

**parathyroid hormone 100mcg powder for injection (Preotact^o)
No. (356/07)**

Nycomed Ltd

9 February 2007

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

parathyroid hormone (Preotact^o) is accepted for restricted use within NHSScotland for women with severe osteoporosis and at least two prior vertebral fractures or equivalent high risk. It is restricted to initiation by specialists experienced in the treatment of osteoporosis following assessment of fracture risk including measurement of bone mineral density.

Parathyroid hormone reduced risks of vertebral fracture compared to placebo. A significant reduction in the incidence of vertebral but not hip fractures has been demonstrated. It has comparable cost-effectiveness to an alternative anabolic agent.

Overleaf is the detailed advice on this product.

**Vice-Chairman,
Scottish Medicines Consortium**

Indication

Treatment of osteoporosis in postmenopausal women at high risk of fractures. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated.

Dosing information

100mcg by subcutaneous injection once daily for up to two years

Product availability date

October 2006

Summary of evidence on comparative efficacy

Recombinant human parathyroid hormone (PTH) is an anabolic agent identical to endogenous PTH, which stimulates bone formation by direct effects on bone forming cells (osteoblasts), and thereby indirectly increases intestinal absorption of calcium and increases tubular re-absorption of calcium and excretion of phosphate in the kidney. The mechanism of action of anabolic agents differs from antiresorptive drugs such as bisphosphonates in that they stimulate bone formation and improve bone microarchitecture.

Bone mineral density

A double-blind trial recruited 238 women aged 55 to 85 years who were at least five years post-menopause and had a T-score < -2.5 at the spine, femoral neck or total hip or had at least one risk factor for osteoporosis (age \geq 65years, history of post-menopause fracture or maternal history of hip fracture) and a T-score < -2.0 at any of these sites. They received oral calcium 400mg to 500mg and vitamin D 400IU per day and were randomised equally to one of four treatments each administered daily: (1) PTH 100mcg subcutaneous (sc) injection in year one followed by oral alendronate 10mg in year two; (2) PTH 100mcg sc injection plus alendronate 10mg in year one followed by alendronate 10mg in year two; (3) PTH 100mcg sc injection in year one followed by placebo in year two: or (4) alendronate 10mg daily for two years. The primary outcome was mean change from baseline in bone mineral density (BMD) of the lumbar spine, assessed via dual energy x-ray absorptiometry (DEXA) scan. At one year, there were no significant differences between the groups for this, with mean changes of 6.3%, 6.1% and 4.6% in the respective groups that received PTH, PTH plus alendronate and alendronate. At year two, the mean increase in BMD of 12% seen in subjects who received PTH in year one followed by alendronate in year two was significantly greater than in each of the other groups. The mean increases in BMD for combination therapy in year one followed by alendronate in year two and for alendronate over both years were significantly greater than the 4.1% increase in subjects who received PTH in year one and placebo in year two.

BMD was assessed as a secondary outcome in the trial described below and an open-label extension to the study that facilitated treatment up to 24 months. The increase in lumbar BMD with PTH at 18 months of 6.5% was significantly greater than the 0.3% decrease with placebo. At 24 months the increase from baseline in lumbar spine and femoral neck BMD was 6.8% and 2.2% respectively.

Vertebral fractures

A double-blind trial recruited women who were at least one year post-menopause and who had a T-score at the lumbar spine, femoral neck or total hip < -2.5 (if aged 45-54 years) or < -2.0 (if aged \geq 55 years) and 1 to 4 vertebral fractures (only one of which was lumbar) or who

had a T-score at the lumbar spine, femoral neck or total hip < -3.0 (if aged 45-54 years) or < -2.5 (if aged ≥55 years). They received oral calcium 700mg and vitamin D 400IU daily and were randomised equally to placebo or PTH 100mcg sc injection daily for 18 months. The primary outcome was the incidence of new and/or worsened vertebral (thoracic and lumbar) fractures, assessed via semi-quantitative analysis of radiographs, in the intention-to-treat (ITT) population that included all subjects who had received at least one dose of study drug. This was significantly lower with PTH compared to placebo: 1.4% (n=18/1286) vs. 3.4% (n=42/1246), an absolute risk reduction of 2% and a relative risk reduction of 58% (95% confidence intervals (CI): 28% to 76%). The incidence of new vertebral fractures was also significantly lower with PTH compared to placebo: 1.3% (n=17/1286) vs. 3.4% (n=42/1246), an absolute risk reduction of 2.1% and a relative risk reduction of 61% (95% CI: 31% to 78%). There were no differences between groups in incidences of non-vertebral fractures.

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

The most common adverse effects with PTH were hypercalciuria and hypercalcaemia, which were reported by 39% and 25% of patients who received the licensed dose of PTH in the placebo-controlled trial described previously and a dose-finding study, with nausea (13.5%), headache (9.3%) and dizziness (3.9%) also commonly reported. In the trial that compared PTH to the bisphosphonate, alendronate, the incidences of adverse effects were similar with both drugs, although the types of adverse effects differed, with hypercalcaemia not observed with the bisphosphonate.

Summary of clinical effectiveness issues

Some vertebral fractures can be asymptomatic. The trial described previously that assessed fracture rate used a semi-quantitative analysis of radiographs to measure this outcome and did not provide additional data on relative rates of fractures that required clinical attention or intervention. Therefore, the effect of PTH on these is unknown.

The majority of women recruited to the trials described previously were at least five years post-menopause. Therefore, there are limited data on the benefits to be expected with PTH in women less than five years post-menopause.

Subgroup analysis of the placebo-controlled trial described previously indicates that patients with previous fractures and those with a very low lumbar BMD may obtain greater benefits with PTH than the total trial population.

The trial comparing PTH with alendronate assessed BMD, but not fracture rates. PTH was associated with a slightly greater non-significant increase in lumbar spine BMD compared to alendronate (6.3% vs. 4.6%). However, anti-fracture efficacy is not solely related to BMD and estimates of the relative benefits on fracture rates with the drugs cannot be derived from this outcome.

It has been suggested that the sequence in which anabolic agents and bisphosphonates are given is important; some studies have indicated that the response to PTH may be delayed or blunted when it is given after antiresorptive therapy.

There are no trials directly comparing PTH with teriparatide, which is the N-terminal (amino-acids 1-34) active fragment of the 84 amino-acid PTH molecule. In women who were at least

five years post-menopause and had osteoporosis plus at least one vertebral fracture, the licensed dose of teriparatide for a median of 19 months (range 18 to 23 months) was associated with a significantly lower rate of new vertebral fractures compared to placebo: 5% vs. 14.3%, corresponding to an absolute risk reduction of 9.3% and a relative risk reduction of 65% (95% CI: 45% to 78%). These patients appear to have a higher risk of vertebral fracture than those in the placebo-controlled trial of PTH, which limits an indirect comparison of the two drugs. There are no trials directly comparing PTH with any other drugs licensed for the treatment of postmenopausal osteoporosis; therefore, efficacy and safety relative to these are unknown.

Unlike teriparatide injection, this PTH preparation does not require refrigeration which may be an advantage for some patients.

Other data were also assessed but remain commercially confidential.*

Summary of comparative health economic evidence

The manufacturer provided an economic evaluation examining the cost-effectiveness of PTH in women at a high risk of vertebral fracture defined as women aged over 65 with two or more prior vertebral fractures and a T-score < -2.5. PTH was compared to three treatment strategies: no treatment, alendronate and teriparatide. The comparison with no active treatment was of limited relevance as the chosen patient population (those at high risk) should be on active treatment. The comparison with teriparatide was the more relevant option considered in the model. The Markov model structure was appropriate and looked at the flow of costs and benefits over a ten year time horizon. PTH and teriparatide were assumed to be used for a maximum treatment duration of 18 months. Utility values were taken from a published UK health technology assessment.

Compared to teriparatide, the manufacturer asserted that there was no significant difference between the two products in terms of outcomes and because PTH is slightly cheaper it would be preferred on cost-minimisation grounds. An indirect comparison with teriparatide was therefore necessary. This used clinical data on the fracture rates from the overall PTH trial population rather than a high-risk subgroup as patient numbers within this subgroup were small and not sub-randomised within the trial. As noted above, in practice benefits with PTH greater than those observed in the total trial population may be achieved in higher risk patients and as such the method the manufacturer chose for the analysis may be conservative. The incremental cost per QALY (ICER) of PTH compared to alendronate ranged from £107k to £150k per quality adjusted life year (QALY), depending on patient age. Cost effectiveness against alendronate was not demonstrated.

The analysis was presented concisely, used a range of comparators and included adequate sensitivity analysis to show the variability in the results. The results showed that the incremental cost effectiveness ratio for PTH dominates teriparatide and PTH is preferred on cost-minimisation grounds. PTH offers a treatment alternative for high-risk patients who would be eligible for treatment with teriparatide.

Summary of patient and public involvement

Patient Interest Group Submission: National Osteoporosis Society

Additional information: guidelines and protocols

The January 2005 National Institute for Health and Clinical Excellence (NICE) health technology assessment number 87: bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women is currently under review and an updated version, that includes strontium ranelate, is expected to be published in March 2007.

The June 2003 Scottish Intercollegiate Guidelines Network (SIGN) publication number 71, management of osteoporosis recommends the use of bisphosphonates, raloxifene and intranasal calcitonin for postmenopausal women with osteoporosis.

Additional information: previous SMC advice

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice on 8th December 2003 that teriparatide (Forsteo[®]) is accepted for restricted use within NHS Scotland for the treatment of established (severe) osteoporosis in post-menopausal women. This medicine should be restricted to initiation by specialists experienced in the treatment of osteoporosis following assessment of fracture risk including measurement of BMD. It is the first product to be licensed specifically for established (severe) post-menopausal osteoporosis. It has shown efficacy in reducing vertebral and non-vertebral fractures in post-menopausal women with prior vertebral fractures, particularly in a sub-group with documented severe osteoporosis. At the recommended daily dose it is expensive but appears to be cost-effective in women with proven osteoporosis who have developed fractures.

After review of a full submission, SMC issued advice on 8th July 2005 that strontium ranelate (Protelos[®]) is accepted for restricted use within NHS Scotland for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures when bisphosphonates are contra-indicated or not tolerated and then only in women aged over 75 with a previous fracture and T-score < -2.4 or other women of equivalent high risk. In the trial population of postmenopausal women, strontium ranelate reduced the risk of developing a vertebral fracture by 41%. In women aged ≥ 74 years with a femoral neck bone mineral density (BMD) T-score < -2.4 the risk of hip fractures was reduced by 36%. However equivalent cost-effectiveness to bisphosphonate therapy has not been demonstrated.

After review of a full submission, SMC issued advice on 6th January 2006 that ibandronic acid (Bonviva[®]) is accepted for use within NHS Scotland for the treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Ibandronic acid 150mg monthly is superior to daily ibandronic acid in terms of lumbar spine bone mineral density at 1 year. Compared with placebo, daily administration of ibandronic acid results in a relative risk reduction for vertebral fractures of 62%. Unlike some other bisphosphonates, efficacy in reducing femoral neck fractures (and other non-vertebral fractures) has not been established.

After review of an abbreviated submission, SMC issued advice on 9th May 2003 that risedronate sodium (Actonel[®]) once weekly formulation is recommended for general use within NHS Scotland. Risedronate sodium (Actonel[®]) is a once weekly formulation which

offers a convenient, cost neutral alternative to once daily medication for the prophylaxis and treatment of osteoporosis in postmenopausal women.

After review of an abbreviated submission, SMC issued advice on 4th October 2005 that alendronate / colecalciferol (Fosavance[®]) is accepted for use within NHS Scotland for the treatment of postmenopausal osteoporosis in patients at risk of vitamin D insufficiency who require treatment with both alendronate and vitamin D and for whom once-weekly administration is appropriate. The combination preparation is cost-saving compared to the two drugs administered separately. Weekly administration of vitamin D represents a departure from routine clinical practice. In patients who also require calcium supplementation this will have to be administered separately, using a calcium preparation that does not also contain vitamin D.

Additional information: comparators

Oral formulations of the bisphosphonates, ibandronic acid, risedronate, alendronate and etidronate and the oestrogen receptor modulator, raloxifene, and an intranasal formulation of calcitonin are licensed for treatment of postmenopausal osteoporosis. These have been recommended by NICE and SIGN. Strontium ranelate is also licensed for treatment of postmenopausal osteoporosis and has been accepted by SMC for restricted use within NHS Scotland. Teriparatide, which is a fragment of PTH hormone, is licensed for treatment of severe osteoporosis in postmenopausal women and has been accepted by SMC for restricted use within NHS Scotland.

Additional information: costs

Drug	Dose range	Annual cost (£)
Parathyroid hormone	100mcg sc daily	3394
Teriparatide	20mcg sc daily	3544
Calcitonin	200units in daily	547
Strontium ranelate	2g po daily	334
Ibandronic acid	150mg po monthly	257
Risedronate	5mg po daily or 35mg po weekly	249-264
Raloxifene	60mg po daily	222
Alendronate	10mg po daily or 70mg po weekly	95-301
Cyclical etidronate / Calcium carbonate	400mg po daily for 14 days 1.25g po daily for 76 days	86

Doses are shown for general comparison and do not imply therapeutic equivalence;
sc = subcutaneous injection; in = intranasal spray; po = orally;

Additional information: budget impact

The manufacturer estimated that 690 patients at high risk of fracture (over 65 with at least one vertebral fracture and who will experience another) would be eligible for PTH treatment each year. The estimated gross drug budget impact was £2.2M in year 1 rising to £3.5M by year 5. SMC clinical experts have indicated that, based on the number of women currently receiving teriparatide, the eligible patient population may be much lower. The manufacturer estimated that PTH may reduce the net drug budget as it has a lower acquisition cost than teriparatide.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 10 January 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: <http://www.scottishmedicines.org.uk/>*

The undernoted references were supplied with the submission.

Hodsman AB, Hanley DA, Ettinger MP et al. Efficacy and safety of human parathyroid hormone-(1-84) in increasing bone mineral density in postmenopausal osteoporosis. J Clin Endocrinol Metab 2003; 88: 5212–20.

Black DM, Greenspan SL, Ensrud KE et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med 2003; 349: 1207–15.

Black DM, Bilezikian JP, Ensrud KE et al. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. N Engl J Med 2005; 353: 555–65.