Emerging Drug List

TERIPARATIDE FOR THE TREATMENT OF OSTEOPOROSIS

Generic (Trade Name): Teriparatide (Forteo™)
Manufacturer: Eli Lilly
Indication: In the US teriparatide is indicated for the treatment of osteoporosis in postmenopausal women who are at risk for fracture and to increase bone mineral density (BMD) in men with primary or hypogonadal osteoporosis.¹

Current Regulatory Status: Teriparatide was approved by the US Food and Drug Administration in November 2002.² Teriparatide is currently under review by Health Canada and a potential Canadian marketing date has not been established (Stephanie Batoules, Eli Lilly Canada, Inc., Scarborough, ON: personal communication, 2003 Jan 20). Teriparatide was previously marketed in the US under the trade name Parathar™ (Rhone-Poulenc Rorer) and was used to aid clinicians in creating a differential diagnosis between hypoparathyroidism and pseudo-hypoparathyroidism. The manufacturer voluntarily withdrew the drug from the US market in January 1997.³

Description: Natural human PTH (hPTH) contains 84 amino acids. Teriparatide is a synthetic, recombinant polypeptide hormone consisting of the first 34 amino acids of hPTH.³ Teriparatide appears to stimulate osteoblasts to form new bone (as does hPTH). The anabolic effects of teriparatide in humans can cause an increase in skeletal mass, bone formation and resorption and bone strength. Teriparatide is available as 20 mcg cartridges to be administered by subcutaneous (SC) injection with the use of a pen device.³

Current Treatment: Current options for treating osteoporosis include bisphosphonates (e.g. alendronate, etidronate, risedronate), hormone replacement therapy (HRT as an oral, topical or transdermal formulation), raloxifene and salmon calcitonin (both nasal and SC).⁴

Cost: In the US the wholesale price of teriparatide is US$20 per day or US$7,300 per year.⁵ No cost information for Canada is available at this time.

Evidence: The efficacy of teriparatide in osteoporosis has been evaluated in several randomized controlled trials including comparative trials.⁶-¹⁴ The published trials describe the use of teriparatide in postmenopausal women, women receiving the gonadotropin-releasing hormone analog nafarelin, postmenopausal women also receiving corticosteroids and men with idiopathic osteoporosis. Studies in men and postmenopausal women with osteoporosis are briefly discussed below.

Teriparatide vs. placebo: Neer et al. compared teriparatide 20 or 40 mcg daily to placebo in 1,637 postmenopausal women with osteoporosis for two years.⁷ All women received calcium (1,000 mg daily) and vitamin D (400-1,200 units daily). Teriparatide use was...
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associated with a 9.7% and 13.7% increase in lumbar spine BMD and a 2.8% and 5.1% increase in femoral neck BMD from baseline (20 and 40 mcg doses, respectively). New vertebral fractures occurred in 14%, 5% and 4% of women in the placebo, teriparatide 20 mcg and 40 mcg groups, respectively (NNT for 40 mcg daily is 10, 95% CI: 8 to 17). New nonvertebral fractures occurred in 10%, 6% and 6% of women in the placebo and teriparatide groups, respectively (NNT for 40 mcg daily is 25, 95% CI: 14 to 127).

The data from the Neer et al. trial were re-evaluated to examine the effects of teriparatide specifically in the older population and was recently published by Marcus et al. The results of the re-analysis showed that teriparatide resulted in a greater increase in vertebral BMD in women over 65 years of age than in younger women. There was no difference, however, in the relative risk reduction for vertebral fractures amongst the different age groups.

**Teriparatide vs. HRT:** Lindsay et al. compared teriparatide 25 mcg SC daily combined with HRT versus HRT alone in 34 postmenopausal women with osteoporosis over a three year period. At the completion of the trial, women in the teriparatide group experienced a mean increase in BMD of 13% in the lumbar vertebrae (p<0.001 compared to placebo) and 2.7% in the hip (p=0.005 compared to placebo), while women in the control group had no significant change from baseline.

**Teriparatide vs. alendronate:** Body et al. compared the effects of teriparatide to alendronate on BMD, nonvertebral fracture rates and bone turnover in 146 postmenopausal women with osteoporosis over a two year treatment period in a randomized, double-blind, parallel-group study. The subjects were randomized to teriparatide 40 mcg SC daily with oral placebo or alendronate 10 mg orally daily with SC placebo. The median duration of treatment was 14 months. Lumbar spine BMD was significantly greater in the teriparatide group compared to alendronate at three months (12.2 vs. 5.6%, p<0.001) and at endpoint (15.1 vs. 6.6%, p<0.001). Femoral neck BMD and total body BMD was also significantly greater in the teriparatide group compared to alendronate (p<0.001). Nonvertebral fractures were significantly lower with teriparatide compared to alendronate (4.1 vs. 13.7%, p=0.042).

**Teriparatide in men:** Kurland et al. evaluated teriparatide 25 mcg SC daily in 23 men (mean age 50 yrs, 95% CI: 46 to 54) with idiopathic osteoporosis in a randomized, placebo-controlled, 18 month trial. All men also received daily calcium 1,500 mg and vitamin D 400 units. At 18 months teriparatide was associated with a 13.5% increase in bone mass at the lumbar spine (p<0.001 compared to placebo) and 2.9% increase in femoral neck BMD (p<0.05 vs. baseline).
Orwoll et al. recently published a larger study in 437 men with spine or hip BMD greater than two standard deviations below normal. Men were randomized to teriparatide 20 or 40 mcg daily or placebo. At 11 months spine BMD was increased by 5.9% and 9.0% over baseline in the 20 and 40 mcg groups respectively. Femoral neck BMD was increased by 1.5% and 2.9% in the 20 and 40 mcg groups, respectively (p<0.05 for all results).

Teriparatide was generally well tolerated in clinical trials. Teriparatide increased the number of patients experiencing dizziness by 2.6% (95% CI: 0 to 5) and leg cramps by 1.3% (95% CI: 0.2 to 2.9) in two phase III trials. Other adverse effects that were reported with more frequency with teriparatide than placebo include nausea, headache, asthenia, hypertension, syncope, dyspepsia, constipation, vomiting, arthralgia, depression, insomnia, rhinitis, cough, dyspnea and rash.

Teriparatide use in rats was associated with an increased incidence of osteosarcoma. These studies used 3 to 60 times the human dose. No cases of osteosarcoma have been reported in humans, however, a US FDA black box warning indicates teriparatide should not be used in patients that have an increased risk of osteosarcoma (e.g. patients with Paget's disease, high alkaline phosphatase levels).

Teriparatide is the first agent that functions by stimulating new bone formation. Other PTH-based therapies are currently being investigated in clinical trials. Additional trials have also investigated the use of combining PTH with bisphophonates, calcitonin and HRT. Canadian clinical practice guidelines already anticipate PTH will become a first line treatment for women with severe osteoporosis. Randomized controlled trials have so far demonstrated teriparatide's ability to reduce clinically important fractures in postmenopausal women. Additional comparative and pharmacovigilance evidence of clinically important effects will help establish the relative merits and risks of PTH-based therapies.

References:
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This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada.

These summaries have not been externally peer reviewed.

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