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REGIONAL DRUG AND THERAPEUTICS CENTRE

DRUG UPDATE

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# PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

**Long-term HRT should no longer be used as a first-line therapy for the prevention of osteoporosis in postmenopausal women over 50 years; it may be used in younger women who have experienced a premature menopause. All postmenopausal women should be given appropriate lifestyle advice to prevent bone loss including an adequate calcium and vitamin D intake. Most of these women do not require drug treatment unless they have previously sustained a fragility fracture or are considered to be at particularly high risk. In such cases, alendronate or risedronate would be suitable first-line treatments.**

## What is it?

Osteoporosis is defined as a progressive, systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[1] Women are at greater risk of developing osteoporosis as they achieve a lower peak bone mass than men and bone loss is accelerated following the menopause.[2] In the UK, one in three women over the age of 50 will develop osteoporosis and almost half of all women experience an osteoporotic fracture by the age of 70.[3] This Drug Update focuses on drug treatments for the prevention of postmenopausal osteoporosis in light of the findings of recent studies suggesting that the risks of long-term HRT outweigh the benefits in osteoporosis prevention.[4,5] The treatment of diagnosed osteoporosis is not addressed.

## Hormone replacement therapy

The Women's Health Initiative (WHI) study, a randomised, controlled study involving 16,608 healthy postmenopausal women, found that HRT is associated with a significant reduction in fracture risk, a secondary endpoint of the study.[4] Epidemiological studies suggest that continuous lifelong use of HRT is required for it to be an effective method of preventing hip fractures.[6,7]

Studies published recently, particularly the WHI and the Million Women studies, have raised concerns about the long-term safety of HRT.[4,5] The EMEA Scientific Committee (Committee for Proprietary Medicinal Products, CPMP), having recently reviewed the safety of HRT, has concluded that the benefit/risk balance of long-term use of HRT (including tibolone) as a first-line therapy for the prevention of osteoporosis is unfavourable; this conclusion has been endorsed by the CSM.[8,9]

## Bisphosphonates

Three bisphosphonates are currently licensed in the UK for the prevention and treatment of postmenopausal osteoporosis; alendronate, cyclical etidronate and risedronate. Meta-analyses of randomised, placebo-controlled trials have shown that these bisphosphonates prevent bone loss (evaluated by bone mineral density (BMD) measurement) in postmenopausal women with normal BMD or osteopenia and no history of fractures; there is currently no evidence that bisphosphonates reduce fracture risk in this group of women.[10-12] However, women included in prevention trials were at a low absolute risk of fragility fracture and these trials are generally performed over a relatively short period of time so long-term anti-fracture efficacy cannot be assessed accurately.[1] Further long-term trials are needed before bisphosphonates can be recommended in this group of women. In postmenopausal women with diagnosed osteoporosis, risedronate or alendronate reduce the risk of both vertebral and non-vertebral fractures, and etidronate reduces the risk of vertebral fractures.[13]

All bisphosphonates have been associated with gastrointestinal adverse effects. Serious oesophageal reactions may occur rarely. The risk of these symptoms can be reduced by taking the drugs with a full glass of water and by avoiding lying flat within 30 minutes of ingestion.[13]

## Raloxifene

Raloxifene is a selective oestrogen receptor modulator (SERM) licensed for the prevention and treatment of postmenopausal osteoporosis. A pooled analysis of 2 randomised, controlled trials reported that postmenopausal women taking raloxifene for 5 years were less likely to develop osteoporosis (absolute risk reduction (ARR) of 16%, p=0.001) or osteopenia (ARR of 10%, p=0.038) compared with those on placebo, however this was assessed solely by measurement of BMD and no fracture data were provided.[14] In postmenopausal women with osteoporosis, raloxifene has been shown to reduce the risk of vertebral fractures.[13]

Perimenopausal hot flushes may be aggravated by raloxifene and the risk of venous thromboembolism is similar to that of HRT. Raloxifene may reduce the risk of oestrogen receptor positive breast cancer.[13,15]

## Calcium & vitamin D supplements

All postmenopausal women should aim to take 1000 mg of calcium daily. Calcium derived from the diet is as effective as calcium in tablet form.[2] Vitamin D supplementation is not required for active women under 65 years of age. However, women over 65 years should aim to take 10 mg (400 IU) daily of vitamin D, this dose is only achieved in most cases by giving a supplement.[2]

## What are the risk factors?

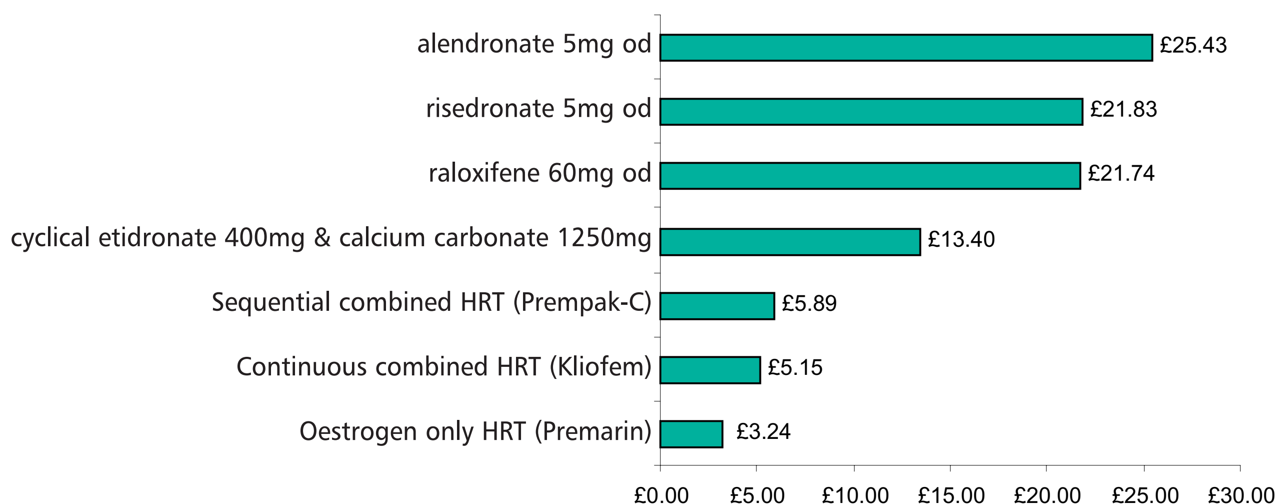
The strongest risk factors for osteoporosis are female sex, age >60 years or a family history of the disease.[2] Other risk factors include caucasian origin, early menopause, low BMI (<19 kg/m$^2$), smoking, low calcium and vitamin D intake, sedentary lifestyle, long term use of oral corticosteroids (≥ 3 months) and diseases associated with malabsorption.[2,13] Alcohol intake is though to be a risk factor, however the evidence is not consistent.[2] There appears to be an additive effect of risk factors.[2] Current risk scores for osteoporosis are not of satisfactory quality and have not been validated.[2]

## Who should be treated?

Long-term HRT is no longer recommended as a first-line therapy for the prevention of osteoporosis in postmenopausal women over 50 years; it may be used in younger women who have experienced a premature menopause.[9] All postmenopausal women should be given appropriate lifestyle advice including good calcium and vitamin D intake, weight-bearing exercise, smoking cessation, and avoidance of excessive alcohol intake.[13]

Drug treatment for the prevention of osteoporosis is not recommended for most postmenopausal women with risk factors and no history of fragility fractures, however it may occasionally be justified in some women considered to be at particularly high risk of the disease. In such cases, alendronate or risedronate would be suitable first-line drugs.[15]

NICE guidance on technologies for the prevention of osteoporosis in postmenopausal women was due in June 2004, however it has been delayed until more data are available on the contribution of risk factors to osteoporotic fractures.[16]




N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

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KEY RCT - randomised controlled trial, CT - controlled trial, MA - meta analysis, R - review, G - guidelines

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