

Teriparatide

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

- Teriparatide is the first licensed treatment for established osteoporosis in postmenopausal women that acts by stimulating bone formation. It is a recombinant polypeptide fragment of human parathyroid hormone (rhPTH (1-34)) and is given by daily subcutaneous (sc) injection.
- In a pivotal trial, teriparatide increased bone mineral density (BMD) in the spine and femoral neck of postmenopausal women to a greater extent than placebo. Over a median of 19 months, the rate of new vertebral (5%) and non-vertebral fractures (6.3%) was significantly less with teriparatide than with placebo (14.3% and 9.7%, respectively).
- There are few direct comparative studies. Unpublished interim data from one study suggest that teriparatide is more effective than alendronate in increasing spinal BMD.
- Preliminary data indicate that teriparatide can be used safely with hormone replacement therapy with additive effect. However, studies with other PTH preparations suggest no increased benefit when calcitonin is added to PTH and a potential detrimental effect when combined with alendronate.
- Teriparatide is licensed for a maximum of 18 months treatment. Prescribing will be specialist initiated and likely to be limited to patients unresponsive to, or intolerant of, other treatments and who already have, or are at high risk of osteoporotic fracture.

Introduction

Teriparatide is a recombinant polypeptide consisting of the initial 34 amino acids of human parathyroid hormone (hPTH 1-34). In contrast to other available treatments for osteoporosis, teriparatide acts by stimulating bone formation, rather than inhibiting bone resorption.

Evidence

The efficacy of teriparatide in the treatment of osteoporosis in postmenopausal women has been investigated in one pivotal trial.¹ This multicentre study randomised 1637 women to one of two doses of teriparatide (20microgram or 40microgram) or placebo, administered daily by sc injection. Only the results relating to the 20microgram licensed dose are reported below, unless otherwise specified. All subjects received calcium (1000mg) and vitamin D (up to 1200IU) daily. Women were at least 5 years postmenopausal and had a minimum of one moderate, or two mild, atraumatic vertebral fractures.

During a median follow-up of 19 months, new vertebral fractures (identified by radiography) occurred in 5% of patients on teriparatide and in 14.3% of patients on placebo. These data equate to a relative risk of 0.35 (95%CI 0.22 to 0.55, $P \leq 0.001$) and a number needed to treat (NNT) of 11. The number of subjects with symptomatic vertebral fractures was not documented.

New non-vertebral fractures occurred in 6.3% and 9.7% of patients on teriparatide and placebo, respectively (relative risk 0.65, 95%CI 0.43 to 0.98, $P = 0.04$), giving an NNT of 29. Four patients receiving placebo and two on teriparatide suffered hip fractures.

Teriparatide increased BMD in the spine by a mean of 9% and femoral neck by 3%, compared to a mean increase of 1.1% and a decrease of 1%, respectively, with placebo. A statistically significant increase in spinal BMD was evident after 3 months of treatment.²

A further analysis of study data

Brand Name, (Manufacturer): Forsteo (Eli Lilly)

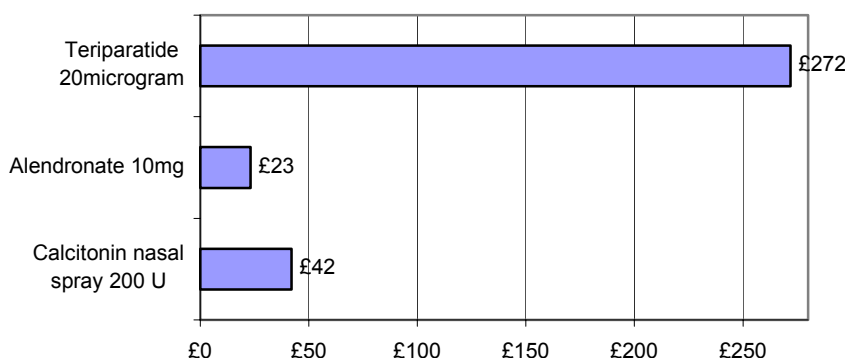
BNF Therapeutic Class: Drugs affecting bone metabolism: 6.6

Licensed Indications: Treatment of established osteoporosis in postmenopausal women.

Dosage and Administration: 20microgram once daily by subcutaneous (sc) injection into the abdomen or thigh. Maximum total duration of treatment is 18 months. Teriparatide is presented in 3ml cartridges containing 28 doses within a pre-filled disposable pen. It must be stored in a refrigerator.

Marketed: November 2003

Cost Comparisons: For 28 days treatment (prices: MIMS Nov 2003)



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

reported that the effect of teriparatide on vertebral fracture rate was largely independent of age, spinal BMD and prevalent fractures at baseline, suggesting that the drug is beneficial across a broad range of age and disease severity.³

In view of the restricted treatment period imposed by the licence, the duration of effect once teriparatide is stopped is of interest. A sub-group of women from the above study were monitored for a further 6 months following treatment withdrawal. Atraumatic non-vertebral fractures were noted in 0.7% of patients previously treated with teriparatide and 2.4% treated with placebo, suggesting a persistence of benefit with teriparatide.⁴ About one-third of patients took other osteoporosis treatments during the follow-up period. Unpublished data suggest that benefits may continue for up to 18 months after treatment with teriparatide is discontinued.²

There are few comparative studies. In the pivotal study,¹ the increase in spinal BMD and reduction in risk of vertebral fractures noted with teriparatide were greater than those reported in studies of antiresorptive agents, e.g. alendronate. However, such cross-trial comparisons require cautious interpretation. The ongoing FACT (Forteo Alendronate Comparison Trial) study, involving 206 postmenopausal women with osteoporosis-related fractures, directly compares teriparatide 20microgram and alendronate 10mg daily. Unpublished interim data indicate that 6 months treatment with teriparatide increases spinal BMD to a greater extent than treatment with alendronate (mean 4.7% vs. 3.2%, respectively).⁵

Combined use of teriparatide with antiresorptive agents might be expected to have an additive effect. A 15 month trial in 247 postmenopausal women with low BMD reported that subjects receiving teriparatide 40microgram daily plus HRT had significantly increased BMD compared to those receiving HRT alone.⁶

Further data on combined use are only available for other preparations of PTH. In a study adding sequential calcitonin to cyclical hPTH (1-34), calcitonin conferred no benefit to cyclical hPTH alone.⁷ Two recent studies reported that using PTH with alendronate resulted in smaller increases in BMD at some

skeletal sites compared to PTH alone.^{8,9} In addition, biochemical markers of bone turnover indicated that bone formation was markedly increased in the PTH group but not in the combination group, suggesting that alendronate may impair the anabolic activity of PTH. These findings indicate that PTH and alendronate should not be used together.

Teriparatide has been shown to favourably influence BMD in men with osteoporosis.¹⁰ A licence for treatment in men has been granted in the US and Switzerland but not in the EU.

Safety

In the pivotal study, 6% of women on teriparatide and 6% on placebo withdrew because of side effects; teriparatide was associated with a higher incidence of dizziness (9%) and leg cramps (3%) than placebo (6% and 1%, respectively).¹ Dose reduction was necessary in 15 women taking teriparatide and three taking placebo due to hypercalcaemia, and one woman in each group withdrew from the study as a consequence of this adverse event. Antibodies to PTH were detected in 3% of women receiving teriparatide and in one receiving placebo, but this had no discernible effect on biochemical parameters.

A dose-dependent association between teriparatide and osteosarcoma has been noted in rats. This finding led to the premature closure of a number of studies, but the trial programme was restarted after extensive analysis of the data. The effect in rats has been tentatively attributed to very high doses given for two-thirds of the animals' lifespan from a young age. No cases of osteosarcoma have been seen in clinical trials with teriparatide or with other PTH products which have been used for up to 3 years.

Appendix I: Bibliography

Place in Therapy

Current treatments for established postmenopausal osteoporosis include bisphosphonates, calcitonin, raloxifene and HRT (now second-line following the results of the WHI trial). There is evidence that these antiresorptive agents reduce vertebral fractures and that bisphosphonates also reduce the risk of hip fracture in women under 80 years of age.

Teriparatide has demonstrated efficacy in increasing BMD, particularly in the spine, and reducing vertebral and non-vertebral fracture rates. Larger trials are needed to assess its effect on rate of hip fracture.

Teriparatide is restricted to a maximum of 18 months use and has to be administered by daily sc injection. Prescribing should be initiated by a specialist and use is likely to be limited to patients who have not responded to, or are intolerant of other agents, and who already have, or are at significant risk of osteoporotic fracture. It should be given with calcium and vitamin D supplements if dietary intake is inadequate, but should not be taken with bisphosphonate therapy.

Key Papers

1. Neer RM, Arnaud CD et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; **344**: 1434-41

Risk Management Issues:

Teriparatide is presented as a multidose cartridge contained in a pre-filled disposable pen. The pen must be stored between 2-8°C at all times and returned to the refrigerator immediately after use. Once opened, the pen must be disposed of after 28 days.

Teriparatide will be supplied direct to patients by Healthcare at Home. A video demonstration of pen use is included in the starter kit and all packs contain a user manual. Training will also be given by a nurse on a home visit and Lilly are providing a 24 hour help line.¹¹

Produced for the UK Medicines Information Service

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The information contained in this document will be superseded in due course. Not to be used for commercial purposes. May be copied for use within the NHS.

Appendix I

Bibliography

References

1. Neer RM, Arnaud CD et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344:1434-41
2. Anon. Forsteo EPAR, EMEA 2003 (CPMP/6598/02) (available at: www.emea.eu.int)
3. Marcus R, Wang O et al. The skeletal response to teriparatide is largely independent of age, initial bone mineral density, and prevalent vertebral fractures in postmenopausal women with osteoporosis. *J Bone Miner Res* 2003;18:18-23
4. Lindsay R, Scheele WH et al. Maintenance of reduction in non-traumatic, non-vertebral fractures 6 months after discontinuation of LY333334 [recombinant human parathyroid hormone (1-34), RHPH (1-34)] use in postmenopausal women with osteoporosis. *Endocrine Society Annual Meeting 2001*. Abstract S20-2
5. Anon. Lilly challenges Merck & Co in osteoporosis. *Scrip* 2002, no. 2799, p21
6. Schneider BS. Executive summary for advisory committee. Forsteo (teriparatide injection, rDNA origin) NDA 21-318. Food and Drug Administration. 27 July 2001 (available at: www.fda.gov)
7. Hodsmann AB, Fraher L et al. A randomized controlled trial to compare the efficacy of cyclical parathyroid hormone versus cyclical parathyroid hormone and sequential calcitonin to improve bone mass in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 1997;82:620-8
8. Black DM, Greenspan SL et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med* 2003;349:1207-15
9. Finkelstein JS, Hayes A et al. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med* 2003;349:1216-26
10. Kurland ES, Cosman F et al. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. *J Clin Endocrinol Metab* 2000;85:3069-76
11. Anon. New osteoporosis drug launched. *Pharm J* 2003;271:637

Also see:

UKMi/NPC. Teriparatide. *New Drugs in Clinical Development*. June 2002. 3/02/05