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NEWSLETTER

Summer 2011

AUCKLAND Bonedensity
Managing Bone Health

TWO NEW OSTEOPOROSIS TREATMENTS FUNDED

Executive Summary

1. Teriparatide (FORTEO) is the first anabolic bone agent to be available in New Zealand. It is given by daily subcutaneous injection for 18 months.
2. Raloxifene (EVISTA) is a daily tablet with a modest oestrogen-like action upon bone.

Teriparatide *(clinically important)*

Teriparatide is the pharmaceutical name for the first 34 amino acids of parathyroid hormone which, in its intact form, consists of 84 amino acids. The intact protein is marketed in some countries for the treatment of osteoporosis, but does not appear to have any specific advantages over teriparatide.

Teriparatide binds to PTH receptors on the osteoblast, **activating these bone building cells**, and indirectly switching on osteoclastogenesis and bone resorption. Thus, it increases both facets of bone turnover. Historically, PTH has been regarded as having a negative effect on bone mass, activating bone resorption more than bone formation, since bone loss has generally been reported in primary hyperparathyroidism. However, when PTH is administered intermittently it appears that the formation – resorption balance is reversed, and while both are increased, **formation is increased more**. Thus teriparatide 20µg daily over 18 months increases spine density by 10%, almost twice as much as the increase seen with alendronate (McClung 2005) though the increases in the femoral neck over this time period are roughly the same as those seen with alendronate. In the phase 3 trial, (Neer 2001) these changes were associated with dramatic decreases in fractures – **a 65% decrease in vertebral fractures** and **a 50% reduction in total non-vertebral fractures**, the latter being rather better than has been observed in similar trials of our current therapies.

Teriparatide is fundamentally different from other available therapies in that it acts primarily by increasing osteoblast activity, so building new bone. Thus, **it is an anabolic therapy**, whereas the **bisphosphonates** and other newer agents, such as denosumab, principally work by inhibiting bone resorption by osteoclasts i.e. they **are antiresorptives**. Anabolics theoretically have the potential to "cure" osteoporosis by restoring bone mass and bone architecture, whereas antiresorptives essentially prevent further deterioration, and probably only achieve increases in bone density through increasing mineralisation of existing bone.

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While the efficacy of teriparatide is exciting, there are issues of safety and convenience that need to be balanced against this. It is administered by **daily subcutaneous injections** which are relatively straight forward since they use a **pen device similar to that used with insulin**. However, this requires substantially more patient buy-in that is necessary with weekly alendronate tablets or annual zoledronate infusions. The original phase 3 trial was terminated prematurely because of the high incidence of osteosarcomas found in a long-term, high-dose, safety study in rats. After almost a decade of clinical use, this has not emerged as a problem in humans, but **the duration of use is still limited to 18-24 months per patient**. A further consideration substantially limiting its use has been price, which has typically been about $10,000 per year. Pharmac have negotiated a reimbursement at about half this level, but it is still more than 10 times more expensive than other agents available in this country.

The conditions for reimbursement of teriparatide have been framed to make it **available for patients who have had further fractures while receiving first-line therapies, such as bisphosphonates**. Thus, patients are required to have had at least two fractures, one of which has occurred after at least 12 months of continuous therapy with alendronate, zoledronate, or raloxifene. In addition, the bone density T-score must be lower than -3.0. There are a number of patients who will meet these criteria and they will be reimbursed for therapy for over a period of 18 months.

There is a range of practice with respect to the management of the other anti-osteoporosis therapies during teriparatide treatment. Usually antiresorptive therapy is discontinued while teriparatide is administered, then reinstituted immediately afterwards, so that the gains in bone density are not lost over the few months after cessation of therapy - a so-called “build and lock” regimen.

Teriparatide is possibly the most effective therapy currently available for patients with osteoporosis. Its restriction to those with severe osteoporosis which responds poorly to antiresorptives is probably appropriate in most cases, because of the cost of the therapy and the need for daily subcutaneous injections. While it can be prescribed by any doctor, it is probably sensible that such patients with severe osteoporosis are managed by doctors with a special interest in the problem. It represents **an important addition to the treatment options available** in osteoporosis, and is available via a Special Authority application.

Raloxifene *(clinically less important)*

Raloxifene is another agent which has been available overseas for almost a decade, but not reimbursed in New Zealand until this year. Like tamoxifen, it was developed as an anti-oestrogen for use in the management of breast cancer but was subsequently found to act on bone as a weak oestrogen agonist. Thus, its effects on bone turnover and bone density are about half those of conventional hormone replacement therapy, but it does reduce vertebral fractures by about 30%. However, it has no effect on non-vertebral fractures or hip fractures. This considerably limits its utility, though **some doctors have used it to maintain bone density in women in their 50s or 60s who are markedly osteopenic** but whose absolute fracture risk is not high enough to justify the use of bisphosphonates. It is generally well tolerated, but does increase hot flushes in some early postmenopausal women. It produces a **reduction in newly diagnosed breast cancers of about 70%**, increases rates of venous thromboembolic events (similar to oestrogen), but does not influence cardiovascular event rates. Thus, finding the appropriate therapeutic niche for raloxifene has been challenging. It is available via a Special Authority application on similar criteria to alendronate and zoledronate.