risk of fractures and other agents are unsuitable	Treatment with alendronate—may reduce the effectiveness of teriparatide; combination not recommended. Effect of combination with other bisphosphonates is not known.	<i>Infrequent</i> hypercalcaemia, myalgia, increased ALP
Corticosteroid-induced osteoporosis in patients at high risk of fractures	Renal Limited clinical experience in renal impairment; avoid if CrCl <30mL/minute. manufacturer discourages use in children and young adults with open epiphyses. Avoid in women planning to conceive or who are not using adequate contraception. Pregnancy Breastfeeding	<i>Rare</i> allergic reactions

**Strontium Ranelate (Protos)**

[treatment – (Grade A)]

Indication	Contraindication	Side effects
Treatment of postmenopausal osteoporosis to reduce the risk of fracture.	Known hypersensitivity to strontium ranelate or to any of the excipients	<i>Common</i> Headache, disturbances in consciousness, memory loss, nausea, diarrhoea, loose stools, venous thromboembolism, blood creatinine phosphokinase (CPK) increase
Treatment of osteoporosis in men at increased risk of fracture.	Severe renal impairment (see Pharmacokinetics – Special Populations)  Current or previous venous thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism.  Temporary or permanent immobilisation (e.g. post-surgical recovery or prolonged bed rest).um ranelate or to any of the excipients  Severe renal impairment (see Pharmacokinetics – Special Populations)  Current or previous venous	<i>Uncommon</i> Seizures.

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thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism.

· Temporary or permanent immobilisation (e.g. post-surgical recovery or prolonged bed rest).

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**Calcium and vitamin D** [prevention (Grade C), treatment (Grade C)]

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<b>Indication</b>	<b>Contraindication</b>	<b>Side effects</b>
Calcium; Adjunctive treatment in osteoporosis	Hypercalcaemia Hypercalciuria, history of nephrolithiasis	<i>Common</i> belching, flatulence, abdominal distension, constipation
Vitamin D; Treatment of osteoporosis, when vitamin D supplementation is recommended	Treatment with digoxin Treatment with calcitriol Decreased gastric acidity Phenylketonuria Sodium restriction Renal Monitor plasma calcium concentration in renal impairment; if necessary, reduce dosage or stop.	<i>Infrequent</i> hypercalcaemia, alkalosis, hypophosphataemia  <i>Rare</i> renal calculi, milk-alkali syndrome IV skin necrosis (extravasation), irritation
	Vitamin D; Hyperphosphataemia (Vitamin D only)	Vitamin D; hypercalcaemia, renal and cardiovascular damage may occur because of ectopic calcification.

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All information obtained from the Australian Medicines Handbook (AMH), January 2012 or the RACGP clinical guidelines 2010b

## Appendix 3 PBS listed pharmaceuticals (by drug) for the treatment of diseases of bone structure and mineralisation

Drug	strength	Indication code	Specific indication	BMD / T-score
Bisphosphonates				
Alendronate Sodium	40 mg alendronic acid	3256	Symptomatic Paget disease of bone	N/A
	70 mg alendronic acid	4122	Corticosteroid-induced osteoporosis in a patient currently on long-term ( $\geq 3$ months), high-dose (7.5 mg/day prednisolone or equivalent) corticosteroid therapy.  Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.  Duration and dose of corticosteroid therapy together with 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.	$\leq -1.5$
		4133	Osteoporosis in a patient aged 70 years or older.  Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.  Date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement must be documented in the	$\leq -2.5$

			patient's medical records when treatment is initiated.	
		4123	<p>Established osteoporosis in a patient with fracture due to minimal trauma.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>Fracture must have been demonstrated radiologically and the year of plain x-ray, CT or MRI scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a <math>\geq 20\%</math> reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body or a <math>\geq 20\%</math> reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.</p>	N/A
Alendronate Sodium with Colecalciferol	70 mg alendronic acid + 70 micrograms colecalciferol	N/A	For preservation of bone mineral density in patients on long-term glucocorticoid therapy where patients are undergoing continuous treatment with a dose $\geq 7.5$ mg of prednisone or equivalent per day. Prescribers need to demonstrate that the patient has been on continuous therapy for $\geq 3$ months and demonstrate that the patient is osteopenic.	$< -1.0$
		4070	<p>Corticosteroid-induced osteoporosis in a patient currently on long-term (<math>\geq 3</math> months), high-dose (7.5 mg/day prednisolone or equivalent) corticosteroid therapy.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>Duration and dose of corticosteroid therapy together with 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.</p>	$\leq -1.5$

		4087	<p>Osteoporosis in a patient aged 70 years or older.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>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.</p>	≤-2.5
		4087	<p>Established osteoporosis in a patient with fracture due to minimal trauma.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>Fracture must have been demonstrated radiologically and the year of plain x-ray, CT or MRI scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a ≥20% reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body or a ≥ 20% reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.</p>	N/A
	70 mg + 140 microg	N/A	For preservation of bone mineral density in patients on long-term glucocorticoid therapy where patients are undergoing continuous treatment with a dose ≥7.5 mg of prednisone or equivalent per day. Prescribers need to demonstrate that the patient has been on continuous therapy for ≥ 3 months and demonstrate that the patient is osteopenic.	<-1.0
		4122	Corticosteroid-induced osteoporosis in a patient currently on long-term (≥ 3 months), high-dose (7.5 mg/day prednisolone or equivalent) corticosteroid therapy.	≤-1.5

		<p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>Duration and dose of corticosteroid therapy together with 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.</p>	
	4133	<p>Osteoporosis in a patient aged 70 years or older.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>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.</p>	≤-2.5
	4123	<p>Established osteoporosis in a patient with fracture due to minimal trauma.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>Fracture must have been demonstrated radiologically and the year of plain x-ray, CT or MRI scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a ≥20% reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body or a ≥ 20% reduction in any of these heights compared to the vertebral body above or below the affected vertebral body</p>	N/A

Alendronate Sodium with Colecalciferol and Calcium Carbonate	70 mg + 140 microg + 500 mg	N/A	For preservation of bone mineral density in patients on long-term glucocorticoid therapy where patients are undergoing continuous treatment with a dose $\geq 7.5$ mg of prednisone or equivalent per day. Prescribers need to demonstrate that the patient has been on continuous therapy for $\geq 3$ months and demonstrate that the patient is osteopenic.	<-1.0
		4122	<p>Corticosteroid-induced osteoporosis in a patient currently on long-term (<math>\geq 3</math> months), high-dose (7.5 mg/day prednisolone or equivalent) corticosteroid therapy.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>Duration and dose of corticosteroid therapy together with 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.</p>	$\leq -1.5$
		4133	<p>Osteoporosis in a patient aged 70 years or older.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>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.</p>	$\leq -2.5$
		4123	<p>Established osteoporosis in a patient with fracture due to minimal trauma.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this</p>	N/A

			<p>condition.</p> <p>Fracture must have been demonstrated radiologically and the year of plain x-ray, CT or MRI scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a <math>\geq 20\%</math> reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body or a <math>\geq 20\%</math> reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.</p>	
Risedronate Sodium	5 mg	N/R	For preservation of bone mineral density in patients on long-term glucocorticoid therapy where patients are undergoing continuous treatment with a dose $\geq 7.5$ mg of prednisone or equivalent per day. Prescribers need to demonstrate that the patient has been on continuous therapy for $\geq 3$ months and demonstrate that the patient is osteopenic.	$< -1.0$
		4122	Corticosteroid-induced osteoporosis in a patient currently on long-term ( $\geq 3$ months), high-dose (7.5 mg/day prednisolone or equivalent) corticosteroid therapy.	$\leq -1.5$
		4117	<p>Osteoporosis in a patient aged 70 years or older.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>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.</p>	$\leq -3.0$
		4123	<p>Established osteoporosis in a patient with fracture due to minimal trauma.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this</p>	N/A

			<p>condition.</p> <p>Fracture must have been demonstrated radiologically and the year of plain x-ray, CT or MRI scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a <math>\geq 20\%</math> reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body or a <math>\geq 20\%</math> reduction in any of these heights compared to the vertebral body above or below the affected vertebral body</p>	
	30 mg	3256	Symptomatic Paget disease of bone	N/A
	35 mg	N/R	For preservation of bone mineral density in patients on long-term glucocorticoid therapy where patients are undergoing continuous treatment with a dose equal to or greater than 7.5 mg of prednisone or equivalent per day. Prescribers need to demonstrate that the patient has been on continuous therapy for 3 months or more and demonstrate that the patient is osteopenic.	<-1.0
		4122	Corticosteroid-induced osteoporosis in a patient currently on long-term ( $\geq 3$ months), high-dose (7.5 mg/day prednisolone or equivalent) corticosteroid therapy.	$\leq -1.5$
		4117	<p>Osteoporosis in a patient aged 70 years or older.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>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.</p>	$\leq -3.0$
		4123	Established osteoporosis in a patient with fracture due to minimal trauma.	N/A

			<p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>Fracture must have been demonstrated radiologically and the year of plain x-ray, CT or MRI scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a <math>\geq 20\%</math> reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body or a <math>\geq 20\%</math> reduction in any of these heights compared to the vertebral body above or below the affected vertebral body</p>	
	Tablet 35 mg (enteric coated)	N/A	<p>For preservation of bone mineral density in patients on long-term glucocorticoid therapy where patients are undergoing continuous treatment with a dose equal to or greater than 7.5 mg of prednisone or equivalent per day. Prescribers need to demonstrate that the patient has been on continuous therapy for 3 months or more and demonstrate that the patient is osteopenic.</p>	$\leq -1.0$
		4122	<p>Corticosteroid-induced osteoporosis in a patient currently on long-term (<math>\geq 3</math> months), high-dose (7.5 mg/day prednisolone or equivalent) corticosteroid therapy.</p>	$\leq -1.5$
		4117	<p>Osteoporosis in a patient aged 70 years or older.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>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.</p>	$\leq -3.0$
		4123	<p>Established osteoporosis in a patient with fracture due to minimal trauma.</p>	N/A

			<p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>Fracture must have been demonstrated radiologically and the year of plain x-ray, CT or MRI scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a <math>\geq 20\%</math> reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body or a <math>\geq 20\%</math> reduction in any of these heights compared to the vertebral body above or below the affected vertebral body</p>	
	150 mg	4122	Corticosteroid-induced osteoporosis in a patient currently on long-term ( $\geq 3$ months), high-dose (7.5 mg/day prednisolone or equivalent) corticosteroid therapy.	$\leq -1.5$
		4117	<p>Osteoporosis in a patient aged 70 years or older.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>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.</p>	$\leq -3.0$
		4123	<p>Established osteoporosis in a patient with fracture due to minimal trauma.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p>	N/A

			<p>Fracture must have been demonstrated radiologically and the year of plain x-ray, CT or MRI scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a <math>\geq 20\%</math> reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body or a <math>\geq 20\%</math> reduction in any of these heights compared to the vertebral body above or below the affected vertebral body</p>	
Risedronate Sodium and Calcium Carbonate	35 mg + 500 mg	N/R	For preservation of bone mineral density in patients on long-term glucocorticoid therapy where patients are undergoing continuous treatment with a dose equal to or greater than 7.5 mg of prednisone or equivalent per day. Prescribers need to demonstrate that the patient has been on continuous therapy for 3 months or more and demonstrate that the patient is osteopenic.	<-1.0
		4122	Corticosteroid-induced osteoporosis in a patient currently on long-term ( $\geq 3$ months), high-dose (7.5 mg/day prednisolone or equivalent) corticosteroid therapy.	$\leq -1.5$
		4117	<p>Osteoporosis in a patient aged 70 years or older.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>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.</p>	$\leq -3.0$
		4123	<p>Established osteoporosis in a patient with fracture due to minimal trauma.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p>	N/A

			<p>Fracture must have been demonstrated radiologically and the year of plain x-ray, CT or MRI scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a <math>\geq 20\%</math> reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body or a <math>\geq 20\%</math> reduction in any of these heights compared to the vertebral body above or below the affected vertebral body</p>	
	35 mg + 1.25g (enteric coated)	N/A	For preservation of bone mineral density in patients on long-term glucocorticoid therapy where patients are undergoing continuous treatment with a dose equal to or greater than 7.5 mg of prednisone or equivalent per day. Prescribers need to demonstrate that the patient has been on continuous therapy for 3 months or more and demonstrate that the patient is osteopenic.	<-1.0
		4122	Corticosteroid-induced osteoporosis in a patient currently on long-term ( $\geq 3$ months), high-dose (7.5 mg/day prednisolone or equivalent) corticosteroid therapy.	$\leq -1.5$
		4117	<p>Osteoporosis in a patient aged 70 years or older.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>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.</p>	$\leq -3.0$
		4123	<p>Established osteoporosis in a patient with fracture due to minimal trauma.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p>	N/A

			<p>Fracture must have been demonstrated radiologically and the year of plain x-ray, CT or MRI scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a <math>\geq 20\%</math> reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body or a <math>\geq 20\%</math> reduction in any of these heights compared to the vertebral body above or below the affected vertebral body</p>	
Risedronate Sodium and Calcium Carbonate with Colecalciferol	35 mg + 2.5 g + 22 microg	N/R	<p>For preservation of bone mineral density in patients on long-term glucocorticoid therapy where patients are undergoing continuous treatment with a dose equal to or greater than 7.5 mg of prednisone or equivalent per day.</p> <p>Prescribers need to demonstrate that the patient has been on continuous therapy for 3 months or more and demonstrate that the patient is osteopenic.</p>	<-1.0
		4122	Corticosteroid-induced osteoporosis in a patient currently on long-term ( $\geq 3$ months), high-dose (7.5 mg/day prednisolone or equivalent) corticosteroid therapy.	$\leq -1.5$
		4117	<p>Osteoporosis in a patient aged 70 years or older.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this condition.</p> <p>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.</p>	$\leq -3.0$
		4123	<p>Established osteoporosis in a patient with fracture due to minimal trauma.</p> <p>Patient must not receive concomitant treatment with any other PBS-subscribed anti-resorptive agent for this</p>	N/A

			<p>condition.</p> <p>Fracture must have been demonstrated radiologically and the year of plain x-ray, CT or MRI scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a <math>\geq 20\%</math> reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body or a <math>\geq 20\%</math> reduction in any of these heights compared to the vertebral body above or below the affected vertebral body</p>	
Disodium Etidronate	200 mg	3257	Paget disease of bone when calcitonin has been found to be unsatisfactory due to lack of efficacy	N/A
		3258	Paget disease of bone when calcitonin has been found to be unsatisfactory due to unacceptable side effects	
		1153	Heterotopic ossification	
Disodium Etidronate and Calcium Carbonate	200 mg + 1.25g	2646	Established osteoporosis in patients with fracture due to minimal trauma	N/A
Disodium Pamidronate	15 mg/5 mL injection, 1 x 5	3341	Hypercalcaemia of malignancy refractory to anti-neoplastic therapy	N/A
	30 mg/10 mL injection, 1 x 10 mL vial	3341	Hypercalcaemia of malignancy refractory to anti-neoplastic therapy	N/A
	60 mg/10 mL injection, 1 x 10 mL vial	3341	Hypercalcaemia of malignancy refractory to anti-neoplastic therapy	N/A

	90 mg	3341	Hypercalcaemia of malignancy refractory to anti-neoplastic therapy	N/A
		3342	Multiple myeloma	
		3343	Bone metastases from breast cancer	
	4 vials powder 15 mg + 4 ampoules solvent 5 ml	3341	Treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy	N/A
	2 vials powder 30 mg + 2 ampoules solvent 10 ml	3256	Paget disease of bone	N/A
		N/R	Treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy	
		3256	Symptomatic Paget disease of bone	
		N/R	Treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy	
	Concentrated injection 15 mg in 5 mL	N/R	Treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy	N/A
		3256	Symptomatic Paget disease of bone	
		N/R	Treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy	
	Concentrated injection 30 mg in 10 mL	N/R	Treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy	N/A
		3256	Symptomatic Paget disease of bone	
		N/R	Treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy	
	Concentrated injection 60 mg in 10 mL	N/R	Treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy	N/A
		3256	Symptomatic Paget disease of bone	
		N/R	Treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy	
	Concentrated injection 90 mg	N/R	Treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy	N/A

	in 10 mL			
	90 mg injection [1 x 90 mg vial] (&) inert substance diluent [1 x 10 mL ampoule], 1 pack	N/R	Hypercalcaemia of malignancy refractory to anti-neoplastic therapy  Multiple myeloma  Bone metastases from breast cancer	N/A
	30 mg injection [2 x 30 mg vials] (&) inert substance diluent [2 x 10 mL ampoules], 1 pack	N/R  3256	Treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy  Symptomatic Paget disease of bone	N/A
	15 mg injection [4 x 15 mg vials] (&) inert substance diluent [4 x 5 mL ampoules]	N/R  3256	Treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy  Symptomatic Paget disease of bone	N/A
Clodronate sodium	400 mg	N/R	Maintenance treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy;  Multiple myeloma	N/A

			Bone metastases from breast cancer	
	800 mg	N/R	Maintenance treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy;  Multiple myeloma  Bone metastases from breast cancer	N/A
-Tiludronate Disodium	200 mg	3256	Symptomatic Paget disease of bone	N/A
-Ibandronic Acid	6 mg/6 mL injection, 1 x 6 mL vial	3343	Bone metastases from breast cancer	N/A
	50 mg	N/R	Bone metastases from breast cancer	N/A
Zoledronic Acid	4 mg/5 mL injection, 1 x 5 mL vial	N/R 3342 3343 4052 3341	Multiple myeloma  Bone metastases from breast cancer  Bone metastases from castration-resistant prostate cancer  Treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy	N/A
	5 mg/100 mL injection, 1 x 100 mL vial	4100	Corticosteroid-induced osteoporosis in a patient currently on (prednisolone or equivalent) corticosteroid therapy.  The Clinical criteria is:  Patient must currently be on long-term (at least 3 months), high-dose (at least 7.5 mg per day prednisolone or	≤-1.5

		<p>equivalent) corticosteroid therapy,</p> <p>AND the Clinical criteria is:</p> <p>Patient must have a Bone Mineral Density (BMD) T-score of -1.5 or less,</p> <p>AND the Clinical criteria is:</p> <p>Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this condition,</p> <p>AND the Clinical criteria is:</p> <p>Patient must not receive more than one PBS-subsidised treatment per year.</p> <p>The duration and dose of corticosteroid therapy together with 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.</p>	
	4149	<p>Osteoporosis</p> <p>The Population criteria is:</p> <p>Patient must be aged 70 years or older,</p> <p>AND the Clinical criteria is:</p> <p>Patient must have a Bone Mineral Density (BMD) T-score of -3.0 or less,</p> <p>AND the Clinical criteria is:</p> <p>Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this</p>	≤-3.0

		<p>condition,</p> <p>AND the Clinical criteria is:</p> <p>Patient must not receive more than one PBS-subsidised treatment per year.</p> <p>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.</p>	
	4157	<p>Established osteoporosis</p> <p>The Clinical criteria is:</p> <p>Patient must have fracture due to minimal trauma,</p> <p>AND the Clinical criteria is:</p> <p>Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this condition,</p> <p>AND the Clinical criteria is:</p> <p>Patient must not receive more than one PBS-subsidised treatment per year.</p> <p>The fracture must have been demonstrated radiologically and the year of plain x-ray or computed tomography (CT) scan or magnetic resonance imaging (MRI) scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.</p>	N/R

		N/R	Symptomatic Paget disease of bone.  Only 1 treatment each year per patient will be PBS-subsidised	
		3947	Osteoporosis in a patient aged 70 years of age or older	≤-3.0
		3946	Established osteoporosis in a patient with fracture due to minimal trauma	N/A
		N/R	Symptomatic Paget disease of bone  Only 1 treatment each year per patient will be PBS-subsidised	N/A
	4 mg/5 mL injection, 1 x 5 mL vial 10 mg	3342	Multiple myeloma	N/A
		3343	Bone metastases from breast cancer	N/A
		4052	Bone metastases from castration-resistant prostate cancer	N/A
		3341	hypercalcaemia of malignancy refractory to anti-neoplastic therapy	N/A
Selective estrogen receptor modulator (SERM)				
raloxifene hydrochloride	60 mg	4071	Established post-menopausal osteoporosis  The Clinical criteria is:  Patient must have fracture due to minimal trauma,  AND the Clinical criteria is:  Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this	N/A

			<p>condition.</p> <p>The fracture must have been demonstrated radiologically and the year of plain x-ray or computed tomography (CT) scan or magnetic resonance imaging (MRI) scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.</p>	
Monoclonal antibody				
Denosumab	120 mg/1.7ml	4158	Bone metastases from breast cancer	N/A
		4150	Bone metastases from castration-resistant prostate cancer	
	60 mg/ml	4094	<p>Osteoporosis</p> <p>The Population criteria is:</p> <p>Patient must be female,</p> <p>AND the Population criteria is:</p> <p>Patient must be aged 70 years or older,</p> <p>AND the Clinical criteria is:</p> <p>Patient must have a Bone Mineral Density (BMD) T-score of -2.5 or less,</p> <p>AND the Clinical criteria is:</p>	<p>≤-2.5</p> <p>N/A</p>

			<p>Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this condition.</p> <p>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.</p>	
		4145	<p>Established post-menopausal osteoporosis</p> <p>The Clinical criteria is:</p> <p>Patient must have fracture due to minimal trauma,</p> <p>AND the Clinical criteria is:</p> <p>Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this condition.</p> <p>The fracture must have been demonstrated radiologically and the year of plain x-ray or computed tomography (CT) scan or magnetic resonance imaging (MRI) scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.</p>	
Carbamazepine	200 mg		<p>Continuing therapy only.</p> <p>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</p>	N/A

			Note For item codes 2419H and 1706T, pharmaceutical benefits that have the form tablet 200 mg are equivalent for the purposes of substitution.	
		N/R	For item codes 5040G and 1724R, pharmaceutical benefits that have the form tablet 200 mg are equivalent for the purposes of substitution.	N/A
Parathyroid Hormone				

Final

Teriparatide	20 microgram/dose injection, 1 x 2.4 mL cartridge	<p>Initial treatment, as the sole PBS-subsidised agent, by a specialist or consultant physician, for severe, established osteoporosis in a patient with a very high risk of fracture who:</p> <p>(a) has a bone mineral density (BMD) T-score of -3.0 or less; and</p> <p>(b) has had 2 or more fractures due to minimal trauma; and</p> <p>(c) has experienced at least 1 symptomatic new fracture after at least 12 months continuous therapy with an anti-resorptive agent at adequate doses.</p> <p>A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.</p> <p>If treatment with anti-resorptive therapy is contraindicated according to the relevant TGA-approved Product Information, details of the contraindication must be provided at the time of application.</p> <p>If an intolerance of a severity necessitating permanent treatment withdrawal develops during the relevant period of use of one anti-resorptive agent, alternate anti-resorptive agents must be trialled so that the patient achieves the minimum requirement of 12 months continuous therapy. Details of accepted toxicities including severity can be found on the Medicare Australia website at <a href="http://www.medicareaustralia.gov.au">www.medicareaustralia.gov.au</a> and must be provided at the time of application.</p> <p>Anti-resorptive therapies for osteoporosis and their adequate doses which will be accepted for the purposes of administering this restriction are alendronate sodium 10 mg per day or 70 mg once weekly, risedronate sodium 5 mg per day or 35 mg once weekly or 150 mg once monthly, raloxifene hydrochloride 60 mg per day (women only), denosumab 60 mg once every 6 months, disodium etidronate 200 mg with calcium carbonate 1.25 g per day, strontium ranelate 2 g per day and zoledronic acid 5 mg per annum.</p> <p>Details of prior anti-resorptive therapy, fracture history including the date(s), site(s), the symptoms associated with</p>	≤-3.0
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			<p>the fracture(s) which developed during the course of anti-resorptive therapy and the score of the qualifying BMD measurement must be provided to Medicare Australia at the time of application.</p> <p>Note</p> <p>No applications for increased maximum quantities and/or repeats will be authorised.</p>	
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			<p>Continuing treatment for severe established osteoporosis where the patient has previously been issued with an authority prescription for this drug.</p> <p>Teriparatide must only be used for a lifetime maximum of 18 months therapy (18 pens). Up to a maximum of 18 pens will be reimbursed through the PBS.</p> <p>Note</p> <p>No applications for increased maximum quantities and/or repeats will be authorised.</p> <p>Continuing treatment for severe established osteoporosis where the patient has previously been issued with an authority prescription for this drug.</p> <p>Teriparatide must only be used for a lifetime maximum of 18 months therapy (18 pens). Up to a maximum of 18 pens will be reimbursed through the PBS.</p> <p>Note</p> <p>No applications for increased maximum quantities and/or repeats will be authorised.</p>	
strontium ranelate	2 g	4117	<p>Osteoporosis</p> <p>The Population criteria is:</p> <p>Patient must be aged 70 years or older,</p>	≤-3.0

		<p>AND the Clinical criteria is:</p> <p>Patient must have a Bone Mineral Density (BMD) T-score of -3.0 or less,</p> <p>AND the Clinical criteria is:</p> <p>Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this condition.</p> <p>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.</p>	
	4123	<p>Established osteoporosis</p> <p>The Clinical criteria is:</p> <p>Patient must have fracture due to minimal trauma,</p> <p>AND the Clinical criteria is:</p> <p>Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this condition.</p> <p>The fracture must have been demonstrated radiologically and the year of plain x-ray or computed tomography (CT) scan or magnetic resonance imaging (MRI) scan must be documented in the patient's medical records when treatment is initiated.</p> <p>A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to</p>	N/A

			the vertebral body above or below the affected vertebral body..	
Calcitriol	0.25 microg	1165	Hypocalcaemia due to renal disease.	N/A
		1166	Hypoparathyroidism.	N/A
		1167	Hypophosphataemic rickets.	N/A
		1467	Vitamin D-resistant rickets.	N/A
		2636	Established osteoporosis in patients with fracture due to minimal trauma.	N/A
1153 Heterotopic ossification.				
1165 Hypocalcaemia due to renal disease.				
1166 Hypoparathyroidism.				
1167 Hypophosphataemic rickets.				
1467 Vitamin D-resistant rickets.				
2636 Treatment for established osteoporosis in patients with fracture due to minimal trauma. The fracture must have been demonstrated radiologically and the year of plain x-ray or CT-scan or MRI				

scan must be documented in the patient's medical records when treatment is initiated.

A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.

2645 Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a patient aged 70 years of age or older with a Bone Mineral Density (BMD) T-score of -3.0 or less. The date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement must be documented in the patient's medical records when treatment is initiated.

2646 Treatment as the sole PBS-subsidised anti-resorptive agent for established osteoporosis in patients with fracture due to minimal trauma. The fracture must have been demonstrated radiologically and the year of plain x-ray or CT-scan or MRI scan must be documented in the patient's medical records when treatment is initiated.

A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.

#### Note

Anti-resorptive agents in established osteoporosis include alendronate sodium, risedronate sodium, denosumab, disodium etidronate, raloxifene hydrochloride, strontium ranelate and zoledronic acid.

2647 Treatment as the sole PBS-subsidised anti-resorptive agent for established post-menopausal osteoporosis in patients with fracture due to minimal trauma. The fracture must have been demonstrated radiologically and the year of plain x-ray or CT-scan or MRI scan must be documented in the patient's medical records when treatment is initiated.

A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in

any of these heights compared to the vertebral body above or below the affected vertebral body.

#### Note

Anti-resorptive agents in established osteoporosis include alendronate sodium, risedronate sodium, denosumab, disodium etidronate, raloxifene hydrochloride, strontium ranelate and zoledronic acid.

2758 Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a woman aged 70 years or older with a bone mineral density (BMD) T-score of -3.0 or less.

The date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement must be documented in the patient's medical records when treatment is initiated.

3070 Treatment as the sole PBS-subsidised anti-resorptive agent for corticosteroid-induced osteoporosis in a patient currently on long-term (at least 3 months), high-dose (at least 7.5 mg per day prednisolone or equivalent) corticosteroid therapy with a Bone Mineral Density (BMD) T-score of -1.5 or less. The duration and dose of corticosteroid therapy together with 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.

3256 Symptomatic Paget disease of bone.

3257 Symptomatic Paget disease of bone when calcitonin has been found to be unsatisfactory due to lack of efficacy

3258 Symptomatic Paget disease of bone when calcitonin has been found to be unsatisfactory due to unacceptable side effects

3341 Treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy

3342 Multiple myeloma

3343 Bone metastases from breast cancer

3256 Symptomatic Paget disease of bone.

3257 Symptomatic Paget disease of bone when calcitonin has been found to be unsatisfactory due to lack of efficacy.

3258 Symptomatic Paget disease of bone when calcitonin has been found to be unsatisfactory due to unacceptable side effects.

3933 Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a patient aged 70 years of age or older with a Bone Mineral Density (BMD) T-score of -2.5 or less. The date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement must be documented in the patient's medical records when treatment is initiated.

3945 Treatment as the sole PBS-subsidised anti-resorptive agent for corticosteroid-induced osteoporosis in a patient currently on long-term (at least 3 months), high-dose (at least 7.5 mg per day prednisolone or equivalent) corticosteroid therapy with a Bone Mineral Density (BMD) T-score of -1.5 or less.

3946 Treatment as the sole PBS-subsidised anti-resorptive agent for established osteoporosis in a patient with fracture due to minimal trauma.

A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.

In all cases, the fracture must have been demonstrated radiologically and the year of plain x-ray or CT-scan or MRI scan must be documented in the patient's medical records when treatment is initiated.

Only 1 treatment each year per patient will be PBS-subsidised.

3947 Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a patient aged 70 years of age or older with a Bone Mineral Density (BMD) T-score of -3.0 or less.

The date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement must be documented in the patient's medical records when treatment is initiated.

Only 1 treatment each year per patient will be PBS-subsidised.

3987

Treatment as the sole PBS-subsidised anti-resorptive agent for established post-menopausal osteoporosis in a woman with fracture due to minimal trauma. The fracture must have been demonstrated radiologically and the year of plain x-ray or CT-scan or MRI scan must be documented in the patient's medical records when treatment is initiated.

A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in

any of these heights compared to the vertebral body above or below the affected vertebral body.

Note

Anti-resorptive agents in established osteoporosis include alendronate sodium, risedronate sodium, denosumab, disodium etidronate, raloxifene hydrochloride, strontium ranelate and zoledronic acid.

4052 Bone metastases from castration-resistant prostate cancer.

4054 Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a woman aged 70 years of age or older with a Bone Mineral Density (BMD) T-score of -2.5 or less.

The date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement must be documented in the patient's medical records when treatment is initiated.

Source: Pharmaceutical Benefits Scheme (PBS) as on 01/09/2012 <<http://www.pbs.gov.au/browse/body-system?depth=3&codes=m05b>>. Authority required to access details of indication for each drug.

## Appendix 4 PBS anti-osteoporotic medication, listed according to eligible indication

Indication	ARTG	PBS (indicated T-score)
Prevention and/or treatment of osteoporosis	Alendronate sodium: 120028, 76851; Risedronate sodium: 141530, 150618, 166838, 166853, 166942, 74135, 82746	No drug specifically indicated
Treatment for established osteoporosis (T-score $\leq$ -2.0) (MBS item 12321)	Alendronate sodium: 76851, 9333, 161137, 73520, 67262, 73772; Disodium etidronate: 46852	No drug specifically indicated
<b>Risk factors for osteoporosis</b>		
Postmenopausal women, with fracture	Alendronate sodium: 157805, 68428, 120028, 53158, 67262, 76851, 98944; Disodium etidronate: 46852; Zoledronic acid: 134664	Raloxifene hydrochloride , Raloxifene hydrochloride (with fractures), Denosumab (with fractures), Strontium ranelate (with fractures)
Previous fractures (including minimal trauma fractures)(MBS item 12306, 12321)	Alendronate sodium: 161137, 67262, 73772, 76851, 93333, 98944; Zoledronic acid: 134664	Alendronate sodium , Alendronate sodium with Colecalciferol , Alendronate sodium with Colecalciferol and Calcium carbonate , Risedronate sodium , Risedronate sodium and Calcium carbonate , Risedronate sodium and Calcium carbonate with Colecalciferol , Disodium etidronate and Calcium carbonate , Zoledronic acid , Denosumab (for postmenopausal women), Teriparatide ( $\leq$ -3.0), Strontium ranelate (for postmenopausal women), Raloxifene hydrochloride (for postmenopausal women), Calcitriol .
70 years or over (MBS item 12323)	No drug specifically indicated	Alendronate sodium ( $\leq$ -2.5), Alendronate sodium with Colecalciferol ( $\leq$ -2.5), Alendronate sodium with Colecalciferol and Calcium carbonate ( $\leq$ -2.5), Risedronate sodium ( $\leq$ -3.0), Risedronate sodium and Calcium carbonate ( $\leq$ -3.0), Risedronate sodium and Calcium carbonate with Colecalciferol ( $\leq$ -3.0), Zoledronic acid ( $\leq$ -3.0), Denosumab ( $\leq$ -2.5), Strontium ranelate ( $\leq$ -3.0 for women)
Corticosteroids use (MBS item 12312)	Alendronate sodium: 68428, 80333, 53158, 67262, 76851, 9333, 98944; Disodium etidronate: 46852; Risedronate sodium: 117667, 138211, 141530, 150618, 166838, 166853, 166942, 74135, 82746; Zoledronic acid: 134664;	Alendronate sodium ( $\leq$ -1.5), Alendronate sodium with Colecalciferol ( $\leq$ -1.5), Alendronate sodium with Colecalciferol and Calcium carbonate ( $\leq$ -1.5), Risedronate sodium ( $\leq$ -1.0 if patients on steroids for > 3 months), Risedronate sodium ( $\leq$ -1.5), Risedronate sodium and Calcium carbonate (NR), Risedronate sodium and Calcium carbonate with Colecalciferol ( $\leq$ -1.5), Zoledronic acid ( $\leq$ -1.5)
Male Hypogonadism (MBS item 12312)	No drug specifically indicated	No drug specifically indicated

Female Hypogonadism lasting >6 months before age of 45 (MBS item 12312)	No drug specifically indicated	No drug specifically indicated
Primary Hyperparathyroidism (MBS item 12315)	No drug specifically indicated	No drug specifically indicated
Chronic renal disease (MBS item 12315)	No drug specifically indicated	No drug specifically indicated
Chronic liver disease (MBS item 12315)	No drug specifically indicated	No drug specifically indicated
Rheumatoid arthritis (MBS item 12315)	No drug specifically indicated	No drug specifically indicated
Conditions associated with thyroxine excess (MBS item 12315)	No drug specifically indicated	No drug specifically indicated
Proven malabsorptive disorders (MBS item 12315)	No drug specifically indicated	No drug specifically indicated
Breast cancer patients receiving aromatase inhibitor treatment	No drug specifically indicated	No drug specifically indicated
HIV	No drug specifically indicated	No drug specifically indicated
Paget's disease *	Risedronate sodium: 74136	Alendronate sodium, Risedronate sodium, Disodium etidronate, Disodium pamidronate, Zoledronic acid, Tiludronate disodium
Heterotopic ossification*	No drug specifically indicated	Disodium etidronate
hypercalcaemia of malignancy*	Sodium clodronate tetrahydrate: 181921, 181922, 66703, 66704,	Disodium pamidronate, Sodium clodronate tetrahydrate, Zoledronic acid
Multiple myeloma*	No drug specifically indicated	Disodium pamidronate, Sodium clodronate tetrahydrate, Zoledronic acid
Bone metastases from breast cancer*	No drug specifically indicated	Ibandronic acid, Disodium pamidronate, Sodium clodronate tetrahydrate, Zoledronic acid
Bone metastases from prostate cancer*	No drug specifically indicated	Zoledronic acid

\*not considered as a risk factor for osteoporosis; NR: Not reported.

Source: Pharmaceutical Benefits Scheme (PBS) as on 01/09/2012 <<http://www.pbs.gov.au/browse/body-system?depth=3&codes=m05b>>. Authority required to access details of indication for each drug (including indicated T-score).

## Appendix 5 Medicare Benefits Schedule - Note D1.27

Category 2 - DIAGNOSTIC PROCEDURES AND INVESTIGATIONS D1.27 Bone Densitometry - (Items 12306 to 12323)

Item 12321 is intended to allow for bone mineral density measurement following a significant change in therapy - e.g. a change in the class of drugs - rather than for a change in the dosage regimen.

Item 12323 enables the payment of a Medicare benefit for a bone densitometry service performed on a patient aged 70 years or over. The Government has decided to expand access to Medicare subsidised bone mineral density testing to coincide with the expanded eligibility for the osteoporosis medication 'alendronate' under the Pharmaceutical Benefits Scheme.

An examination under any of these items covers the measurement of 2 or more sites, interpretation and provision of a report. Two or more sites must include the measurement of bone density of the lumbar spine and proximal femur. If technical difficulties preclude measurement at these sites, other sites can be used for the purpose of measurements. The measurement of bone mineral density at either forearms or both heels or in combination is excluded for the purpose of Medicare benefit.

### Referrals

Bone densitometry services are available on the basis of referral by a medical practitioner to a specialist or consultant physician. However, providers of bone densitometry to whom a patient is referred for management may determine that a bone densitometry service is required in line with the provisions of Items 12306, 12309, 12312, 12315, 12318, 12321 and 12323.

For Items 12306 and 12309 the referral should specify the indication for the test, namely:

- (a) 1 or more fractures occurring after minimal trauma; or
- (b) monitoring of low bone mineral density proven by previous bone densitometry.

For Item 12312 the referral should specify the indication for the test, namely:

- (a) prolonged glucocorticoid therapy;
- (b) conditions associated with excess glucocorticoid secretion;
- (c) male hypogonadism; or
- (d) female hypogonadism lasting more than 6 months before the age of 45.

For Item 12315 the referral should specify the indication for the test, namely:

- (a) primary hyperparathyroidism;
- (b) chronic liver disease;
- (c) chronic renal disease;

- (d) proven malabsorptive disorders;
- (e) rheumatoid arthritis; or
- (f) conditions associated with thyroxine excess.

For Item 12318 the referral should specify the indication for the test, namely:

- (a) prolonged glucocorticoid therapy;
- (b) conditions associated with excess glucocorticoid secretion;
- (c) male hypogonadism;
- (d) female hypogonadism lasting more than 6 months before the age of 45;
- (e) primary hyperparathyroidism;
- (f) chronic liver disease;
- (g) chronic renal disease;
- (h) proven malabsorptive disorders;
- (i) rheumatoid arthritis; or
- (j) conditions associated with thyroxine excess.

#### Definitions

Low bone mineral density is present when the bone (organ) mineral density falls more than 1.5 standard deviations below the age matched mean or more than 2.5 standard deviations below the young normal mean at the same site and in the same gender.

For Items 12312 and 12318

- (a) 'Prolonged glucocorticoid therapy' is defined as the commencement of a dosage of inhaled glucocorticoid equivalent to or greater than 800 micrograms beclomethasone dipropionate or budesonide per day; or
- (b) a supraphysiological glucocorticoid dosage equivalent to or greater than 7.5 mg prednisolone in an adult taken orally per day;

for a period anticipated to last for at least 4 months.

Glucocorticoid therapy must be contemporaneous with the current scan. Patients no longer on steroids would not qualify for benefits.

For Items 12312 and 12318

- (a) Male hypogonadism is defined as serum testosterone levels below the age matched normal range.

(b) Female hypogonadism is defined as serum oestrogen levels below the age matched normal range.

For Items 12315 and 12318

A malabsorptive disorder is defined as one or more of the following:

- (a) malabsorption of fat, defined as faecal fat estimated at greater than 18 gm per 72 hours on a normal fat diet; or
- (b) bowel disease with presumptive vitamin D malabsorption as indicated by a sub-normal circulating 25-hydroxyvitamin D level; or
- (c) histologically proven Coeliac disease.

Related Items: 12306, 12309, 12312, 12315, 12318, 12321, 12323