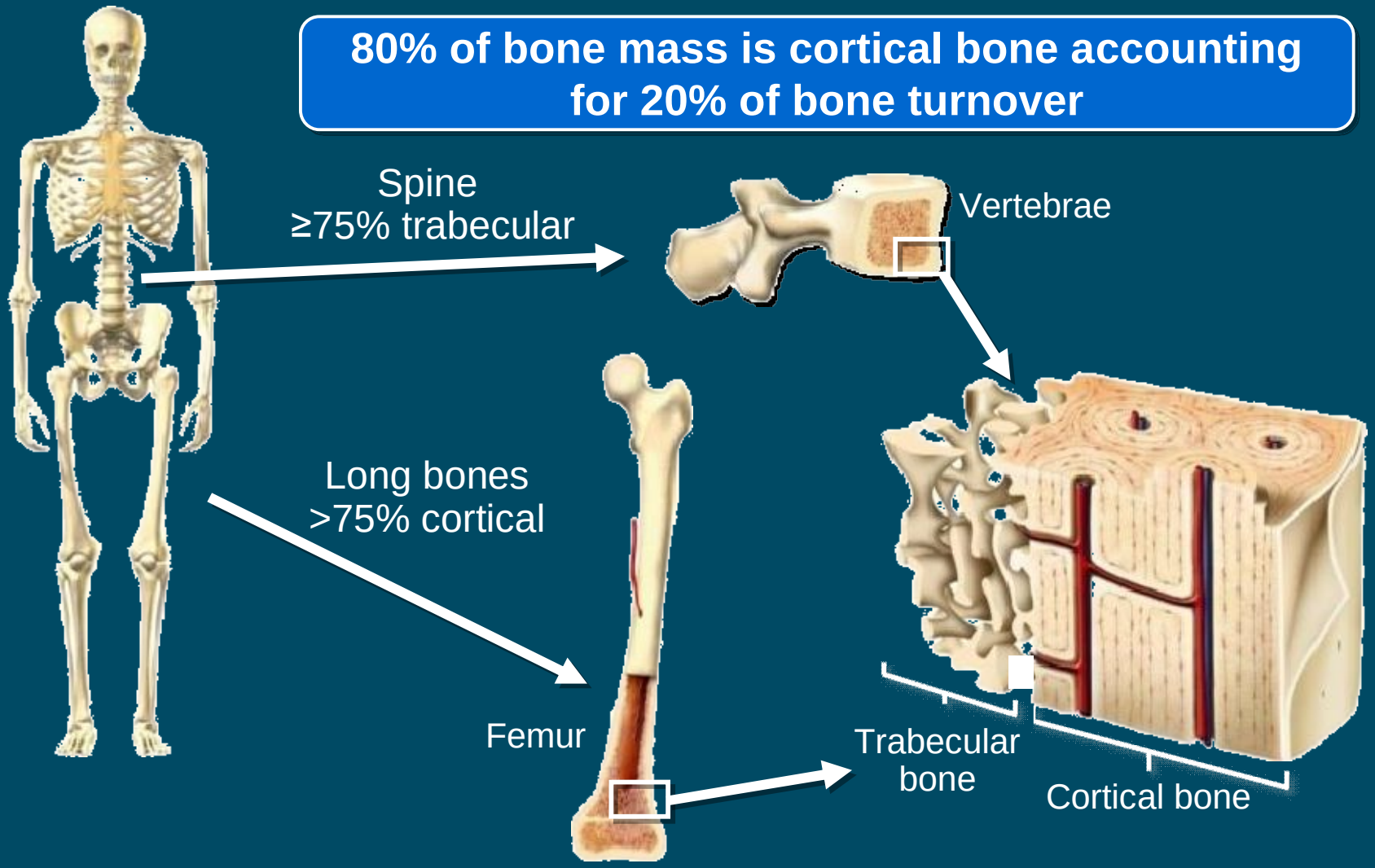
PATHWAYS IN Osteoporosis

Pathophysiology of osteoporosis

Trabecular and cortical bone loss in postmenopausal women

IL/DNB/0035/14
November 2014

The Distribution of Trabecular and Cortical Bone Varies Throughout the Skeleton



Adapted from: Dempster DW. *Primer on the metabolic bone diseases and disorders of bone metabolism. 6th ed*. 2006;p.7–11.

Osteoporosis is a Disease with Increased Fracture Risk Across the Entire Skeleton

Definition of osteoporosis:

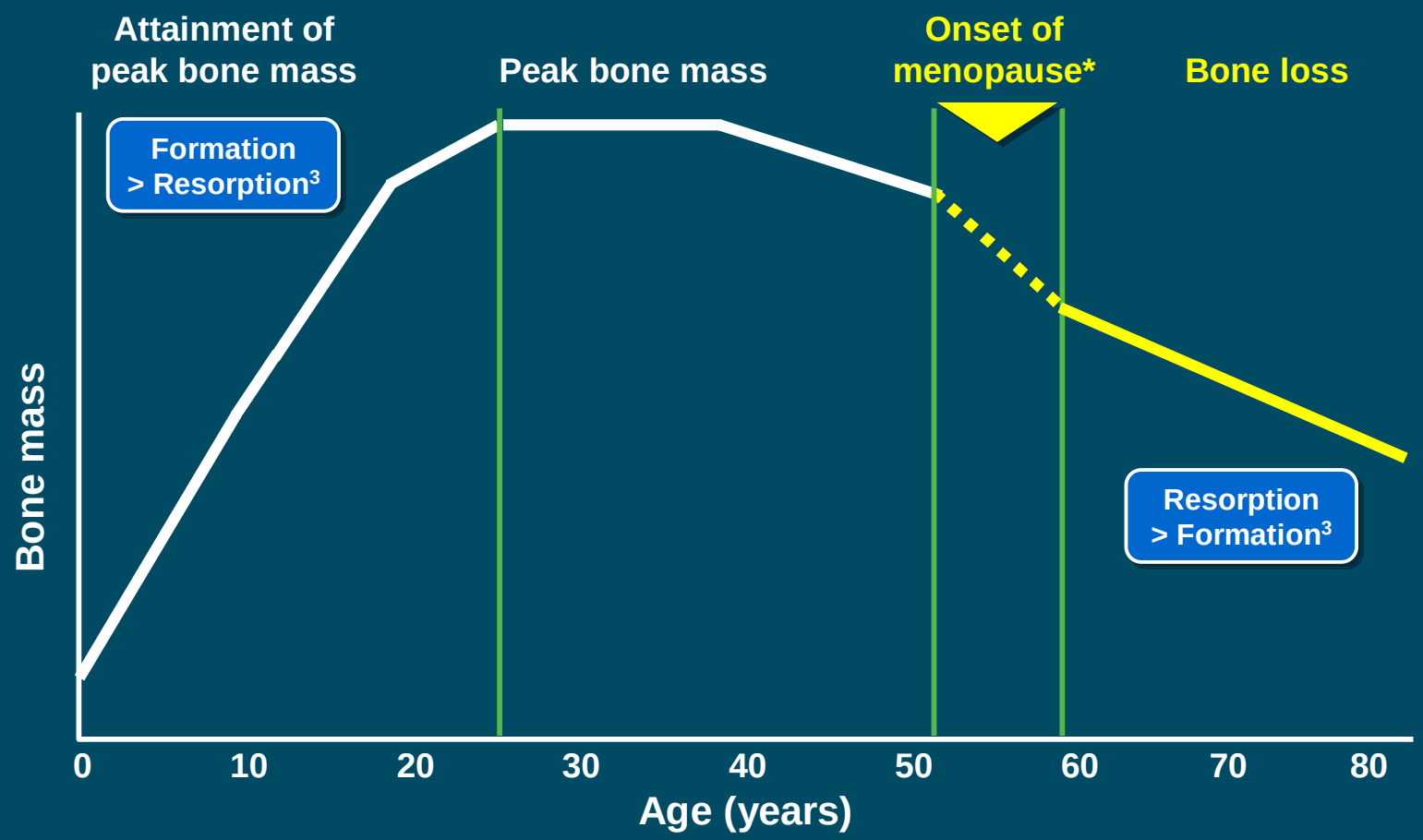
- Compromised bone strength predisposes person to increased risk of fracture[1]
- Bone strength reflects the integration of bone density and bone quality[1]

> "Osteoporosis is one of the most common and debilitating chronic diseases, and a global healthcare problem."
>
> International Osteoporosis Foundation[2]

> "Osteoporosis has financial, physical, and psychosocial consequences, all of which significantly affect the individual, the family, and the community."
>
> NIH Consensus Statement[1]

1. NIH Consensus Development Panel. *JAMA* 2001;285:785–795.
2. International Osteoporosis Foundation. http://testsite.iofbonehealth.org/docs/patients-public/about-osteoporosis/frequently-asked-questions-about-osteoporosis.html. Accessed August 2012.

Bone Mass Rapidly Decreases with the Onset of Menopause[1,2]

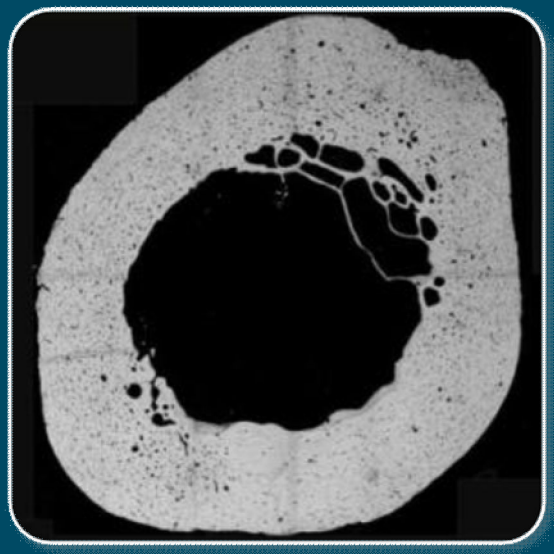


*Menopause occurs for approximately one year period during this time frame

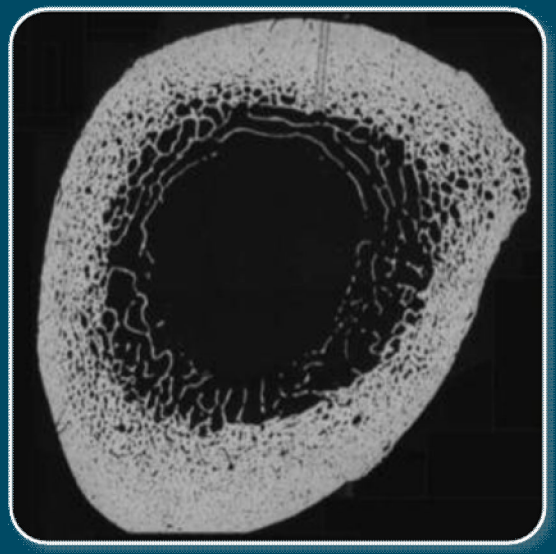
1. Adapted from: Lanham-New SA. *Proc Nutr Soc*. 2008;67:163–176.
2. Sambrook P, *et al. Baillieres Clin Rheumatol* 1993;7:445–457.
3. Kholsa S, *et al.* [2]*Trends Endocrinol Metabol* 2012 (in press).

Cortical Porosity Increases with Age After Menopause

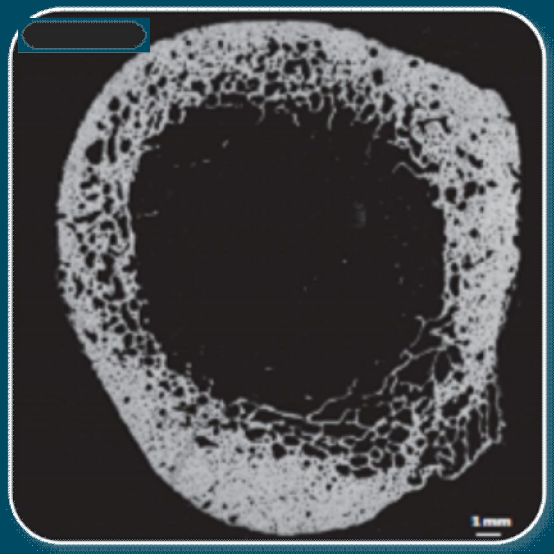
Cross-sectional images of distal radius



29-year-old woman



63-year-old woman

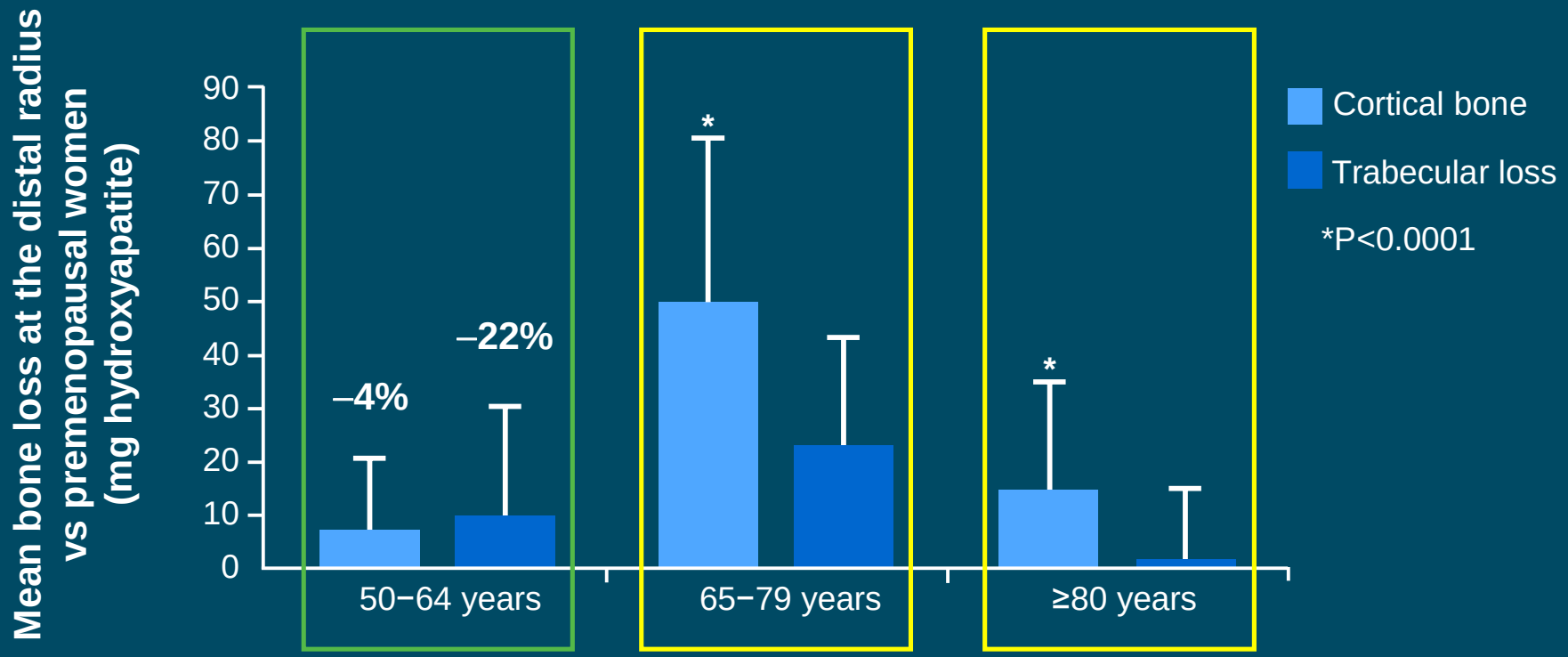


90-year-old woman

Zebaze RM, *et al. Lancet* 2010;9727:1729–1736.

Cortical Bone is Lost Later in Life

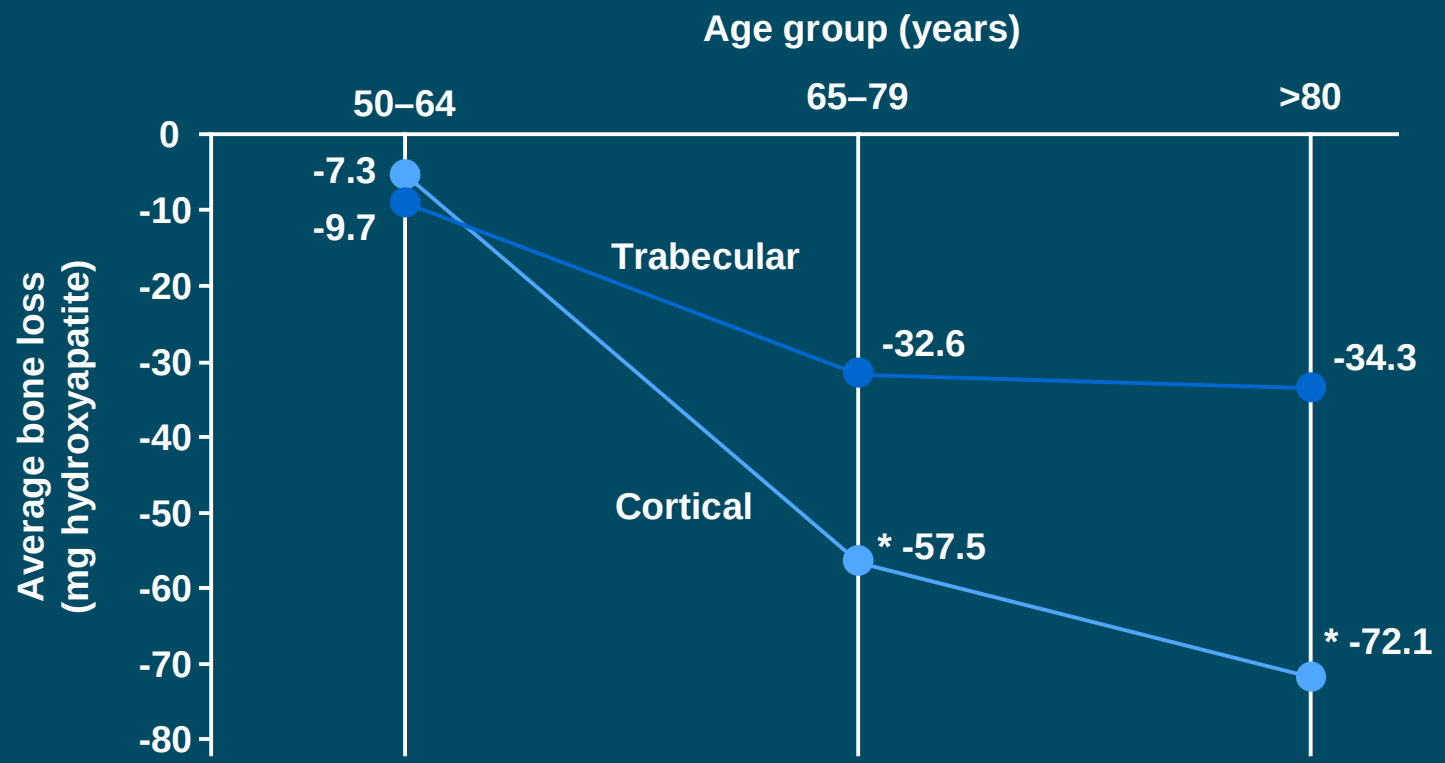
- **Rapid bone loss after menopause is mainly trabecular**
- **The majority of bone loss in the 65–79 year age group is cortical**
- **After age 80 years, ~90% of bone loss is cortical**



Zebaze RM, *et al*. *Lancet* 2010;9727:1729–1736.

Age-related Cortical and Trabecular Bone Loss in Postmenopausal Women

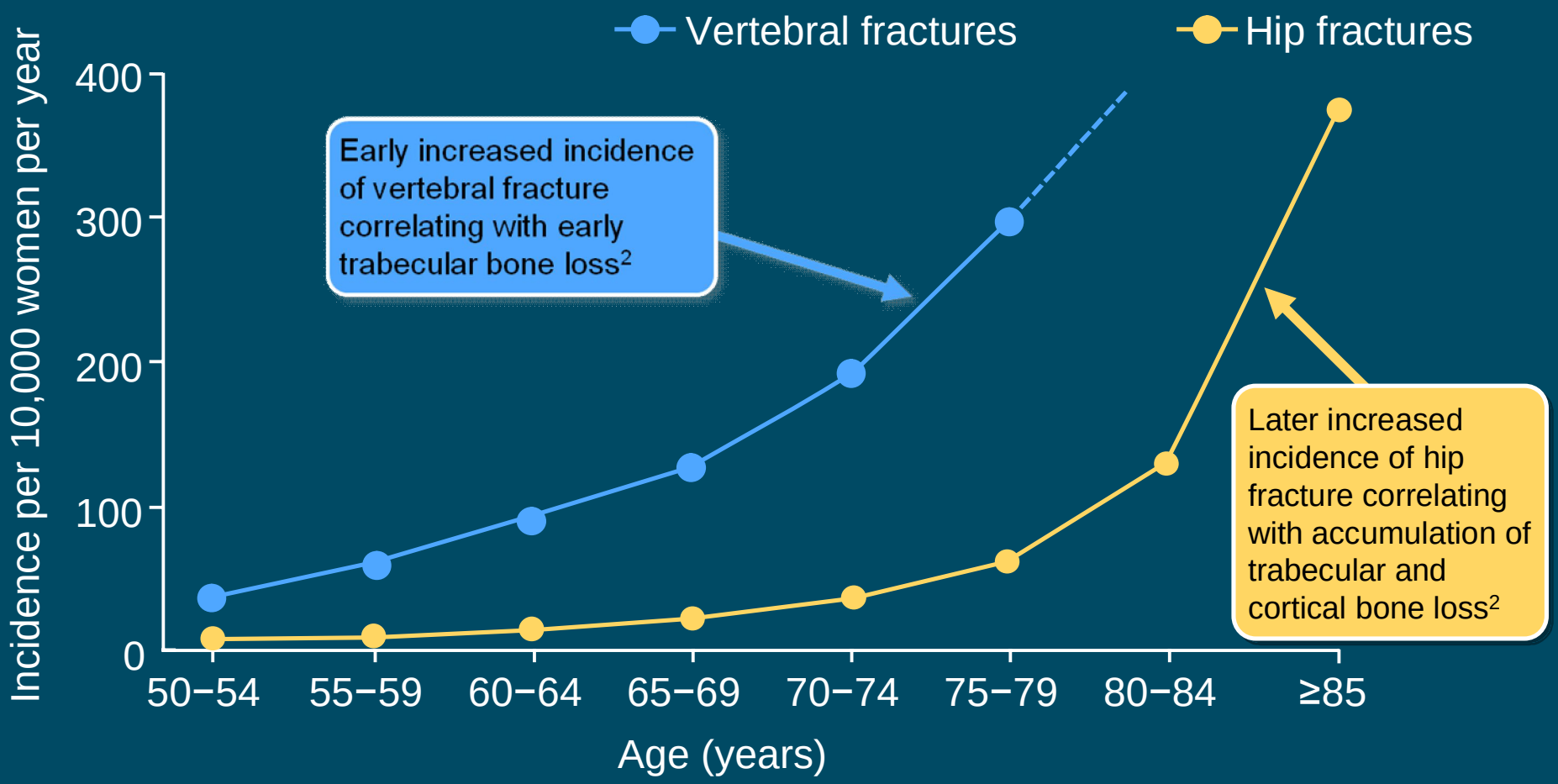
Cumulative age-related bone loss



*P<0.001

Zebaze RM, *et al*. *Lancet* 2010;9727:1729–1736.

Vertebral and Hip Fracture Rates Exponentially Increase with Trabecular and Cortical Bone Loss[1]



1. Adapted from: Sambrook P, Cooper C. *Lancet* 2006;367:2010–2018.
2. Cooper C. Trends Endocrinol Metab 1992;3:224–229.

PATHWAYS IN Osteoporosis

Burden of osteoporosis

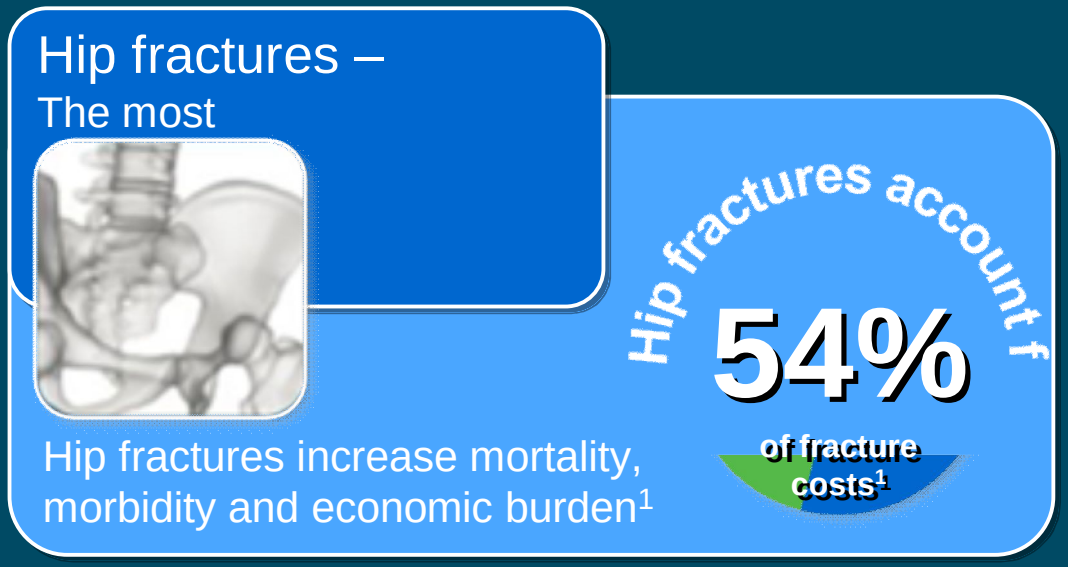
Hip Fractures Lead to Significant Clinical, Social, and Economic Burden

- Hip fractures are associated with a significant increase in mortality, even in the 60–69 year age group[1]
- 40% of women who fracture a hip will never be able to walk again without assistance, and fewer than 20% will recover to their pre-fracture competence in activities[2]
- Hip fractures are the most important factor contributing to the cost burden of osteoporosis, including hospitalizations
  - they account for 14% of incident fractures but 72% of fracture costs in the US[3]

1. Center JR, *et al. Lancet* 1999;353:878–882.
2. Cooper C. *Am J Med* 1997;103:12S–19S.
3. Burge R, *et al. J Bone Miner Res* 2007;22:465–475.

Some Fractures have More Impact than Others

- Almost 20% of patients die within the first year after a hip fracture[1]

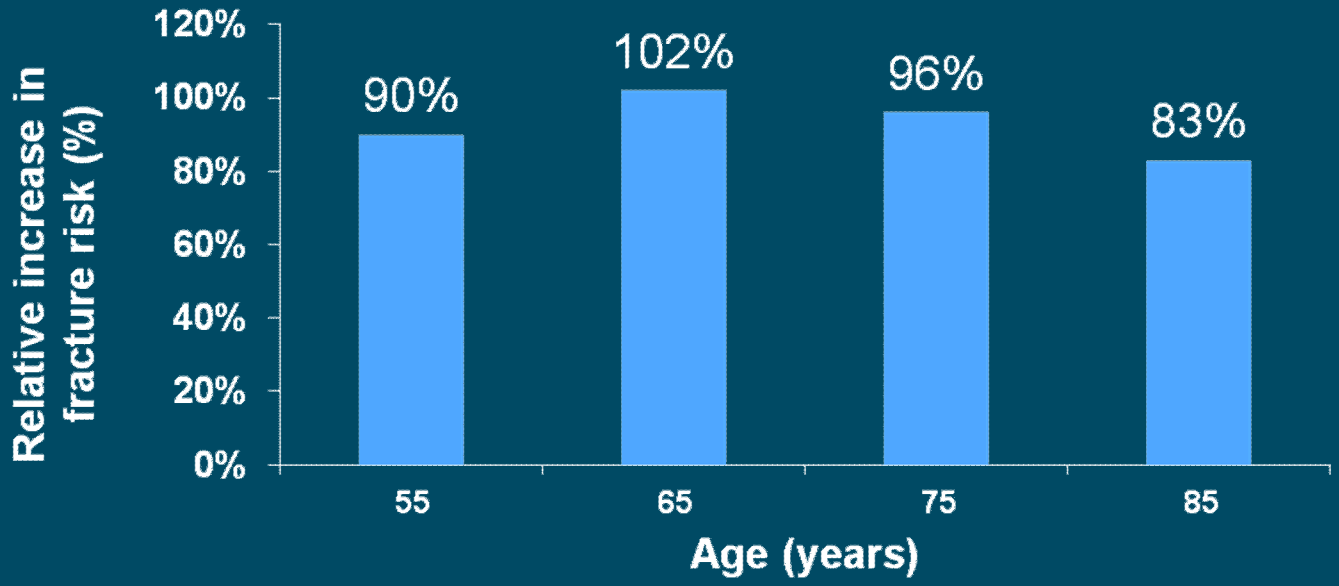


- Over 50% of previously mobile patients who have had a hip fracture will not be able to walk without assistance after 1 year[2]

1. Ström O, *et al. Arch Osteoporos* 2011;6:59–155.
2. Keene GS, *et al. BMJ* 1993;307:1248–1250.

Previous Fracture Doubles the Risk of Any Subsequent Fractures

Relative increase in fracture risk in patients who have had a previous fracture[1]

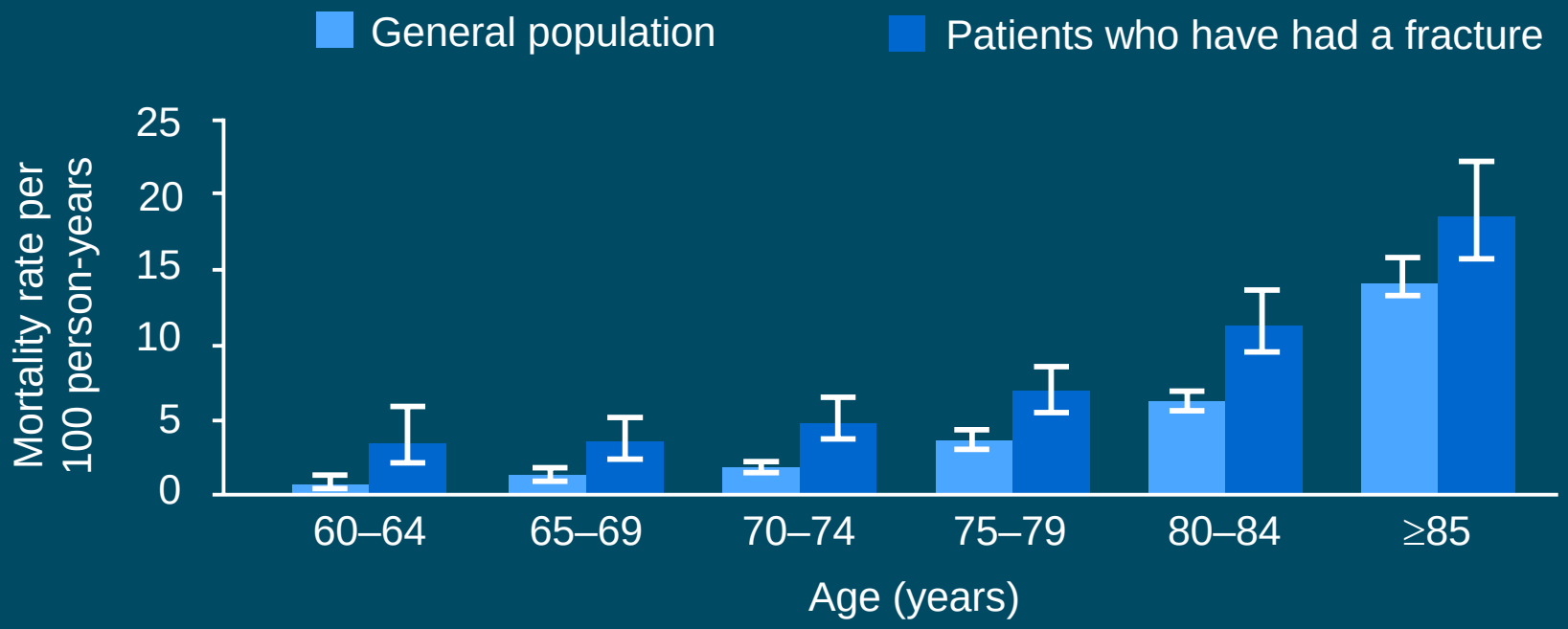


- A previous fracture can double the risk of a subsequent fracture[1]
- A previous vertebral fracture quadruples the risk of a subsequent vertebral fracture[2]

1. Adapted from: Kanis JA, *et al. Bone* 2004;35:375–382.
2. Klotzbuecher CM, *et al. J Bone Min Res* 2000;15:721–739.

A Fracture Increases the Risk of Mortality

Mortality rates in women who have experienced a fracture vs the general population, according to age

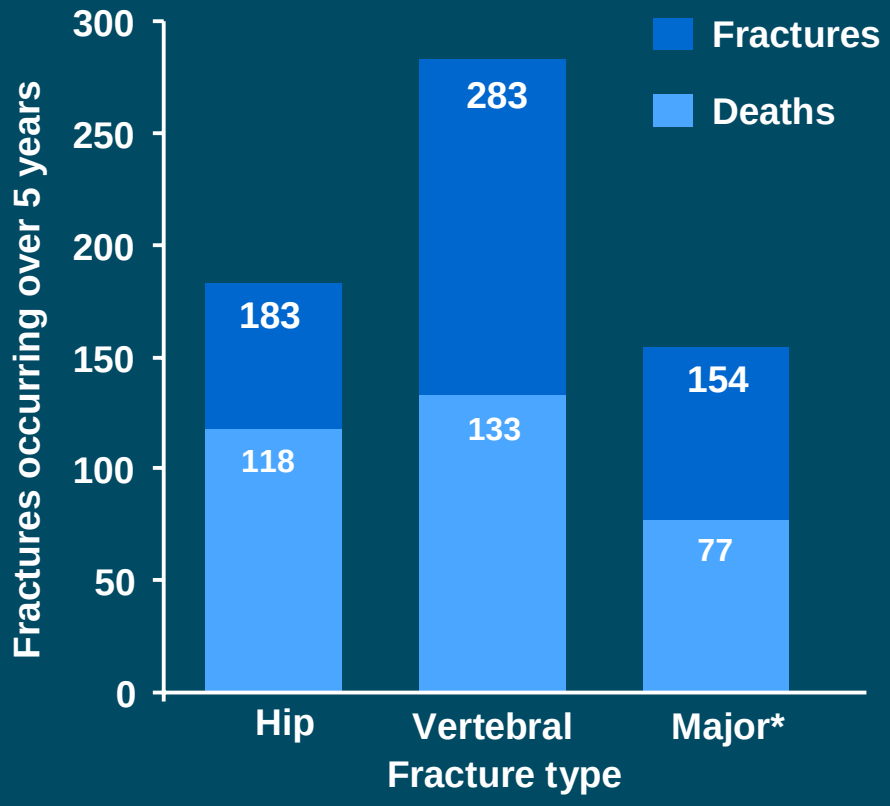


- A subsequent fracture increases the mortality risk further

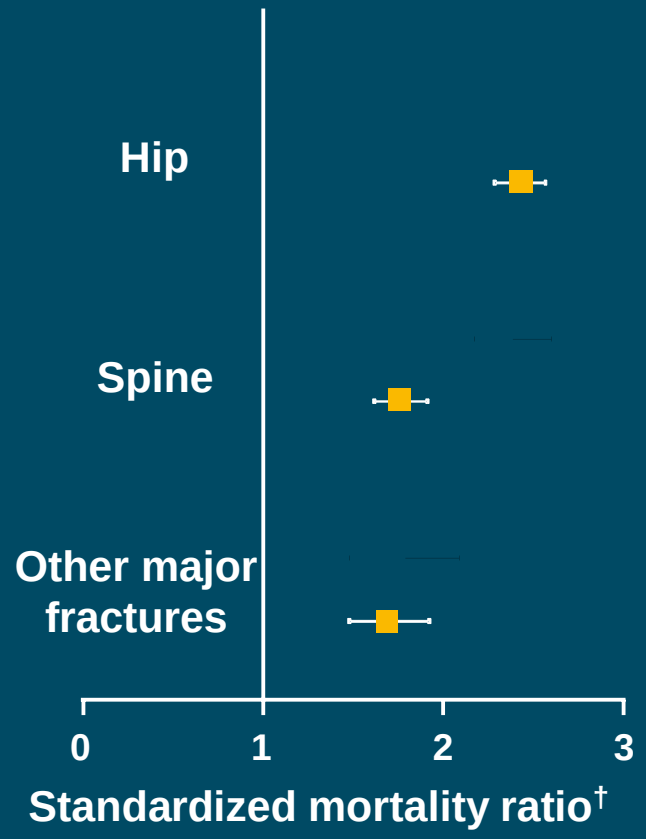
Bliuc D, *et al. JAMA* 2009;301:513–521.

Fractures are Associated with a Significant Increase in Mortality

High incidence of fracture and death in women



Increased mortality in fractured women patients compared with general population



*Includes pelvic, distal femur, proximal tibia, multiple rib, and proximal humerus
†Ratio of observed to expected deaths, by gender and fracture type

Adapted from: Bliuc D, *et al. JAMA* 2009;301:513–521.

Prolia - indication

- **Therapeutic indications**
- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures.
- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures
- Prolia PI MOH approved

Prolia – active ingredients and administration

Generic name of the drug and active ingredient

Prolia 60 mg solution for injection in a pre-filled syringe.

Each pre-filled syringe contains 60 mg of denosumab in 1 ml of solution (60 mg/ml).

Dosage and method of administration

The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm.

Patients must be adequately supplemented with calcium and vitamin D

Administration should be performed by an individual who has been adequately trained in injection techniques.

Prolia

MANUFACTURER

- Amgen Europe B.V.
- Breda
- The Netherlands

LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd.

25 Basel St., Petach Tikva 4900202

Prolia is a registered trademark of Amgen Inc., and is being used under license by GlaxoSmithKline.

Prolia – important information

- לדיווח תופעות לוואי il.safety@gsk.com **או** בטלפון 03-9297100
- שרות מידע רפואי il.medinfo@gsk.com
- **למידע מלא יש לעיין בעלון לרופא כפי שאושר ע"י משרד הבריאות**

Prolia - Contraindications

- **Contraindications**
- Hypocalcaemia
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of PI
- Pregnancy: Prolia may cause fetal harm when administered to a pregnant woman. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent lymph nodes, abnormal bone growth and decreased neonatal growth. Prolia is contraindicated in women who are pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

For full information please see MOH approved PI

Special warnings and precautions for use

- Calcium and Vitamin D supplementation
- Adequate intake of calcium and vitamin D is important in all patients.
- Precautions for use
- ***Hypocalcemia* -** It is important to identify patients at risk for hypocalcaemia. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. If any patient presents with suspected symptoms of hypocalcaemia during treatment calcium levels should be measured. Patients should be encouraged to report symptoms indicative of hypocalcaemia.
- In the post-marketing setting, severe symptomatic hypocalcaemia has been reported , with most cases occurring in the first weeks of initiating therapy, but it can occur later.

For full information please see MOH approved PI

Special warnings and precautions for use

- ***Skin Infections*** - Patients receiving Prolia may develop skin infections (predominantly cellulitis) leading to hospitalization. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.
- **Osteonecrosis of the jaw** has been reported rarely in clinical studies and in the post marketing setting in patients receiving denosumab at a dose of 60 mg every 6 months for osteoporosis. Known risk factors for ONJ include previous treatment with bisphosphonates, older age, poor oral hygiene, invasive dental procedures (e.g. tooth extractions, dental implants, oral surgery), and co-morbid disorders (e.g. pre-existing dental disease, anaemia, coagulopathy, infection), smoking, a diagnosis of cancer with bone lesions, concomitant therapies (e.g., chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck). It is important to evaluate patients for risk factors for ONJ before starting treatment. A dental examination with appropriate preventive dentistry is recommended prior to treatment with Prolia in patients with concomitant risk factors. All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling during treatment with Prolia. While on treatment, patients should avoid invasive dental procedures if possible.

For full information please see MOH approved PI

Special warnings and precautions for use

- ***Atypical Subtrochanteric and Diaphyseal Femoral Fractures -*** Atypical low-energy or low trauma *fractures of the* shaft have been reported in patients receiving Prolia. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with anti-resorptive agents. During Prolia treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Interruption of Prolia therapy should be considered, pending a risk/benefit assessment, on an individual basis.
- ***Suppression of Bone Turnover -*** In clinical trials in women with postmenopausal osteoporosis, treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment with Prolia are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. Monitor patients for these consequences.

For full information please see MOH approved PI

Special warnings and precautions for use

- ***Dry natural rubber*** - The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.
- ***Renal impairment*** - Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in these patients, see above.
- Warnings for Excipients
- Patients with rare hereditary problems of fructose intolerance should not use Prolia. This medicinal product contains less than 1 mmol sodium (23 mg) per 60 mg i.e. essentially ‘sodium-free’.

For full information please see MOH approved PI