All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report:

Parathyroid hormone (PTH) (Preotact®)
Nycomed UK Ltd

Advice No: 0307 – June 2007

Recommendation of AWMSG:

Parathyroid hormone (Preotact®) is recommended for restricted use within NHS Wales for the treatment of postmenopausal women with osteoporosis at high risk of fractures. It should be considered as an alternative to teriparatide only in patients who are intolerant of that agent†, or where the storage or administration issues are deemed to provide significant added benefit. It should only be initiated by specialists experienced in the treatment of osteoporosis.

† See NICE recommendations – page 2

This report should be cited as:

All Wales Medicines Strategy Group. Final Appraisal Report – Parathyroid hormone (Preotact®) June 2007

1.0 RECOMMENDATION OF AWMSG:

The advice represents the view of the All Wales Medicines Strategy Group and was arrived at after evaluation of the evidence submitted by the manufacturers up to and including 15th January 2007. Local Health Boards and Trusts are expected to follow recommendations from AWMSG within 3 months of Ministerial endorsement. AWMSG advice is interim to NICE guidance should this be subsequently published. Individual clinicians should take account of guidance issued by NICE or AWMSG when exercising their clinical judgement, unless there is evidence to justify not doing so in the light of the particular circumstances of an individual patient.

Date: 12th June 2007

Parathyroid hormone (Preotact®) is recommended for restricted use within NHS Wales for the treatment of postmenopausal women with osteoporosis at high risk of fractures. It should be considered as an alternative to teriparatide in patients who are intolerant of that agent†, or in whom the storage or administration issues are deemed to provide significant added benefit. It should only be initiated by specialists experienced in the treatment of osteoporosis.

† As a treatment 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 intolerance to bisphosphonates **and** who have a **very high risk of fracture** as indicated by **:**

a) an extremely low BMD (with a T-score of approximately – 4 SD or below)

or

b) a very low BMD (with a T-score of approximately –3 SD or below) plus multiple fractures (i.e. more than two) plus one, or more, additional age -independent risk factor/s :

- aged 75 and older, without the need for a DEXA scan
- aged between 65 and 74, if osteoporosis is confirmed with a DEXA scan
- aged under 65, only if their bone mineral density is very low (a T-score of –3 SD or below), or if they have a confirmed diagnosis of osteoporosis and have one or more of the following risk factors:

    - they are very underweight; this means that they have a 'body mass index' or BMI of less than 19 kg/m2 – the BMI is calculated by measuring someone's weight in relation to their height
    - they had a mother who had a hip fracture before the age of 75
    - they had an early menopause that was untreated
    - they have a medical condition that increases the risk of osteoporosis – for example, rheumatoid arthritis, chronic inflammatory bowel disease, hyperthyroidism or coeliac disease
    - they have a medical condition that doesn't allow them to move.

"NICE Technology Appraisal 87. January 2005"

Key factors influencing recommendation:

Currently there are no trials directly comparing parathyroid hormone (PTH (1-84)) (Preotact®) with other licensed therapies for the treatment of postmenopausal osteoporosis with fracture outcome data.

PTH (1-84) has been shown to reduce the incidence of 'non-clinical' vertebral fractures (i.e. found on x-ray rather than causing symptoms such as pain) in postmenopausal women, but not non-vertebral fractures, such as those of the hip, compared to placebo. Furthermore, in the pivotal Phase III Treatment of Osteoporosis with PTH (TOP) trial, the extent of the effect on vertebral fractures depended on assumptions about fractures in one third of patients who withdrew from the trial prematurely.

The majority (69%) of the selected population within the main Phase III TOP trial had not received any prior treatment for osteoporosis, and are therefore considered low risk, which does not necessarily reflect the licensed indication.

The model used assumed a two-year benefit for PTH (1-84) but the primary efficacy analysis of the TOP study was assessed at 18 months. The NNT for prevention of one non-clinical vertebral fracture over two years is 51.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:

Preotact ® is indicated for the treatment of osteoporosis in postmenopausal women at high risk of fractures [1].

2.2 Dosing:

100 micrograms of parathyroid hormone is administered once daily as a subcutaneous injection into the abdomen. It is injected using the re-usable Preotact ® pen. Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate[1].

Data supports continuous treatment for up to 24 months, and on completion patients can be treated with a bisphosphonate to further increase bone mineral density [1].

There is no data available to support its use in severe renal or hepatic impairment [1].

2.3 Market authorisation date: 24th April 2006 [2]

2.4 UK Launch date: 2nd October 2006 [2]

3.0 DECISION CONTEXT:

This assessment aims to review the evidence submitted by the company on the clinical and cost effectiveness of Preotact® (parathyroid hormone [PTH 1-84]) as an anabolic agent for the treatment of osteoporosis in postmenopausal women at high risk of fracture.

Osteoporosis is a skeletal disease characterised by low bone mass and microarchitectural deterioration resulting with an increase in bone fragility and hence susceptibility to fracture. There has been an exponential growth in the diagnosis and treatment of osteoporosis over the last ten years[3]. The primary goals of treatment for postmenopausal osteoporosis (PMO) are to maintain or improve the quality of bone

and to prevent further fractures [4]. In the early 1990s, therapies for the prevention and treatment of osteoporosis included hormone replacement therapy (HRT) and calcitonin[3,5]. More recently, strontium ranelate or the bisphosphonates such as alendronate and risedronate, and the selective oestrogen receptor modulator (SERM) raloxifene, have also become available and act by reducing bone loss [6-9]. Strontium ranelate also has anabolic effects on bone [6].

Anabolic treatments, such as parathyroid hormone (PTH), offer an alternative therapeutic approach for patients at high risk of fracture. Their mechanism of action differs from that of antiresorptive drugs in that they stimulate bone formation and improve bone microarchitecture[4]. Selected patients at high risk, and those who have not responded to or are unable to tolerate bisphosphonates, could benefit from treatment with an anabolic that builds new bone earlier in the treatment pathway, to reduce the risk of subsequent fractures [10].

PTH (1-84) is the longest chain parathyroid hormone currently licensed[11]. An alternative is Forsteo® (PTH [1–34]) also known generically as teriparatide, which was approved for the treatment of postmenopausal women and men at high risk of fracture in the USA in 2002[12].The use of PTH (1-84) in the management of severe osteoporosis must be considered in relation to treatment with bisphosphonates and teriparatide as previous guidance relating to their use has been published by the National Institute for Health and Clinical Excellence (NICE) and the All Wales Medicines Strategy Group (AWMSG) respectively (refer to section 9.3).

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

PTH (1-84) has been shown to reduce the incidence of vertebral fractures in this patient population but not hip fractures. However in the pivotal Phase III trial, the extent of the effect depended on assumptions about fractures in one third of patients who withdrew from the trial prematurely. Although the relative risk reduction was consistent in patients with or without prevalent fractures, the absolute risk reduction was much higher in patients with vertebral fractures at study entry. Sub-group analysis suggests those patients with previous fractures and those with very low lumbar bone mineral density (BMD) may obtain the greatest benefit from treatment with PTH (1-84). Other trials included in the company submission assessed BMD but not fracture rates. Since the risk of fracture is not only related to BMD, the benefits of anti-fracture efficacy for PTH (1-84) cannot be derived solely from this outcome. There is evidence to support increase in BMD with alendronate follow-on treatment from PTH (1-84) for one year, but this has not been compared with bisphosphonate treatment alone.

The majority of women enrolled in the clinical trials available from the company submission were at least five years post-menopausal. Therefore data on the benefit of PTH (1-84) in women less than five years from menopause is limited.

The European Public Assessment Report (EPAR) highlights that the recommended duration of randomised treatment is at least three years in order to provide fracture and bone safety data. However, the pivotal trial was designed prior to this recommendation and consequently safety data for PTH (1-84) treatment is currently limited to two years.

The adverse event (AE) profile of PTH (1-84) includes hypercalciuria and hypercalcaemia reflecting a known pharmacodynamic action of parathyroid hormone. However, both AEs were reported more frequently than for the other licensed parathyroid hormone, PTH 1-34 (teriparatide). A high dropout rate in both the PTH (1-

84) treated group and the placebo group was reported in the pivotal Phase III trial and was attributed mainly due to withdrawal of consent, and adverse events. Nevertheless PTH (1-84) overall appeared to be well tolerated in the clinical studies available.

PTH (1-84) may be an alternative treatment for patients who have established severe osteoporosis and are at high risk of subsequent fractures but the evidence is not strong and there are no comparisons with other active treatment providing evidence of fracture reduction. Also, due to the lack of robust comparative clinical trial evidence, the Committee is unable to support the preferred use of PTH (1-84) over teriparatide.

4.2 Review of the evidence on cost-effectiveness

There are a number of uncertainties in the model that have not been fully addressed via sensitivity analyses. These include the assumption of two-year benefit for PTH (1-84), and the application of incorrect discount rates. The fact that data for PTH (1-84) is obtained from a low risk population rather than one that reflects the high risk, modelled population is also a concern, although given the similarity in the relative risk (RR) and 95% confidence interval (95%CI) for PTH (1-84) and teriparatide (obtained from a high risk secondary prevention population), this may not necessarily exclude its usefulness.

The primary analysis is of limited value, due to the inappropriate comparator. The base case analysis of PTH (1-84) (followed by alendronate) versus alendronate alone generates incremental costs per QALY that are outside what may be deemed conventionally cost effective, and the sensitivity analysis that was conducted around this comparison does not provide sufficient evidence to change this view. The analysis of PTH (1-84) versus teriparatide may reasonably be interpreted to indicate similar costs per QALY for a high-risk population.

PTH (1-84) may be a cost-effective use of resources in NHS Wales, but only for treating patients who have established severe osteoporosis (with two or more prevalent vertebral fractures). Although there is clinical evidence of improved efficacy in giving bisphosphonate treatment following treatment with PTH (1-84), the economic evidence indicates that this strategy is not cost-effective compared with giving bisphosphonate therapy alone. Therefore, if PTH (1-84) is to be used, it should be reserved for use in patients who cannot take bisphosphonate therapy.

5.0 LIMITATIONS OF DECISION CONTEXT:

- Currently there are no trials directly comparing PTH (1-84) with other licensed therapies for the treatment of postmenopausal osteoporosis.
- A head-to head trial comparing PTH (1-84) to the alternative parathyroid hormone, teriparatide is necessary in order to confirm relative efficacy and safety.
- Further trials involving a larger study population at high-risk of fractures would help to confirm the safety and efficacy of PTH (1-84) in the patient population for which it is licensed.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY:

6.1 Clinical efficacy:

The company have based their submission on a Phase II dose-finding study[13] and also a pivotal Phase III trial with an open-label extension study [11,14-16] and is supported by two Phase III active control studies; one comparing PTH (1-84) with the bisphosphonate, alendronate [17,18] and the other comparing PTH (1-84) to HRT (made available in abstract form) [19].

6.1. 1 Phase II dose-finding study[13]

Hodsman and colleagues performed a multicentre, randomised, double-blind, placebo controlled, dose-finding study of PTH (1-84). Two hundred and six female patients between the ages of 50 and 75 with PMO (lumbar spine BMD greater than 2.5 standard deviations below the young adult mean) self-administered dosages of 50 micrograms, 75micrograms, 100 micrograms of PTH (1-84) or placebo by daily injection for 12 months. All patients received calcium and vitamin D supplements.

PTH (1-84) treatment induced significant time-related and dose-related increases in lumbar spine BMD. After three months at the 100 micrograms dose, BMD was significantly higher than at baseline. In contrast to the effects of lower doses, no tendency for the response to plateau was revealed over time for the 100 micrograms dose. At the end of the study (12 months from baseline), the mean increases were 3.0%, 5.1%, and 7.8% for the 50 microgram, 75 microgram and 100 microgram doses, respectively; all increases were significant greater than baseline. Placebo treatment resulted in a non-significant 0.9% increase. Differences between each treatment dose and placebo at 12 months were all significant, and the difference between the 100 micrograms dose and the next highest dose (75 micrograms) was also statistically significant ($p<0.05$)[11,13].

Points to note:

- Changes in the total hip and femoral neck BMD were modest and did not differ significantly from placebo for all three doses. A decrease in hip BMD (0.9%) occurred over the first six months of treatment with the 100 micrograms dose, but reversed over the second six months (1.6%).
- The effect of baseline BMD T-score on lumbar spine BMD response to PTH (1-84) was reported for the 100 micrograms dose. Patients with the lowest lumbar spine BMD T-score at baseline tended to show the greatest increase in BMD, although the difference did not reach statistical significance ($p=0.053$).

6.1.2 Pivotal Phase III Treatment of Osteoporosis with PTH (TOP) Trial [14-16]

This was a randomised, double-blind, placebo-controlled, parallel-group trial carried out in North America and Europe. It was designed to evaluate the reduction of new or worsened vertebral fractures and changes in BMD, as well as safety, in women with PMO receiving PTH (1-84) for 18 months.

The trial population consisted of 2,532 women aged 45 or over (mean age 64.4±7.7 years) who had been postmenopausal for at least one year. All subjects had low bone mass and/or at least one prevalent vertebral fracture upon entry into TOP. Postmenopausal women 45 to 54 years of age were included if their BMD was three standard deviations or more (T-score less than or equal to –3.0) below the mean peak bone mass of young adult women at the lumbar spine, femoral neck, or total hip with no prevalent vertebral fracture or if the BMD T-score was –2.5 and they had one to four vertebral fractures before enrolment. Participants 55 years of age or older were included if the BMD T-score was –2.5 and they had no vertebral fractures or if the BMD T-score was –2.0 and they had one to four vertebral fractures. Women were excluded if baseline serum calcium level was greater than 2.66 mmol/L or if urinary calcium-creatinine ratio was one or more. Further details of the main inclusion criteria can be found in Appendix 1.

Patients were randomised to receive either 100micrograms PTH (1-84) or placebo, administered as a daily subcutaneous injection. All patients received daily supplements of calcium (700 mg) and vitamin D (400 international units [IU]) throughout the study. The study protocol allowed for a discontinuation of calcium supplementation and a reduction in the dosing frequency of the study drug in the event of hypercalcaemia or hypercalciuria (refer to Appendix 1).

The primary efficacy endpoint was the incidence of new or worsened vertebral fractures (in all women, and in women with and without a prevalent fracture who had received at least one dose of study drug) and was assessed via semi-quantitative analysis of radiographs at baseline, month 18, or final study visit. Secondary efficacy endpoints included fracture incidence at other sites and time points, changes in BMD at various sites and measures of bone structure and turnover [12,16].

Sixty women had a new (n = 59) or worsened (n = 1) fracture. The single worsened fracture occurred in the PTH group, at month 18. Fewer women in the PTH (1-84) group (18 [1.4%]) had a new or worsened vertebral fracture than in the placebo group (42 [3.4%]) (relative risk, 0.42 [95% CI, 0.24 to 0.72]; p = 0.001). Fifty-one women (95%CI: 32 to 129 women) needed to be treated with PTH (1-84) to prevent a new or worsened fracture in one woman[15]. When the single participant with a worsened fracture was excluded from the analysis, the relative risk (RR) for a new vertebral fracture in the PTH (1-84) group was 0.39 (95%CI: 0.22 to 0.69) compared with placebo with a number needed to treat for benefit (NNT_B) of 49 (95%CI: 31 to 116). These results are based on the assumption that no fractures occurred in the 831 patients who discontinued the trial early. The estimate of benefit for a new or worsened vertebral fracture changed to a RR of 0.60 (95%CI: 0.36 to 1.0, p = 0.05) with PTH (1-84) if patients who prematurely discontinued the trial had fractures at a rate equivalent to that of all patients who completed the trial. This changed to a RR of 0.62 (95%CI: 0.37 to 1.04, p = 0.07) if patients who prematurely discontinued the trial had fractures at a rate equivalent to that of placebo recipients who completed the trial [15].

The relative risk for a first vertebral fracture at month 18 in PTH (1-84) treated women without a vertebral fracture at baseline was 0.32 (95%CI: 0.14 to 0.75;p = 0.006) with an NNT_B of 71 (95%CI: 42 to 248). In PTH-treated women with a prevalent vertebral fracture at baseline, the relative risk for a new vertebral fracture was 0.47 (95%CI: 0.23 to 0.98) with an NNT_B of 22 (95%CI: 11 to 422). These results are on the assumption that patients who discontinued the trial prematurely had no vertebral fractures.

In the total population the absolute risk (AR) of new and/or worsened vertebral fractures was 3.4% (42 new vertebral fractures) in placebo and 1.4% (17 new vertebral fractures) in the PTH (1-84) group. In the sub-population of patients with prevalent fractures the AR for placebo was 8.94% and in the PTH (1-84) group was 4.24% giving an absolute risk reduction (ARR) of 4.7%. In a sub-population of high-risk patients with prevalent fractures and a T-score of less than –3.0, the AR of new and/or worsened vertebral fractures was 13.4% in placebo and 5.4% in the PTH (1-84) group. This gives an overall ARR of 8.0% in this population[15].

The incidence of fractures at the hip and femoral neck was low during this study, so it was not possible to detect an effect of PTH (1-84) on fractures at these sites. However, the increase in BMD showed positive effects of treatment with PTH (1-84) at both these sites.

There was a high dropout rate with only 1,701 patients completing the study (877 [70%] in the placebo group and 824 [64%] in the PTH group). Dose reduction was required in 434 women in the PTH group (34%) compared to 9% of the placebo group.

Points to note:

- PTH (1-84) reduced the incidence of vertebral fractures in this patient population. However the extent of the effect depended on assumptions about fractures in one third of patients who withdrew from the trial prematurely[15].
- Although the relative risk reduction was consistent in patients with or without prevalent fractures, the absolute risk reduction was much higher in patients with vertebral fractures at study entry[16]. (Notably, only 19% of participants in this study had experienced a previous vertebral fracture, three-quarters of which had only one fracture at baseline).

- Sub-group analysis indicates that patients with previous fractures or a very low lumbar BMD may obtain the greatest benefits with PTH (1-84) than the total trial population.
- The majority of the selected population (69%) had not received any prior treatment for osteoporosis.
- Patients with less than five years from menopause and younger than 55 years of age were underrepresented in this trial. Therefore, there is limited data on the benefits of PTH (1-84) in this population.
- According to the Committee for Medicinal Products for Human Use (CHMP) recommendations, the primary variable should be based on the new axial or peripheral fractures and not worsening of previous fractures, as in this study[15]. However, the inclusion of worsening fractures in addition to new fractures as a primary combined endpoint did not influence the efficacy data since only one worsened fracture was reported in the intention-to-treat (ITT) population.
- The trial assessed fracture rate radiographically and did not provide additional data on relative rates of clinical fractures that required intervention. Therefore, the affect of PTH (1-84) on these is not known.
- Main reasons for dropout in both groups were withdrawal of consent, and adverse events discussed in Section 6.2.[15]
- Endogenous PTH and vitamin D levels could affect patient response to the drug but were not assessed in the study. Greenspan and colleagues have noted this as a study limitation [15].

6.1.3 Open label extension study (OLES)[11,16]

Patients entered into the 18-month TOP study had the option of continuing in the OLES study, which allowed women to receive treatment with PTH (1-84) for up to 24 months. The primary objective was to evaluate the safety of continued dosing up to a maximum of 24 months (in TOP and OLES combined), in postmenopausal women with osteoporosis. The secondary objectives were to evaluate the changes in BMD, bone mineral content (BMC), and bone mineral area (BMA) at several skeletal sites; the incidence of vertebral and non-vertebral clinical fractures as before (refer to section 6.1.2).

A total of 1681 patients participated in this extension study to receive open-label PTH (1-84), of whom 900 (54%) had been treated previously with placebo and 781 (46%) had been in the PTH (1-84) treatment group[16]. Out of the 1,681participants 1,401 patients (83%) completed the study. Approximately 62% of the PTH (1-84)/PTH (1-84) treatment group completed 24 months of treatment, and 29% of the placebo/PTH (1-84) group completed 18 months of treatment.

Continued treatment with PTH (1-84) for up to a further six months resulted in a continued increase in BMD. At 24 months, the increase from baseline in lumbar spine and total hip BMD was 7.1% and 1.2% respectively in the PTH (1-84)/PTH (1-84) group. At the femoral neck, BMD also increased by 1.8% at Month 18 and increased further to 2.2% at Month 24.

From the OLES baseline to Month 18, there were six new fractures and one worsened fracture in the placebo/ PTH group and two new fractures and four worsened fractures in the PTH (1-84)/ PTH (1-84) group. More patients in the placebo/PTH (1-84) group (29 patients) than in the PTH (1-84)/PTH (1-84) group (19 patients) had non-vertebral clinical fractures.

Points to note:

- A total of 52% patients had exposure to active treatment in TOP and OLES studies combined.
- PTH (1-84) would appear to be effective in increasing BMD at skeletal sites rich in trabecular bone, such as lumbar spine, and less effective at sites that have a greater proportion of cortical bone, such as total hip.
- As this study was an open-label extension of the TOP study, EPAR determined that no valid efficacy data could be derived from this analysis and the study was considered as supportive evidence only[16].

6.1.4 Parathyroid hormone and alendronate (PaTH) trial[17] and extension study [1,18]

The PaTH study was a randomised, placebo controlled, two-year, multicentre, double-blind trial to assess the efficacy of PTH and alendronate as monotherapy and in combination for treatment of postmenopausal women between 55 and 85 years of age. Of the 238 patients enrolled at baseline a total of 165 women (69 %) had a T-score below –2.5, and 112 (47 %) reported at least one fracture after menopause [1]. The participants were randomly assigned to one of the following treatment groups; PTH (1-84) 100 micrograms, alendronate 10 mg, or the combination of both, and followed for 12 months. In the second year of the study women in the original PTH (1-84) group were randomly assigned to receive either alendronate or matching placebo, and women in the other two groups received alendronate.

At one year, the increases in lumbar spine BMD above baseline were similar in the PTH (1-84) and combination-therapy groups (6.3 and 6.1 %, respectively), but smaller in the alendronate group (4.6 %). Increases in BMD at the total hip were 0.3, 1.9, and 3.0 % for the 3 groups, respectively. At the end of year two, 12 months after PTH (1-84) was discontinued, there was a 12.1 % mean increase in dual energy X-ray absorptiometry (DXA) spine BMD for patients who received alendronate for the second year. For the patients who received placebo during the second year, the mean percent increase was 4.1 % compared to baseline, but had decreased slightly compared to the end of 12 months of PTH (1-84) treatment. For the mean change in hip BMD, there was a 4.5 % increase from baseline with one year of alendronate compared to a 0.1 % decrease after one year of placebo.

Points to note:

- Combining PTH (1-84) with alendronate use has not been shown to provide any advantage over either form of treatment alone.
- A reduction in bone formation of 15.7% after 12 months of combined treatment seemed to indicate that alendronate compromises the anabolic effects of PTH.
- A significant increase in the mean serum uric acid concentration in the PTH (1-84) group (1.03 mg/dl) and the combination therapy group (0.85 mg/dl; $p<0.001$) was documented, whereas there was no change in the alendronate group.

6.1.6 Prevention of Osteoporosis in Women on Estrogen Replacement (POWER) study [16,19]

The POWER study has recently been completed, and the results are currently published in abstract form only[16,19]. This is a Phase III randomised, double-blind,

placebo controlled study conducted in 180 women (mean age 58.8 years; mean 12.6 years postmenopausal) with low BMD (lumbar spine T-scores less than or equal to minus two) who had received HRT for at least six months. Patients were randomised to daily injections of PTH (1-84) 100 micrograms and HRT (n=90) or HRT alone (n=90). Calcium (700–1,050 mg/day) and vitamin D (800 IU/day) was also given to all participants.

An increase in lumbar spine BMD was seen in both groups at Months 18 and 24. However, BMD increased significantly more in subjects receiving PTH (1-84) and HRT compared with HRT alone at Month 18 (6.42%; $p<0.001$) and Month 24 (6.53%; $p<0.001$). In the PTH (1-84)/HRT group, significant increases over baseline were seen at Months 18 and 24 (7.9% and 8.6% respectively; both $p<0.001$). At the femoral neck, PTH (1-84)/HRT treatment resulted in a significant increase in BMD relative to the increase observed with HRT alone (2.27% versus 0.47%; $p=0.024$). Markers of bone turnover (bone-specific alkaline phosphatase and N-telopeptide) were consistently increased in the PTH (1-84)/HRT group compared with the HRT-alone group.

Points to note:

- The incidence of fractures in this study population was very low and the impact of PTH (1-84) on clinical fracture was therefore not assessed [12].
- At 24 months of combined PTH (1-84)/HRT therapy is associated with significant increases in lumbar spine BMD compared with HRT alone, suggesting that HRT augments but does not blunt the anabolic effects of PTH (1-84) [16].
- Although slight increases in total hip and femoral neck BMD are seen with combined therapy over HRT alone, the difference is not significant ($p = 0.88$ and 0.11 respectively).

6.2 Safety:

- Nausea, headaches, vomiting, dizziness, hypercalcaemia and hypercalciuria have all been all reported as adverse events (AEs) more frequently seen with PTH (1-84) therapy than placebo from the clinical trials available. Nevertheless, PTH (1-84) overall appeared to be well tolerated.
- The pivotal TOP study, which treated 1341 patients with PTH (1-84) showed an incidence of 26.8% for hypercalcaemia (>2.68 mmol/dl) and 44.2% for hypercalcuria (levels not stated). However, it is reported that these particular AEs rarely led to withdrawal from the study[11].
- EPAR highlights that the recommended duration of randomised treatment is at least three years in order to provide fracture and bone safety data. However, the pivotal trial was designed prior to this recommendation and consequently safety data for PTH (1-84) treatment is currently limited to two years.
- PTH physiologically increases calcium levels and all trials included a supplement of calcium and vitamin D. Therefore, patients initiated on PTH (1-84) therapy should be monitored at months one, three and six for elevated levels of serum and/or urinary calcium. Monitoring beyond six months is not necessary for those patients whose total serum calcium is within the normal limits at six months.

- Monitoring of uric acid levels is required with PTH (1-84), as the PaTH study documented a significant increase in the mean serum uric acid concentration in both the PTH treatment groups.

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

- Teriparatide
- Calcitonin
- Bisphosphonates (risedronate, alendronate)
- SERMS e.g. raloxifene
- Strontium ranelate

7.2 Comparative effectiveness:

There are no further published direct comparative studies with alternative licensed therapies for osteoporosis other than those made available in the company submission. In the absence of such studies, WMP have drawn together a number of relevant facts in an attempt to compare across current treatments options available.

- The reduction in vertebral fracture rate for teriparatide is derived from the results of the study by Neer and colleagues[20]; a large, secondary prevention, fracture outcome trial comparing teriparatide with placebo over an 18-month treatment period. Although carried out in a higher-risk population, this study is the closest match available to the TOP study in terms of protocol and outcomes. On comparing both trials, PTH (1-84) has a lower ARR than teriparatide. This comparison must be viewed with due consideration to the fact that the TOP trial included a lower-risk patient population (only 19% patients with prevalent fractures) than those for teriparatide (100% subjects with more than one prevalent fracture) which could result in a lower than anticipated overall incidence of new fractures.
- Like PTH (1-84), a number of other licensed therapies such as calcitonin, bisphosphanates, raloxifene and strontium ranelate have shown to reduce the incidence of vertebral fractures. It is difficult to compare the risk reductions as the alternative therapies were observed over different durations[4] (refer to Appendix 1, Table 1).
- Preotact® has a seven day travel window in which continuous refrigeration is not required, thus making travel easier for patients. This may possibly be an advantage over teriparatide, which requires constant refrigeration [1,12].

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for the AWMSG to consider are:

1. Whether the additional benefits offered by PTH (1-84) over relevant comparators justify the additional costs, and if so,
2. Whether the total budgetary impact of supporting the use of PTH (1-84) is acceptable.

8.2 Review of published evidence on cost-effectiveness

Standard searches conducted by WMP have not identified any other published economic studies of the use of PTH (1-84). Teriparatide, another recombinant human parathyroid product was assessed by AWMSG in July 2005.

8.3 Review of company's submission on cost-effectiveness

The company's submission describes a Markov model that was used to assess the incremental cost per QALY of PTH (1-84) compared with no active treatment in the secondary prevention of new vertebral factures in a high-risk osteoporotic patient population. This has a 10-year time horizon. A comparator of no active treatment is not appropriate for this patient population, as most high-risk patients would have received or be receiving bisphosphonate treatment. Further analyses were, therefore, also conducted to assess the incremental costs per QALY for PTH (1-84) (followed by alendronate) against alendronate alone and PTH (1-84) against teriparatide. The cost-utility model was not included in the company's submission and so verification of the results is not possible.

There are a number of issues relating to the PTH (1-84) data used in the model, which need to be considered. Data from the TOP study were used to provide the RR of vertebral fracture with PTH (1-84) compared with no treatment in the model [14]. However, the TOP study was conducted in patients who were at relatively low risk of vertebral fracture and do not closely represent the high-risk patient population said to be modelled. It is unclear how this may affect the analysis. The company's submission also claims that the model considers only clinically apparent fractures, but the RR of fracture used in the model for each agent relates to vertebral fractures that were assessed radiologically (i.e. clinical and sub-clinical fractures) in their respective studies.

In addition, the model assumes that benefit with PTH (1-84) is maintained for two years, then declines linearly over the third year and remains at the baseline risk thereafter. It should be noted that the primary efficacy analysis of the TOP study was assessed at 18 months. There is no justification/evidence presented for assuming that 18 months of treatment with PTH (1-84) alone would provide two years of benefit in terms of reduced fracture risk, which would then decline in the third year. This assumption would have the effect of inflating the benefit of PTH (1-84) by six months, whilst minimising the cost component of the incremental cost-effectiveness ratio. Note that this is assumed for all analyses.

The utility values used in the company's submission are based on a quality of life survey conducted in osteoporotic women in seven EU countries, and applied to all patients with vertebral fractures (i.e. clinical fractures and sub-clinical, radiologically detected vertebral fractures). Whether this would be the case equally across all treatment groups is unknown. The company's submission makes no reference to the severity of fractures experienced and does not appear to differentiate between those patients with two prevalent fractures and those with three, four, or five and more. As this is not explored in sensitivity analyses, it is not possible to determine what impact this might have on the results of the analyses.

For the analysis of PTH (1-84) followed by alendronate versus alendronate alone, the model assumes the benefit with PTH (1-84) is maintained for two years, declines linearly over the third year, and from year three onwards the magnitude of benefit of alendronate is assumed to be the same as that seen in the FIT trial of alendronate[21]. This assumption appears to neglect any effects of alendronate (post PTH (1-84)) between 18 months and three years, but would still attract the relevant costs.

The model considers only direct medical resources and costs. No consideration is given to any personal and social service resources or costs, which is a limitation of the model as these could feasibly be substantial for (a proportion of) this patient group. Resource use, costs and health effects of adverse events with PTH (1-84) or the secondary comparators have not been incorporated in the model.

All drug costs are presented in 2006 as pounds (UK£). The model assumes that all patients, whichever treatment they receive, are calcium and vitamin D-replete, and so the costs of these agents are not incorporated. Fracture treatment costs have been obtained from a study of fracture costs in 1995–6 and have been uplifted to 2004 values on the basis that this was the most recent year for which the NHS and Family Health Service index was available. This does leave a discrepancy in the costs. The study on which the fracture treatment costs are based itself relies on a number of assumptions and lends from data produced some years before 1995–6. This method of estimating fracture costs is, therefore, subject to some uncertainty that is not tested.

8.3.1 Summary of key findings from the manufacturer's submission on cost-effectiveness:

Results were presented for patients aged 60, 65, 70, 75, 80 and 85 years. The base case incremental cost per QALY of PTH (1-84) followed by alendronate versus alendronate alone, ranged from £143,742 at age 60 years, £96,239 at 70 years, up to £144,179 at age 85 years.

The incremental cost per QALY of PTH (1-84) relative to teriparatide ranged from -£16,000 to -£24,000 (with PTH (1-84) being less effective, but less expensive than teriparatide).

The RR point estimates for each comparison were used to model the effects of treating a higher risk group of patients with three or more fractures. This reduced the incremental costs per QALY in all comparisons but, qualitatively, the results were unchanged.

For PTH (1-84) followed by alendronate versus alendronate alone, the best-case scenario for PTH (1-84) (RR 0.22) with the worst-case scenario for alendronate (RR 0.68) generated incremental costs per QALY in the range £28,623 to £43,312. Using the worst-case scenario for PTH (1-84) (RR 0.69) and the best-case scenario for alendronate (RR 0.41) resulted in PTH (1-84) being dominated across all age groups.

For PTH (1-84) versus teriparatide, the best-case and worst-case scenarios of each made little difference to the results.

8.4 Review of evidence on budget impact

The perspective adopted by the budget impact analysis is that of NHS Wales. However, it is based on non-Welsh prevalence and incidence data, which have been applied to the Welsh population. As a number of sources of data have had to be used, different age groups are considered and a number of assumptions have been employed, this makes the prevalence and incidence rates inconsistent and subject to uncertainty (sees Appendix 2). No sensitivity analyses have been conducted around any of the assumptions.

The company's submission estimates that the number of women aged 50+ with clinical vertebral fractures in Wales is 19,681. This is likely to be an underestimate, as the methods used assume that the prevalence rate of vertebral fracture (10.15%) in those aged 80+ is the same as in those aged 50-79 (which is unlikely, given the increasing risk of fracture with age). For non-vertebral fractures, a prevalence of 37.3%, as determined in a Scottish study of women aged 65+, has been applied to the Welsh population and suggests 110,408 women aged 65+ have non-vertebral fractures.
This excludes women in nursing or residential care homes, so is likely to be an underestimate.

The annual incidence of clinical vertebral fracture in women without prior fracture is estimated as 0.29%. Applying this incidence to the population in Wales would suggest that 1,262 women aged 55+, experience a first clinical vertebral fracture each year. In the women who have one or more prior fractures, the annual incidence of new clinical fractures is 829. Therefore, summing the number of incident fractures, the company's submission estimates there would be 2,091 new clinical vertebral fractures in women aged 55+ in Wales each year. The yearly incidence of non-vertebral fractures is estimated as 10,868. Therefore, the total number of new fractures per year in Wales has been estimated as 12,959 (2,091 + 10,868). It should be noted that this estimate does not take account of non-vertebral fractures in women aged 55 to 64 years.

8.4.1 Summary of key findings from the manufacturer's submission on budget impact:
The company's submission states that PTH (1-84) is expected to be prescribed in high-risk patients (women aged over 65 years with two or more clinical vertebral fractures).

The number of women aged 65+ in Wales is estimated at 296,000. Applying the prevalence of morphometric vertebral fracture (10.15%) to these women would suggest that 30,044 have experienced at least one fracture. Assuming that only a third comes to clinical attention, then 10,015 women will have at least one clinical vertebral fracture. Using data from the placebo arm of the FIT study of alendronate to derive the annual incidence of a clinical fracture in patients with prior fractures, the company's submission estimates that 506 women aged 65+ will present with two or more clinical vertebral fractures each year, of which 292 will have three or more fractures. The company's submission notes that this indicates a treatment gap when compared with the numbers currently estimated to receive teriparatide.

The direct costs of treatment used in the budget impact analysis consider only the drug costs of PTH (1-84) and alendronate, or teriparatide and alendronate. Eighteen months of treatment with PTH (1-84) costs £4,687.20 per patient compared with £4,893.84 for teriparatide. Alendronate is now available generically and the company's submission has adopted a cost of £10 per month. The budget impact analysis considers that 18 months of PTH (1-84) is followed by 42 months of alendronate. As PTH (1-84) is given for 18 months, the cost of PTH (1-84) will stabilise in the second and subsequent years, but as alendronate is given for 42 months, the alendronate component will continue to grow in the first five years of PTH (1-84) uptake.

The net resource implications, based on 506 eligible high risk patients per year, have been estimated as £1.58 million in year one (i.e. the cost of 12 months of PTH (1-84) only), rising to £2.58 million in year five (the cost of PTH (1-84) and alendronate). This assumes 100% uptake of PTH (1-84) by all eligible high-risk patients. No discounting has been employed.

The company's submission considers that direct savings of £206.64 would be made per patient if PTH (1-84) were used rather than teriparatide.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- It is the opinion of the Committee that PTH (1-84) is not currently suitable for shared care.
- Should this product be endorsed for use in NHS Wales, audit of its effectiveness in line with agreed criteria would be valuable in determining long term strategy for osteoporosis care.

9.2 Related advice:
Refer to section 9.3.

9.3 Previous AWMSG/NICE advice:

The National Institute for Health and Clinical Excellence (NICE) technology appraisal assessing the clinical effectiveness and cost effectiveness of technologies for the secondary prevention of osteoporotic fractures in postmenopausal women was published in January 2005. This makes recommendations about the use of bisphosphonates, raloxifene, and teriparatide [22].

The NICE technology superseded the AWMSG recommendation dated June 2004, which recommended that teriparatide should be supported for the treatment of established severe osteoporosis in postmenopausal women at a quadrupled risk of another osteoporotic fragility fracture within NHS Wales [23, 24].

The NICE appraisal is currently under review and an updated version, that includes strontium ranelate, is expected in March 2007. NICE currently recommends that PTH therapy (teriparatide) should be used only in women who:

- Are aged 65 or over
- Have an unsatisfactory response to bisphosphonates or intolerance to bisphosphonates
- Have an extremely low bone mineral density (BMD) or a very low BMD plus more than two fractures plus at least one additional, age-independent risk factor (low body mass index; family history of maternal hip fracture before the age of 75 years; untreated premature menopause; or conditions associated with prolonged immobility.

9.4 Medical Expert
Medical expert opinion was sought and provided prior to the meeting.

9.5 Patient Interest Group
A patient interest group submission by the National Osteoporosis Society was provided to AWMSG Members.

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APPENDIX 1. Additional clinical information

Bone mineral density and T-score definition:

Bone mineral density measurements are commonly used to diagnose osteoporosis. Such measurements, however, do not reflect all elements of risk, which vary with, for example, the age of the patient, cause of bone loss and site of interest. Typically, bone density is measured using dual energy X-ray absorptiometry (DEXA). Bone with a density below the mean value for a young adult by -1–2.5 standard deviations is said to be osteopenic, or if by more than -2.5 standard deviations, osteoporotic. The number of standard deviations from this mean value is known as the T score. A patient with severe osteoporosis has a T score of -2.5 standard deviations below the mean for a young adult plus one or more fragility fractures (those caused by injury insufficient to fracture normal, non-fragile, bone). A one standard deviation decrease in bone density is associated with up to a three-fold increase in fracture risk. There is evidence that increasing bone mineral density with certain drugs is associated with decreased fracture risk.

TOP study inclusion and exclusion criteria[15]:

The trial included women with mild (serum calcium, 2.55 to 2.66mmol/L) and mild hypercalciuria (24-hour urine calcium 7.6 mmol [302 mg]) at baseline. Women were excluded if they had taken bisphosphonates for a total of more than 12 months or for more than 90 days in the 12 months before enrolment. Previous estrogen therapy was allowed if it had been discontinued for at least four weeks before the screening visit. The trial excluded women who had received PTH (or a peptide fragment or analogue), PTH-related protein, fluoride, or strontium and those who had a history of metabolic bone disease (other than osteoporosis), nephrolithiasis, or clinically significant hepatic or renal disorders. Patients who were taking medications known to affect bone mineral metabolism were not enrolled.

Treatment of hypercalcaemia or hypercalciuria in TOP study [15]:

The trial anticipated that women might need to discontinue calcium supplementation and reduce the dosing frequency of the study drug to prevent excessive increases in serum calcium level, urinary calcium level, or both. was conservatively pre-defined as a single, unconfirmed, predose serum total calcium value greater than 2.66 mmol/L and hypercalciuria was defined as a 24-hour urinary calcium value of 7.6 mmol or more (302 mg) (increased to >9.0 mmol [>360 mg] during the study) or a fasting urinary calcium–creatinine ratio of 1.0 or more. If a woman developed hypercalcaemia or hypercalciuria, the daily calcium supplementation was discontinued; if either condition continued, the dosing frequency of the study drug was reduced.

Table 1: Reduction in vertebral fracture rate for alternative licensed therapies for osteoporosis[4]

Comparator	Reduction in vertebral fracture rate
Calcitonin	Reduction in the cumulative risk of new vertebral fractures reported as 33% over five years of treatment.
Bisphosphanates	Relative risk reductions reported as 41% at three years for residronate, and as 47-50% at three years for alendronate.
Raloxifene	A significant reduction in the incidence, reported as 47% and 31% in women with and without prevalent fractures respectively, over three years.
Stronium ranelate	A significant reduction in the incidence, reported as 41% over three years.

APPENDIX 2 Health economic review

Manufacturer's submission - economic evidence

1. Description of manufacturer's submission

The manufacturer's submission describes a Markov model that was used to assess the incremental cost per QALY of PTH (1-84) compared with no active treatment in the secondary prevention of new vertebral factures in a high-risk osteoporotic patient population. The model describes three states relating to patients with two prior vertebral fractures, three-four prior fractures, or five or more prior fractures, from each of which patients may progress to death, refracture or no fracture.

Secondary analyses were also conducted to assess the incremental costs per QALY for PTH (1-84) against alendronate (a bisphosphonate) and teriparatide (another recombinant human parathyroid hormone product). The cost-utility model has not been included with the manufacturer's submission and so verification of the results is not possible. The manufacturer's submission lists a number of advisors and contributors, but does not specifically state how/if the model was tested externally.

2. Population

The model was designed to assess the cost-utility of PTH (1-84) in the secondary prevention of new vertebral factures in a high-risk osteoporotic patient population. This largely reflects the licensed indication for PTH (1-84).

Data from the TOP study were used to provide the relative risk of vertebral fracture with PTH (1-84) compared with no treatment in the model. The TOP study was conducted in patients who were at relatively low risk of vertebral fracture (81% had not experienced prior vertebral fractures and of the 19% who had, three-quarters had only one fracture at baseline, and 67% had not received bisphosphonate treatment in the previous year). Therefore, the TOP study population does not closely represent the high-risk patient population said to be modelled.

Data for alendronate and teriparatide are taken from higher risk, secondary prevention populations.

3. Perspective and time horizon

The model considers only direct costs from the perspective of the NHS Wales. No consideration is given to any personal and social service costs/resources, which is a limitation of the model as these could feasibly be substantial for this patient group.

The time horizon chosen for the analysis was 10 years, on the basis that the evidence base relating to long-term outcomes in osteoporosis is limited and the longest published follow-up was 10 years (in an alendronate study). Whilst this in itself may not be deemed adequate justification, given the age of the patient group (typically elderly) it would seem reasonable to assume that the time horizon would not extend much beyond 10 years. Treatment with PTH (1-84) t is for a maximum of two years, and the model assumes that the risk of fracture with PTH (1-84) returns to baseline over the course of the third year (NB see section 5).

Each Markov cycle was set at one year. It should be noted that in the TOP study, the reduction in the risk of vertebral fracture at 12 months was a non-statistically significant 28% (P=0.290), yet the model employs the statistically significant primary efficacy endpoint results obtained at 18 months (61% decrease; P=0.001).

4. Comparator

The manufacturer's submission acknowledges that a comparator of no active treatment is not appropriate for the patient population being considered. Most high-risk patients would have received or be receiving bisphosphonate treatment. Although the manufacturer's submission claims that the primary cost-utility analysis of PTH (1-84) against no active treatment is supported most reliably by the available evidence base (see section 5), the secondary analyses against alendronate and teriparatide are likely to be more informative.

5. Clinical inputs

5.1 Clinical effectiveness

5.1.1 Primary analysis: PTH (1-84) for 18 months versus no active treatment

The primary analysis is not considered to be relevant, as 'no active treatment' is not considered to be a realistic alternative, given the availability of alternative agents. However, for completeness, an assessment of the manufacturer's 'primary' analysis is made.

The company's submission states that, "…To maximise the clinical utility of the results, the model was based on clinically apparent fractures only, rather than radiologically identified events…" However, the relative risks of fracture used in the model for PTH (1-84) and its comparators were obtained from studies in which the fractures were assessed radiologically for the primary end point (i.e. clinical and sub-clinical fractures). Although clinically defined fractures were a secondary endpoint in the TOP study, the relative risks used relate to the radiologically assessed primary endpoint.

The TOP study compared PTH (1-84) against no active treatment in patients who were generally at low risk of vertebral fracture. Therefore, the use of the estimated relative risk of fracture from the TOP study in this model of high-risk patients is questionable and it is unclear in which direction it may bias the results. Although patients at higher risk of fracture (as is claimed to be modelled) may have the potential to derive relatively greater benefit from PTH (1-84) (which would mean the current analysis may be biased against PTH (1-84)), the reduction in vertebral fracture risk with PTH (1-84) in the 19% of patients in the TOP study who actually had prevalent vertebral fractures was lower (relative risk of fracture 0.47, 95%CI 0.23 to 0.98) than in the 81% of patients without prevalent vertebral fractures (relative risk of fracture 0.32, 95%CI 0.14 to 0.75). This may have the effect of biasing the analysis in favour of PTH (1-84).

A sensitivity analysis of the relative risk of fracture with PTH (1-84), confined to the upper and lower limit of the 95% confidence interval of the relative risk of new fractures, has been conducted (see section 9).

The relative risk of fracture taken from the TOP study (RR 0.39; 95%CI 0.22 to 0.69) relates to new fractures, rather than new/worsened fractures (i.e. total fractures). In the TOP study, the incidence of worsened fractures was very low (due to the low risk of the patient population), but in a high-risk population the incidence of worsened fractures would reasonably be expected to be higher. As far as it is possible to apply the relative risk of fracture from the TOP study to this model of high risk patients, the relative risk to be used would more appropriately relate to the total fracture incidence (RR 0.42; 95%CI 0.24 to 0.72), which is similar to, but not quite as low as, the relative risk of new fracture used.

This model is stated to analyse the cost-utility of 18 months of PTH (1-84) treatment vs. no active treatment. The model assumes that benefit with PTH (1-84) is maintained for two years and then declines linearly over the third year, and remains at the baseline risk thereafter. It should be noted that the primary efficacy analysis of the TOP study was assessed at 18 months. Only in the open-label OLES extension study was PTH (1-84) given for an additional 6 months (i.e. total PTH (1-84) treatment up to two years) and the efficacy measure in that extension study was lumbar spine bone mineral density (BMD), not vertebral fracture. As was observed in the OLES extension study, following cessation of PTH (1-84) treatment, the BMD declined rapidly. Taken these factors into account, it would seem there is no justification for assuming that 18 months of treatment with PTH (1-84) alone would provide two years of benefit in terms of reduced fracture risk, which would then decline in the third year. This assumption would have the effect of inflating the benefit of PTH (1-84) by six months, whilst minimising the cost component of the incremental cost-effectiveness ratio. Note that this assumption is also used throughout the secondary analyses.

Baseline predicted event rates for the no treatment arm (assumed from the placebo group of the FIT study) are assumed to last throughout follow-up.

5.1.2 Secondary analysis: PTH (1-84) for 18 months followed by alendronate versus alendronate alone.

The company's submission states that, for PTH (1-84) followed by alendronate, the model assumes the benefit with PTH (1-84) is maintained for two years and then declines linearly over the third year (see section 5.1.4 above), and from year-three onwards the magnitude of benefit of alendronate is assumed to be the same as that seen in the FIT trial of alendronate (relative risk of fracture 0.53; 95%CI 0.41 to 0.68). This appears to neglect any effects of alendronate between 18 months and three years. Although the primary endpoint of the FIT study of alendronate was assessed at a mean of 2.9 years, patients in the FIT study would not be expected to be representative of the patient population modelled here, due to different baseline characteristics. For alendronate alone, the relative risk of fracture seen in the FIT study is used throughout follow-up.

5.1.3 Secondary analysis: PTH (1-84) versus teriparatide over 18 months.

The model assumes that benefit with PTH (1-84) is maintained for two years and then declines linearly over the third year, and remains at the baseline risk thereafter (see above). For teriparatide, data were taken from a pivotal study in a high-risk group (Neer and colleagues). The relative risk of vertebral fracture was 0.35 (95%CI 0.22 to 0.55) over around 18 months.

5.1.4 Subsequent fracture risk and mortality following vertebral fracture

Following a fracture, patients are at increased risk of subsequent fractures and mortality. The Markov model employs a five-year tunnel state into which patients who sustain a re-fracture are fed, with updated risks, before being returned to the main Markov cycle. Data to provide the risks of subsequent fracture and mortality rates were obtained from two studies of Swedish patients, which assessed re-fracture rates and deaths following a range of fragility fractures over a five-year period. Age specific all-cause mortality rates for females in the UK were derived from the Government Actuary's Department. Although tables of the data are provided in the company's submission, there are few supporting details to explain exactly how the data are applied.

It is assumed that the risk of re-fracture and mortality between the ages of 60 and 80 years are linear. It is unclear how reliable this assumption is, given that all-cause mortality rates are not linear between these ages.

5.2 Health outcomes

The utility values used in the company's submission (0.83 in the year of vertebral fracture occurred and 0.93 in subsequent years) are based on a quality of life survey conducted in osteoporotic women in seven EU countries. The blanket application of these utility values to all patients with vertebral fractures (i.e. clinical fractures and sub-clinical, radiologically detected vertebral fractures) would have the effect of amplifying the gains to be had from treatment. Whether this would be the case equally across all treatment groups is unknown. The company's submission makes no reference to the severity of fractures experienced and does not appear to differentiate between those patients with two prevalent fractures and those with three-four or five or more. As this is not explored in sensitivity analyses, it is not possible to determine what impact this might have on the results of the analyses.

5.3 Adverse events

The model does not take account of any adverse events with PTH (1-84) or the secondary comparators.

6. Healthcare resource utilisation and cost

The model considers only direct resources and costs. No consideration is given to any personal and social service resources or costs, which is a limitation of the model as these could feasibly be substantial for (a proportion of) this patient group. Resource use and costs of adverse events with PTH (1-84) or the secondary comparators have not been specifically incorporated in the model.

All drug costs are presented in 2006 UK£. The model assumes that all patients, whichever treatment they receive, are calcium and vitamin D-replete, and so the costs of these agents are not incorporated. Fracture treatment costs have been obtained from a study of fracture costs in 1995–6 and have been uplifted to 2004 values on the basis that this was the most recent year for which the NHS and Family Health Service index was available. This does leave a discrepancy in the costs. The study on which the fracture treatment costs are based itself relies on a number of assumptions and lends from data produced some years before 1995–6. This method of estimating fracture costs is, therefore, subject to some uncertainty.

7. Discounting

Outcomes in the model were discounted at 3% and costs at 6% per year. No sensitivity analyses were conducted to explore the effect of different discount rates on the model outputs. This may have some implications as the preferred annual discount rate is 3.5% for both costs and benefits.

8. Results

Results were presented for patients aged 60, 65, 70, 75, 80 and 85 years. The uncertainty analysis only considers whether the means of the simulated outcomes are truly different – it does not evaluate uncertainty in the parameter values themselves.

8.1 Base-case, primary analysis: PTH (1-84) versus no active treatment

The incremental cost per QALY of PTH (1-84) relative to no active treatment ranged from £26,969 for patients aged 60 years, up to £34,826 at age 85 years. The incremental costs per QALY were not linear with age (the lowest point estimate was £21,204 at age 70 years). Note that these values relate to an unrealistic comparison, against no active treatment.

8.2 Base-case, secondary analysis: PTH (1-84) followed by alendronate versus alendronate alone

The incremental cost per QALY of PTH (1-84) followed by alendronate, relative to alendronate alone, ranged from £143,742 at age 60 years, up to £144,179 at age 85 years. The incremental costs per QALY were not linear with age (the lowest point estimate was £96,239 at age 70 years).

8.3 Base-case, secondary analysis: PTH (1-84) versus teriparatide

The incremental cost per QALY of PTH (1-84) relative to teriparatide ranged from -£16,000 to -£24,000 (PTH (1-84) is shown to be less effective but less expensive than teriparatide).

8.4 Subgroup analysis — higher risk patients with three or more prior fractures

The point estimates for each comparison were used to model the effects of treating a higher risk group of patients. For PTH (1-84) versus no active treatment, the incremental costs per QALY ranged from £14,948 (at age 70 years) to £25,635 (at age 85 years). For PTH (1-84) followed by alendronate versus alendronate alone, the incremental costs per QALY ranged from £64,956 to £106,079. For PTH (1-84) versus teriparatide, the corresponding figures were £-11,316 to £-17,727 (i.e. in favour of teriparatide). The interpretation of a negative cost per QALY is impossible as it may be due to a negative value in costs or benefits.

9. Sensitivity analysis

The manufacturer's submission describes a series of one- and two-way sensitivity analyses. No attempt was made at a probabilistic sensitivity analysis.

9.1 One-way sensitivity analysis of relative risk of vertebral fracture with Preotact in the primary analysis

Using the lower limit of the 95%CI for the risk of vertebral fracture with PTH (1-84) (0.22), the incremental costs per QALY for PTH (1-84) versus no active treatment ranged from £16,690 to £26,819. The upper limit of this 95%CI was 0.69, but for some unknown reason the manufacturer's submission states that, in this sensitivity analysis, the upper limit was 0.61, which produces incremental costs per QALY in the range £41,131 to £69,397. The model is sensitive to this parameter, as would be expected, and these results serve to highlight the issues with the use of the relative risk of vertebral fracture from the TOP study.

9.2 Two-way sensitivity analysis of relative risks of fracture with Preotact and alendronate

This analysis compared the best-case scenario for PTH (1-84) with the worst-case scenario for alendronate, and vice versa. Using the lower limit of the 95%CI for Preotact (0.22) and the upper limit of the 95%CI for alendronate (0.68) generated incremental costs per QALY in the range £28,623 to £43,312. Using the upper limit of the 95%CI for PTH (1-84) (0.69) and the lower limit of the 95%CI for alendronate (0.41) resulted in PTH (1-84) being dominated across all age groups.

9.3 Two-way sensitivity analysis of relative risks of fracture with Preotact and teriparatide

This analysis compared the best-case scenario for PTH (1-84) with the worst-case scenario for teriparatide, and vice versa. Using the lower limit of the 95%CI for PTH (1-84) (0.22) and the upper limit of the 95%CI for teriparatide (0.55) generated incremental costs per QALY in the range £1,216 to £1,957. Using the upper limit of the 95%CI for PTH (1-84) (0.69) and the lower limit of the 95%CI for teriparatide (0.22) generated incremental costs per QALY in the range £-2,109 to £-3,203. Again,

however, the interpretation of a negative cost per QALY is impossible as it may be due to a negative value in costs or benefits.

Manufacturer's submission - budget impact analysis

1.0 Description and critique of manufacturer's submission

The manufacturer's submission includes a budget impact analysis, which assessed the likely costs of Preotact over the next five years. The model is populated with data on the incidence and prevalence of fractures; and the estimated use of teriparatide. Only drug costs are included in the analysis.

2.0 Perspective and time horizon

The perspective adopted by the budget impact analysis is that of NHS Wales. However, it is based on non-Welsh prevalence and incidence data, which have been applied to the Welsh population. As a number of sources of data have had to be used, different age groups are considered and a number of assumptions have been employed, which makes the prevalence and incidence rates inconsistent and subject to uncertainty.

3.0 Incident cases

Yearly incidence of clinical vertebral fractures has been derived from the placebo group of the FIT study of alendronate, which was conducted in women aged 55–81 years in the US, and the prevalence of vertebral fractures as estimated above. In mid-2004 there were 484,500 women aged 55+ in Wales. Using the prevalence of 10.15% for morphometric vertebral fracture, 89.85% of these women would not have prevalent fractures, which equates to 435,323 women aged 55+ who do not have a prevalent vertebral fracture. From the FIT study, the annual incidence of clinical vertebral fracture in women without prior fracture was 0.29%. Applying this incidence to the population in Wales would suggest that 1,262 women aged 55+, experience a first clinical vertebral fracture each year. In the women who have one or more prior fractures, the annual incidence of new clinical fractures, as derived from the FIT study, have been applied. This would suggest that 829 new clinical fractures would occur in these women. Therefore, summing the number of incident fractures, the manufacturer's submission estimates there would be 2,091 new clinical vertebral fractures in women aged 55+ in Wales each year.

The yearly incidence of non-vertebral fractures has been assumed from a study that employed All Wales Injury Surveillance System data collected from A&E departments. This indicated that, in the Cardiff area in 1999, the crude rate of fracture in women aged 65+ was 37.7 per 1,000 populations. The manufacturer's submission assumes that all these fractures would be due to osteoporosis, which will be an overestimate. Using data from the Fracture Liaison Service in Glasgow, 98% of fractures are thought to be non-vertebral. Combining these sources generates an estimated 10,868 incident non-vertebral fractures. Therefore, the total number of new fractures per year in Wales has been estimated as 12,959 (2,091 + 10,868). It should be noted that this estimate does not take account of non-vertebral fractures in women aged 55 to 64 years.

4.0 Prevalent cases

The manufacturer's submission estimates that the number of women aged 50+ with clinical vertebral fractures in Wales is 19,681. This is based on UK data from the European Vertebral Osteoporosis Study and the McCloskey method of assessing morphometric vertebral deformity, which indicate that 10.15% of women aged 50–79 years have vertebral fractures. Mid-2004 population estimates suggest there were 487,900 women aged 50–79 years and 92,800 women aged 80+. Assuming that the

prevalence rate in those aged 80+ is the same as in those aged 50–79 (which is unlikely, given the increasing risk of fracture with age), the number of women aged over 50 years with vertebral fracture in Wales would be 59,043. However, only a third of vertebral fractures come to clinical attention, which leads to the estimate of clinical vertebral fractures of 19,681. This is likely to be an underestimate.

For non-vertebral fractures, prevalence as determined in a Scottish study has been used and applied to the Welsh population. The Scottish study surveyed over 4,000 women aged 65+ in Lanarkshire and found that the prevalence of prior fracture was 37.3% (assuming that all fractures that were identified were non-vertebral fractures). In mid-2004, there were 296,000 women aged 65+ in Wales, so applying this prevalence there would be 110,408 women aged 65+ with non-vertebral fractures. This excludes women in nursing or residential care homes, so is likely to be an underestimate.

5. 0 Anticipated use of PTH (1-84)

Welsh Prescription Analysis data from April 2004 to April 2005 was used to establish how many patients were treated in the community with agents used in the treatment/prevention of osteoporosis. The manufacturer's submission estimates that 40,631 patients were receiving bisphosphonates, calcitonin, raloxifene or strontium. These agents may be used for other indications (and other agents may be used for osteoporosis, such as calcium and vitamin D) so this estimate is subject to some uncertainty. The manufacturer's submission also considered teriparatide use, which it estimates may be used in 36 patients in Wales (based on the fact that Healthcare at Home data suggest that 737 people in the UK in February 2006 were currently using teriparatide and Wales makes up 4.9% of the UK population). However, the manufacturer's submission also quotes personal communication with a consultant physician, suggesting that around 80 patients receive teriparatide each year in Wales.

The company's submission states that PTH (1-84) is expected to be prescribed in high-risk patients (women aged over 65 years with two or more clinical vertebral fractures).

The number of women aged 65+ in Wales is estimated at 296,000. Applying the prevalence of morphometric vertebral fracture of 10.15% to these women would suggest that 30,044 have experienced at least one fracture. Assuming that only a third comes to clinical attention, then 10,015 women will have at least one clinical vertebral fracture. Using data from the placebo arm of the FIT study of alendronate to derive the annual incidence of a clinical fracture in patients with prior fractures, the manufacturer's submission estimates that 506 women aged 65+ will present with two or more clinical vertebral fractures each year, of which 292 will have three or more fractures. The manufacturer's submission notes that this indicates a treatment gap when compared with the numbers estimated to receive teriparatide.

6.0 Results

6.1 Base-case

The direct costs of treatment used in the budget impact analysis consider only the drug costs of PTH (1-84) and alendronate, or teriparatide and alendronate. 18 months of PTH (1-84) treatment costs £4,687.20 per patient compared with £4,893.84 for teriparatide. Alendronate is now available generically and the manufacturer's submission has adopted a cost of £10 per month. The budget impact analysis considers that 18 months of PTH (1-84) is followed by 42 months of alendronate. As PTH (1-84) is given for 18 months, the cost of PTH (1-84) will stabilise in the second and subsequent years, but as alendronate is given for 42 months, the alendronate component will continue to grow in the first five years of PTH (1-84) uptake.

The net resource implications, based on 506 eligible high risk patients per year, have been estimated as £1.58 million in year one (i.e. the cost of 12 months of Preotact only), rising to £2.58 million in year five (the cost of PTH (1-84) and alendronate). This assumes 100% uptake of PTH (1-84) by all eligible high-risk patients.

The manufacturer's submission considers that direct savings of £206.64 would be made per patient if PTH (1-84) were used rather than teriparatide.

6.2 Sub-group analysis
No sub-group analysis has been conducted.

7.0 Sensitivity analysis
No sensitivity analyses have been conducted around any of the assumptions.