Osteoporosis. Strontium ranelate, given orally with calcium and vitamin D supplements, has been found to reduce the risk of vertebral[1] and non-vertebral[2] fractures in postmenopausal women with osteoporosis. A pooled analysis of data from these 2 studies concluded that strontium ranelate reduced both vertebral and non-vertebral fractures in patients aged 80 years or older.[3] Protection against fractures was detected within 12 months, and sustained throughout 3 years of treatment. Hip fractures were also reduced over 3 years, but this did not reach statistical significance; the authors concluded that the analysis may not have been sufficiently powered in this respect. A systematic review[4] concluded that while strontium ranelate reduces vertebral fractures, there is less of a reduction with non-vertebral fractures, and the effect on hip fracture remains unclear. Some have cautioned about the interpretation of bone mineral density (BMD) changes with strontium ranelate, since stronger X-ray attenuation by strontium compared with calcium must be corrected for to avoid overestimating the effect. However, increases in BMD could be useful clinically in gauging long-term compliance.[5]

A review[6] of the place of strontium ranelate in therapy considered that although it might be an alternative in patients who could not tolerate a bisphosphonate there was no convincing published evidence to support claims that it stimulated bone formation as well as reducing resorption. Further reviews[4,7] concluded that additional research to confirm its mechanism of action is required and that long-term fracture data are needed, along with comparative trials evaluating the efficacy of strontium ranelate relative to other therapies such as bisphosphonates.

1. Meunier PJ, *et al.* The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004; **350:** 459–68.
2. Reginster JY, *et al.* Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: treatment of peripheral osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 2005; **90:** 2816–22.
3. Seeman E, *et al.* Strontium ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. *J Bone Miner Res* 2006; **21:** 1113–20.
4. O'Donnell S, *et al.* Strontium ranelate for preventing and treating postmenopausal osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 01/06/07).
5. Fogelman I, Blake GM. Strontium ranelate for the treatment of osteoporosis: is useful, but changes in bone mineral density need careful interpretation. *BMJ* 2005; **330:** 1400–1.
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7. Stevenson M, *et al.* The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. *Health Technol Assess* 2007; **11:** 1–134.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Osteovital; Protos; ***Austral.:*** Protos; ***Belg.:*** Protelos; ***Braz.:*** Protos; ***Cz.:*** Osseor; Protelos; ***Denm.:*** Protelos; ***Fr.:*** Protelos; ***Ger.:*** Protelos; ***Gr.:*** Protelos; ***Hong Kong:*** Protos; ***Hung.:*** Protelos; ***Indon.:*** Protos; ***Irl.:*** Protelos; ***Ital.:*** Osseor; Protelos; ***Malaysia:*** Protaxos; ***Neth.:*** Osseor; Protelos; ***NZ:*** Protos; ***Philipp.:*** Protos; ***Pol.:*** Protelos; ***Port.:*** Osseor; Protelos; ***Rus.:*** Bivalos (Бивалос); ***S.Afr.:*** Protos; ***Singapore:*** Protos; ***Spain:*** Osseor; Protelos; ***Swed.:*** Protelos; ***UK:*** Protelos.

Teriparatide *(USAN, rINN)*

(1-34) Human parathormone; (1-34) Human parathyroid hormone; 1-34 Parathormone (human); hPTH 1-34; Human parathormone (1-34); Human parathyroid hormone (1-34); Human PTH (1-34); LY-333334; Parathyroid hormone peptide (1-34); Teriparatid; Teriparatida; Tériparatide; Teriparatidum.

Терипаратид

$C_{181}H_{291}N_{55}O_{51}S_2$.
CAS — 52232-67-4.
ATC — H05AA02.
ATC Vet — QH05AA02.

Teriparatide Acetate *(USAN, rINNM)*

Acetato de teriparatida; Tériparatide, Acétate de; Teriparatidi Acetas.

Терипаратида Ацетат

$C_{181}H_{291}N_{55}O_{51}S_2.xH_2O.yC_2H_4O_2$.
CAS — 99294-94-7 (teriparatide acetate).
ATC — H05AA02.
ATC Vet — QH05AA02.

Adverse Effects and Precautions

Gastrointestinal disturbances, pain in the limb of injection, headache, and dizziness are the most common adverse effects in patients treated with subcutaneous teriparatide. Dizziness, vertigo, and syncope may be associated with transient orthostatic hypotension in some patients, particularly when beginning treatment. Those so affected should not drive or operate potentially hazardous machinery. Asthenia, arthralgia, and rhinitis may occur. Angina pectoris, depression, dyspnoea, leg cramps, pneumonia, urinary disorders, and sciatica have also been reported. A metallic taste, tingling of the extremities, and pain at the site of injection have occasionally been associated with the intravenous infusion of teriparatide acetate. It is a peptide and the possibility of systemic hypersensitivity reactions should be borne in mind. Hypercalcaemia may develop with teriparatide or the acetate and it is therefore contra-indicated in patients with pre-existing hypercalcaemia.

Teriparatide is contra-indicated in patients with severe renal impairment and should be used with caution with those with moderate impairment.

There have been reports of osteosarcoma in *rats* given teriparatide and patients who may be at increased risk, including those with a history of skeletal metastases or previous radiotherapy to the skeleton, should not receive it. It is also contra-indicated in those with metabolic bone disease including Paget's disease and hyperparathyroidism, or unexplained elevations of serum alkaline phosphatase. Use in children or those with open epiphyses is also contra-indicated. In the UK treatment is also limited to a maximum of 18 months.

Pharmacokinetics

Teriparatide is extensively absorbed after subcutaneous injection; peak plasma concentrations are reached after about 30 minutes. Absolute bioavailability is reported to be about 95%. The serum half-life is 5 minutes after intravenous use, and approximately 1 hour after subcutaneous injection (reflecting time needed for absorption from the injection site). No studies have been done on the metabolism or excretion of teriparatide; parathyroid hormone is believed to be enzymatically metabolised in the liver and excreted by the kidneys.

Uses and Administration

Teriparatide is a synthetic polypeptide that consists of the 1-34 amino-acid biologically active N-terminal region of human parathyroid hormone (p.1103). It is used in the treatment of established postmenopausal osteoporosis, especially in those with a high fracture risk, and in men with primary or hypogonadal osteoporosis who are at increased risk of fracture. The usual dose is 20 micrograms subcutaneously daily into the thigh or abdominal wall. Treatment is limited to a maximum of 18 months in the UK, although it has been used for up to 2 years in the USA. Teriparatide acetate has been given by intravenous infusion in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism.

Hypoparathyroidism. Hypoparathyroidism is characterised by a deficiency in endogenous parathyroid hormone, whereas pseudohypoparathyroidism is characterised by resistance to the effects of parathyroid hormone (see p.1087). Teriparatide acetate is used *diagnostically* to distinguish between these 2 conditions.[1] A synthetic 1-38 fragment of human parathyroid hormone (hPTH 1-38) has been used similarly.[2] Teriparatide has also been used to *treat* hypoparathyroidism.[3-5]

1. Mallette LE. Synthetic human parathyroid hormone 1-34 fragment for diagnostic testing. *Ann Intern Med* 1988; **109:** 800–4.
2. Kruse K, Kracht U. A simplified diagnostic test in hypoparathyroidism and pseudohypoparathyroidism type I with synthetic 1-38 fragment of human parathyroid hormone. *Eur J Pediatr* 1987; **146:** 373–7.
3. Winer KK, *et al.* Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism. *JAMA* 1996; **276:** 631–6.
4. Winer KK, *et al.* A randomized, cross-over trial of once-daily versus twice-daily parathyroid hormone 1-34 in treatment of hypoparathyroidism. *J Clin Endocrinol Metab* 1998; **83:** 3480–6.
5. Winer KK, *et al.* Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. *J Clin Endocrinol Metab* 2003; **88:** 4214–20.

Osteoporosis. Parathyroid hormone is capable of stimulating both formation and resorption of bone. Continuous infusion of teriparatide leads to a persistent elevation of parathyroid hormone and greater bone resorption by stimulating osteoclasts, with a net decrease in bone volume, and resultant hypercalcaemia; in contrast, daily (intermittent) injections increase bone volume by increasing osteoblastic proliferation.[1-3] Teriparatide appears to have less effect on cortical than trabecular bone,[3] suggesting that, although it may be helpful in preventing vertebral fractures, its impact on fractures of the proximal femur may be more limited. However, while treatment with teriparatide substantially increases lumbar spine bone mineral density (BMD), beneficial increases are also seen at the hip,[1] and in a pivotal study (the Fracture Prevention Trial)[4] in **postmenopausal** women with osteoporosis (p.1084), it decreased the risk of both vertebral and non-vertebral fracture. In a follow-up study, the reduction in vertebral fracture risk in patients treated with teriparatide for a mean of 19 months persisted for at least an additional 18 months after daily treatment was stopped.[5] Teriparatide appears to improve bone geometry, with no detrimental effect on cortical bone.[6] In the UK, NICE recommends teriparatide as an option for the secondary prevention of osteoporotic fragility fractures in women aged 65 years and older who have had an unsatisfactory response to bisphosphonates or who are intolerant to bisphosphonates, and who have an extremely low BMD (4 standard deviations or more below the mean) or a very low BMD (3 standard deviations or more) plus one or more additional risk factors.[7] It has been pointed out that evidence of reduction in teriparatide's effect with current or recent alendronate therapy (see below) might make its use as a second-line agent problematic.[8]

Data on combination therapy are limited, but some studies suggest that teriparatide with HRT is more effective than HRT alone.[9] The effect of teriparatide with the antiresorptive bisphosphonates has yet to be determined.[2,6,9,10] Although there is some suggestion that teriparatide still increases bone formation after treatment with alendronate,[9] a study in men found that, when given together, alendronate impaired the anabolic effects of teriparatide.[11] For this reason, some consider that teriparatide be started immediately after stopping bisphosphonates.[10] It has been suggested that the degree of suppression of bone turnover before treatment may dictate the response to teriparatide.[6] A study of daily or cyclical teriparatide in women with osteoporosis found that although the teriparatide-induced increase in BMD may be slightly lower in women who had previously taken alendronate than in those who had never received it, the increase in spinal BMD was still impressive. Intermittent cyclical treatment with teriparatide was found to have similar effects on BMD to those induced by daily dosage.[12]

In postmenopausal women with osteoporosis taking HRT and **corticosteroids**,[13] the addition of teriparatide significantly increased BMD of the lumbar spine; modest changes in hip bone mass were not significant.

In **men** with osteoporosis, teriparatide increased BMD in the lumbar spine and at the femoral neck;[9] risk of fracture was also reduced.[1]

1. Cappuzzo KA, Delafuente JC. Teriparatide for severe osteoporosis. *Ann Pharmacother* 2004; **38:** 294–302.
2. Madore GR, *et al.* Parathyroid hormone. *J Am Acad Orthop Surg* 2004; **12:** 67–71.
3. Brixen KT, *et al.* Teriparatide (biosynthetic human parathyroid hormone 1–34): a new paradigm in the treatment of osteoporosis. *Basic Clin Pharmacol Toxicol* 2004; **94:** 260–70.
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5. Lindsay R,*et al.* Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. *Arch Intern Med* 2004; **164:** 2024–30.
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8. Anonymous. Teriparatide for postmenopausal osteoporosis. *Drug Ther Bull* 2004; **42:** 93–5.
9. Quattrocchi E, Kourlas H. Teriparatide: a review. *Clin Ther* 2004; **26:** 841–54.
10. Deal C. The use of intermittent human parathyroid hormone as a treatment for osteoporosis. *Curr Rheumatol Rep* 2004; **6:** 49–58.
11. Finkelstein JS, *et al.* The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med* 2003; **349:** 1216–26.
12. Cosman F, *et al.* Daily and cyclic parathyroid hormone in women receiving alendronate. *N Engl J Med* 2005; **353:** 566–75.
13. Lane NE, *et al.* Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. *J Clin Invest* 1998; **102:** 1627–33.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Forteo; ***Austral.:*** Forteo; ***Belg.:*** Forsteo; ***Braz.:*** Forteo; ***Canad.:*** Forteo; ***Chile:*** Forteo; ***Cz.:*** Forsteo; ***Denm.:*** Forsteo; ***Fin.:*** Forsteo; ***Fr.:*** Forsteo; ***Ger.:*** Forsteo; ***Gr.:*** Forsteo; ***Hong Kong:*** Forteo; ***Hung.:*** Forsteo; ***Irl.:*** Forsteo; ***Israel:*** Forteo; ***Ital.:*** Forsteo; ***Malaysia:*** Forteo; ***Mex.:*** Forteo; ***Norw.:*** Forsteo; ***NZ:*** Forteo; ***Philipp.:*** Forteo; ***Port.:*** Forsteo; ***S.Afr.:*** Forteo; ***Singapore:*** Forteo; ***Spain:*** Forsteo; ***Swed.:*** Forsteo; ***Switz.:*** Forsteo; ***Thai.:*** Forteo; ***UK:*** Forsteo; ***USA:*** Forteo; ***Venez.:*** Forteo.

Tiludronate

ATC — M05BA05.
ATC Vet — QM05BA05.

Tiludronic Acid *(BAN, rINN)*

Acide Tiludronique; Ácido tildrónico; Acidum Tiludronicum; ME-3737; SR-41319; Tiludronihappo; Tiludronik Asit; Tiludronsyra. {[(*p*-Chlorophenyl)thio]methylene}diphosphonic acid.

Тилудроновая Кислота

$C_7H_9ClO_6P_2S$ = 318.6.
CAS — 89987-06-4.
ATC — M05BA05.
ATC Vet — QM05BA05.