ESSENTIAL AND RELEVANT INFORMATION

ProductBrief

Actonel EC – delayed release formulation may improve compliance

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Practice tips

- Long term compliance is critical for the effectiveness of osteoporosis pharmacotherapy. Dispensing the enteric coated formulation of risedronate (if prescribed) may improve compliance in patients who find it difficult to take IR bisphosphonates at least 30 minutes before a meal.
- Bisphosphonates work optimally in the presence of adequate calcium and vitamin D. If calcium and vitamin D supplements (or a combination bisphosphonate product) have not been prescribed, advise the patient to discuss with their doctor whether supplements may be needed. Calcium supplements should not be taken at the same time as bisphosphonates.
- Remind patients of the importance of taking risedronate with a full glass of plain water and remaining upright for at 30 minutes afterwards
- Remind patients of the need to see their doctor for follow-up BMD testing 1 or 2 years after commencing medication to monitor the efficacy of the bisphosphonate treatment.

Introduction

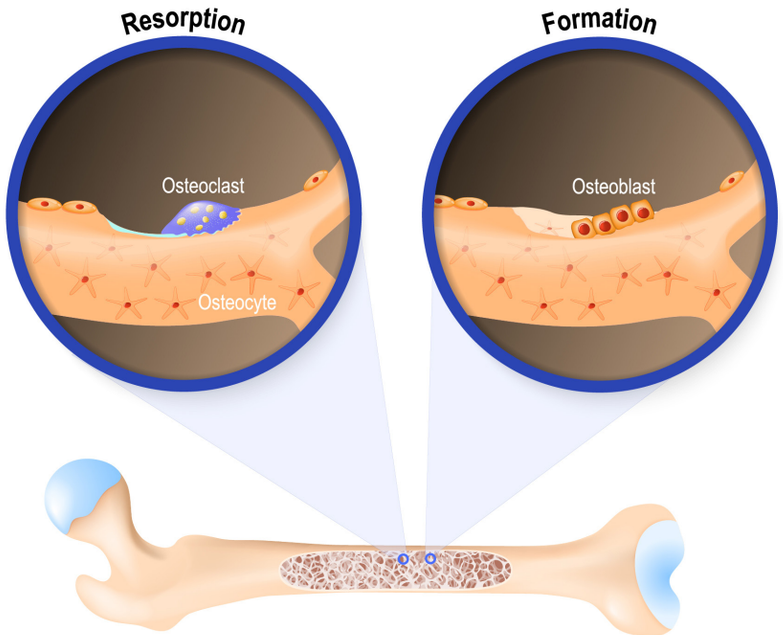
Osteoporosis is characterised by low bone mineral density (BMD) and deterioration of bone architecture, increasing the risk of minimal trauma fractures.[1]

In 2012, 4.74 million Australians over the age of 50 were living with osteoporosis or its precursor osteopenia.[2] By 2022, this figure is estimated to be 6.2 million, a rise of 31%.[2]

Osteoporotic fractures cause pain, reduced mobility, and loss of quality of life. 40% to 60% of hip fracture survivors do not recover their pre-fracture mobility.[3] The risk of death also increases significantly in the years after an osteoporotic fracture. A 2009 Australian study showed elevated standardised mortality ratios ranging from 1.38 (women with a minor fracture) to 3.52 (men with a hip fracture) in the first 5 years after fracture.[4]

Pharmacological management

Most pharmacological agents for osteoporosis act to reduce excessive resorption of bone. First line medications available in Australia are the bisphosphonates and the human monoclonal antibody denosumab. Hormone replacement therapy is an additional first line option for women.[1] Second line anabolic therapies improve BMD and reduce fracture risk by stimulating the formation of new bone by osteoblasts. The only anabolic therapy currently available in Australia is teriparatide, indicated for severe osteoporosis.[1]



Long-term pharmacotherapy is required in most cases of osteoporosis. However, adherence with osteoporosis medications is poor - one third to one half of patients do not take their medication as directed.[5] The need to fast before taking oral bisphosphonates has been identified as one of the top 3 patient-reported reasons for poor adherence.[5]

Bisphosphonates

Bisphosphonates are highly stable inorganic analogues of pyrophosphate, which bind tightly and preferentially to hydroxyapatite crystals in bone. Bisphosphonates inhibit osteoclast-mediated bone resorption, restoring BMD to a level sufficient to reduce the risk of fracture.[5]

Two oral bisphosphonates (alendronate and risedronate) and one intravenous bisphosphonate (zoledronic acid) are approved and on the PBS for the treatment of osteoporosis in Australia.[6-8]

Oral bisphosphonates have poor bioavailability – less than 1% of a dose is absorbed from the gastrointestinal tract.[5] Absorption is partially hindered by binding of bisphosphonates to calcium and other cations in stomach contents. Food or beverages (other than water) should therefore be avoided for up to 2 hours following administration of immediate release (IR) bisphosphonate formulations.[5] However food restrictions are not required with enteric-coated formulations, as the pH-sensitive coating prevents premature release of bisphosphonate into the stomach, protecting the drug from inactivation by stomach contents.[5]

Actonel EC 35mg weekly

Actonel is the proprietary name of the oral bisphosphonate risedronate. Actonel is available in two formulations: uncoated (IR -5mg, 30mg, 35mg and 150mg tablets) and a 35mg enteric coated (EC) delayed release tablet. Each Actonel EC 35mg tablet contains the equivalent of 35mg anhydrous risedronate, with a pH sensitive enteric coating that protects the active ingredients from exposure to stomach contents and eliminates the need for fasting.[5] Actonel EC 35mg also contains the chelating agent EDTA, which competitively binds cations in the stomach and small intestine that would otherwise reduce the bioavailability of the risedronate.[5, 6] Beware of different PBS and RPBS criteria for bisphosphonates and different PBS item codes. Enteric-coated risedronate is PBS listed under a different item code, separate from the other risedronate products, and should not be substituted for another risedronate product.

Dosing and administration

Actonel EC 35mg is taken once a week on the same day, and unlike risedronate IR, can be taken at the same time as food. The tablet should be swallowed whole with plain water (not cut, crushed or chewed) to reduce the risk of oropharyngeal irritation and to preserve the enteric coating.[6] The risk of gastrointestinal adverse effects is reduced if the medication is taken with a full glass of water and the patient remains upright for at least 30 minutes after administration.[6]

Bioavailability

The bioavailability of Actonel EC 35mg is less affected by stomach contents than the IR formulation, meaning that Actonel EC 35mg tablets can be taken before or after a meal. The bioavailability of Actonel EC 35mg taken after a high-fat breakfast is similar to that of Actonel IR 35mg taken 4 hours before breakfast. However, the bioavailability of Actonel EC is 2-fold greater than Actonel IR 35mg when taken 30 minutes before breakfast.[6]

Indications

Actonel is indicated for the treatment of osteoporosis, treatment of glucocorticoid-induced osteoporosis, and the preservation of BMD in patients on long term glucocorticoid therapy.[6]

Contraindications and precautions

Actonel is not recommended in patients with severe renal impairment, and is contraindicated if the patient has hypocalcaemia or is unable to stand or sit upright for at least 30 minutes.[6] Hypocalcaemia must be corrected before starting Actonel therapy.[6] Caution is required in patients with active or historical oesophageal or upper gastrointestinal disorders.[6]

Calcium supplements and antacids can interfere with absorption of Actonel and should not be taken at the same time as Actonel EC 35mg.[6]

Efficacy

Risedronate acts rapidly to reduce fracture risk. Pooled data from four large, randomized placebo-controlled trials in postmenopausal women with osteoporosis found that risedronate 5mg daily significantly reduced the incidence of non-vertebral fractures within 6 months, compared with control (66% reduction, $p=0.048$).[9] After 12 months, non-vertebral fracture incidence was reduced by 74%, compared with control ($p = 0.001$), and after 3 years, by 59% ($p = 0.002$).[9] In a randomised placebo-controlled trial of postmenopausal women with a history of at least one vertebral fracture (n=939), 5mg risedronate IR daily decreased the incidence of new vertebral fractures after the first year of treatment by 65% ($p<0.001$), with a cumulative decrease of 41% over 3 years ($p=0.003$).[10] A study of 640 postmenopausal women with osteoporosis but no history of vertebral fracture demonstrated a risk

reduction of 75% in the incidence of first vertebral fracture after 3 years treatment with risedronate 5mg, compared to placebo (p=0.002).[11]

Risedronate EC 35mg weekly is similar in efficacy to risedronate IR 5mg daily. A non-inferiority trial by McClung, et.al. (2012) randomised 767 postmenopausal women with osteoporosis to risedronate IR 5mg daily (taken at least 30 minutes before breakfast) or risedronate EC 35mg weekly (taken either immediately after or at least 30 minutes before breakfast).[12] Significant increases in both lumbar spine and hip BMD were seen after 6 months of treatment in all 3 arms of the trial. At the 12-month endpoint, risedronate EC 35mg weekly taken after breakfast increased BMD at the lumbar spine by 3.3%, and by 3.4% if taken before breakfast, not statistically different to the 3.1% increase seen with daily risedronate IR 5mg. No significant difference in the number of new vertebral fractures was seen between the 3 treatment groups at 12 months, indicating that weekly risedronate EC 35mg without fasting is as effective as risedronate IR 5mg daily while fasting in reducing the risk of vertebral fracture.[12]

Fracture reduction efficacy has been shown to be maintained with long term risedronate therapy, with annual vertebral fracture incidence remaining at the same reduced level throughout 7 years of treatment. [13] Efficacy persists after risedronate treatment is discontinued, with a 46% reduction in new vertebral fractures after a year off treatment compared to placebo (never treated).[14]

Adverse effects

The adverse event profile for risedronate EC 35mg (taken before or after breakfast) was found in the McClung trial to be similar to that of risedronate 5mg IR (mainly mild to moderate upper or lower gastrointestinal symptoms), with no statistical difference in frequency of adverse events or serious adverse events between the 3 treatment groups.[12] The incidence of serious adverse events was also similar between groups.[12] All three regimens were well tolerated.[12]

Medication-related osteonecrosis of the jaw (MRONJ) is a rare serious adverse effect of longer term (>4 years) bisphosphonate use in osteoporosis, occurring at <1 to 10 cases per 10,000 patients. Duration of therapy is a risk factor (> 4 years), and there is a strong association between MRONJ and dental surgery such as extractions.[1] Good dental hygiene and appropriate preventative dental treatment is recommended prior to bisphosphonate therapy.[6] There are no data available to suggest whether discontinuation of bisphosphonate treatment in patients requiring dental procedures reduces the risk of MRONJ.[6] Recommendations around discontinuation for dental treatment are conflicting.[1]

Atypical fracture of the femur (AFF) is also rarely reported with bisphosphonate use, estimated at 1 fracture per 1000 years of treatment.[15] Over 5 years use of bisphosphonates may be associated with higher risk (100 per 100,000 person years), although there are few data in this area.[1] Case reports suggesting an association between alendronate use and AFF have been published.[16-18] There is little data on the incidence of AFF associated with risedronate. However, studies to date suggest that AFF risk is higher with alendronate compared to risedronate.[17] However, vigilance is required in patients who have undergone prior treatment with alendronate.[6]

Associate Professor Gullotta's take home message

Patient compliance is very important for all medications, but especially in conditions such as osteoporosis with minimal or no symptoms. Remembering to take the medication is a challenge for prescribers and patients alike.

The role of the Pharmacist in osteoporosis is very important in monitoring compliance and looking out for potential side effects that may lead to discontinuation of the medication by patients. The aim of treatment is to improve BMD and prevent fractures, which requires adherence and compliance with long term therapy.

Weekly Actonel enteric coated (EC) formulation is as effective as the immediate release (IR) daily formulations, but has patient acceptability and tolerability advantages over the IR and daily formulations, leading to potential positive impacts on adherence and compliance.

The enteric coated formulation of risedronate has an important pharmacological function. Unlike the IR formulations of risedronate, here are no food restrictions with Actonel EC 35mg, which can be taken with or without breakfast as long as the patient remains upright for at least 30 minutes after taking the tablet.

There are also potential adherence and compliance gains in the weekly dosing regimen of Actonel EC 35mg compared to the daily dosing regimen of IR risedronate 5mg, leading to potential improved bone health outcomes for patients.

It is the role of the Pharmacist to inform the patient of the various bisphosphonate dosages available and advise the patient to discuss these with their doctor, who can prescribe and tailor the best treatment plan for them. Included in this plan would be the role of calcium and vitamin D supplementation if required.

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