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I. INTRODUCTION

Forsteo (teriparatide) was authorised in the European Union for the treatment of established osteoporosis in postmenopausal women on 10 June 2003 (European Commission Decision); on 21 June 2007 (European Commission Decision) the indication was extended to treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture.

This Type II variation is an application to extend the therapeutic indication to include the treatment of glucocorticoid-induced osteoporosis (GIO), the most frequent cause of secondary osteoporosis.

Many studies have documented the association between glucocorticoid therapy and the risk of both hip and vertebral fractures, which is increased even at daily doses of prednisolone as low as 2.5 to 7.5 mg and which increases further with higher daily doses. This risk increases rapidly in the first 3 to 6 months after glucocorticoid therapy is initiated while rapid bone loss is observed. The mechanisms by which glucocorticoids increase fracture risk are complex and only partially understood. Bone loss and reduction in bone mineral density (BMD) certainly contribute, but a component of the increased fracture risk is independent of BMD and may be mediated via changes in the composition of the bone mineral/matrix composite or some other aspects of bone quality. Trabecular bone appears to be preferentially affected and evidence exists that vertebral fracture occurs at a higher BMD in GIO than in post-menopausal osteoporosis (PMO). In addition, glucocorticoid therapy may lead to muscle weakness and hence increase the risk of falls. Many of the diseases for which glucocorticoid therapy is given may also have independent effects on fracture risk, such as rheumatoid arthritis, chronic obstructive pulmonary disease, asthma, and inflammatory bowel disease (role of proinflammatory cytokines). Finally, age and female gender have been confirmed to be important risk factors in GIO.

In a Cochrane review, calcium and vitamin D were shown to produce significant effect on bone loss in the spine and forearm but no fracture data are available (Homik et al, 2000). Bisphosphonates have been widely assessed; the conclusion of a Cochrane review (13 trials, 842 patients) reported a weighted mean difference of the percent change in BMD between the treatment and placebo groups of 4.3% (95% CI 2.7, 5.9) at the lumbar spine and of 2.1% (95% CI 0.01, 3.8) at the lumbar neck. Although there was a 24% reduction in odds of spinal fractures [OR 0.76 (95% CI 0.37, 1.53)], this result was not statistically significant (Homik et al, 2000). However, subgroup and secondary analyses have shown significant vertebral fracture reduction after 12-24 months (alendronate, etidronate, risedronate), but overall, no robust fracture data are available. Nevertheless, these constitute the only drug class currently approved for this indication. Alendronate sodium and risedronate sodium are approved in most EU Member States for the treatment of GIO.
The rationale of using teriparatide in the treatment of GIO is based on the stimulatory effects exerted by teriparatide on bone formation while decreased bone formation is the dominant phenomenon in the occurrence of GIO.

Contrary to primary osteoporosis, no CHMP guidance exists for GIO. However, the Group for the Respect and Excellence in Science (GREES) has issued recommendations for the registration of agents to be used in the prevention and treatment of GIO, which have been further updated in 2005 (Abadie et al, Semin Arthritis Rheum, 2005). These recommendations provide the basis for the assessment of this variation.

The Marketing Authorisation Holder (MAH) submitted this variation to change the Product Information as follows:

a) to extend the therapeutic indication to “Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture”;

b) to update section 5.1 of the Summary of Product Characteristics (SPC) to include efficacy data in relation to this indication;

c) to update section 4.8 of the SPC to include a new adverse drug reaction (ADR) reported post-marketing (“serious back cramp”).

II. CLINICAL ASPECTS

2.1 Clinical Pharmacology

No further pharmacokinetic studies were conducted. Pharmacodynamic data (bone markers) are provided in the clinical trial.

Upon CHMP’s Requests for Supplementary Information, the potential interactions between teriparatide and glucocorticoids were discussed by the MAH.

Being a peptide hormone, teriparatide is metabolised by non-specific peptidases. Thus, it would not be likely to alter the metabolism of glucocorticoids which occurs by microsomal enzymes in the liver and other tissues, nor would its metabolism be altered by glucocorticoids. Most of the known glucocorticoid drug interactions are the results of either induction or inhibition of P450 enzymes whereas teriparatide and other peptides do not directly interact with the P450 system.

In the comparative clinical study versus alendronate sodium (see “Efficacy data”), the mean glucocorticoid dose at baseline and 18 months was not significantly different between treatment groups either in the overall population or in those patients who maintained glucocorticoid therapy. Furthermore, the number of patients who increased, decreased, or did not change their glucocorticoid dose from visit to visit was not significantly different between treatments. Changes in BMD at the lumbar spine, femoral neck, and total hip as well as changes in markers of bone turnover were consistent with what had been measured in patients with osteoporosis not taking glucocorticoids during treatment with these medications. Adverse events were not significantly different between treatment groups except for insomnia (see “Safety data”).

In conclusion, the absence of a formal interaction study was considered acceptable.
2.2 Efficacy data

This variation is supported by the results of a single phase 3 trial comparing the effects of Forsteo with those of alendronate sodium on lumbar spine bone mineral density in GIO (study GHBZ).

a) Study design

Study GHBZ was a randomised double-blind double dummy comparative trial vs. alendronate sodium. Patients of both genders receive either teriparatide at a daily dose of 20 µg s.c. and an oral placebo or alendronate at a daily dose of 10 mg p.o. and a subcutaneous injection of placebo. In addition, all patients receive elemental calcium (approximately 1000 mg/d) and vitamin D (approximately 800 UI/d). The overall duration of treatment is 36 months.

The study comprises 2 phases.

- The primary phase corresponding to the first 18 months of therapy started in 2002 and was completed in July 2006; its results are submitted with this variation and address the primary objective of the trial, namely the lumbar spine BMD response.

- The continuation phase with an additional 18-month therapy is ongoing; it addresses the same objectives as the primary phase as well as additional secondary objectives, in particular the effects on fracture risk. Of note, patients and investigators remain blinded until the end of the trial.

b) Study organisation

The trial is being conducted in 76 sites in Latin America, where the majority of patients have been enrolled (57%), in the US (30%), and in Europe (14%); the 14 centres in Europe (Germany, Belgium, Austria, Finland, Denmark, and Norway) have only recruited female patients.

c) Study objectives and endpoints

The primary objective of the trial was to determine whether the increase from baseline to 18 months in lumbar spine BMD (as determined by dual x-ray absorptiometry - DXA) induced by teriparatide statistically significantly exceeds that obtained with alendronate in women and men who had been taking glucocorticoids (GC) for ≥ 3 months.

The main secondary objectives were to address the same question in the population of women only and to describe the time course of BMD response. Other secondary efficacy endpoints included the changes in lumbar spine BMD at 24 and 36 months, in femoral neck and total hip BMD at 18, 24, and 36 months, the time course of all BMD responses and of biochemical markers of bone turnover, and finally the incidence of new fractures (vertebral and non vertebral) at 36 months.

d) Study population

Study patients were adults older than 21 years of both genders with osteoporosis associated with sustained GC therapy. This was defined as an average dose of at least 5 mg of prednisone or its equivalent for a minimum of 3 consecutive months preceding screening. Osteoporosis was defined as follows:

- BMD T score ≤ -2.0 at the total hip, femoral neck, or lumbar spine
- Or, at least one known prior fragility fracture likely associated with GC therapy and BMD T score ≤ -1.0 at the total hip, femoral neck, or lumbar spine

e) Statistical analysis

The sample size was increased during the study from 300 (150 per treatment group) to approximately 450 in order to ensure the enrolment of about 300 women in the trial; the enrolment of additional females (in Europe) allowed the primary hypothesis to also be tested with sufficient power in a females-only subgroup. Drop-outs were assumed to be about 5% and 20% of the study sample before and after a post-baseline BMD measurement, respectively. This sample size allowed at least 90% power to detect a between-treatment difference in lumbar spine BMD of 0.015 gm/cm² with a standard deviation of 0.04 gm/cm². A separate randomisation by country was stratified by gender and previous use of bisphosphonates.
The primary analysis was performed in the Full Analysis Set (FAS), defined as all randomised and treated patients (at least one dose) according to the treatment assigned. An “endpoint analysis” was performed, where the last observed measurement obtained after randomisation was used. Adjustment was made for the stratification variables only, with three geographic regions being defined. The actual change in anteroposterior lumbar spine BMD from baseline to endpoint was analysed using an ANOVA (analysis of variance) with 2-sided significance level of 0.05. The results of the primary analysis were qualitatively compared to the results from the Per Protocol Set.

If the primary analysis reached statistical significance for both the combined male/female and females-only datasets, a strategy for testing the time-course of BMD response was employed using the mixed model repeated measures (MMRM) method and a pre-specified sequence of 2-sided hypotheses tested at level 0.05. Furthermore, the analysis of fracture data at 18 months was added to the planned analyses. The analysis of vertebral fractures was based on the readings of the central laboratory in subjects who had both baseline and post-baseline spinal radiographs; clinical non vertebral fractures (traumatic or fragility) were diagnosed locally.

Exploratory analyses were conducted on the change in lumbar spine BMD in subgroups defined according to age, gender, region, Body Mass Index, presence of a prevalent vertebral fracture, menopausal status, prior use of bisphosphonates, primary disease, baseline GC dose, and duration of GC therapy.

f) Patient disposition
Out of 712 patients screened, 429 were randomised; the same number of patients (214) was allocated and treated in each treatment group. A similar number of patients, slightly more with Forsteo than alendronate (150 vs. 144), completed the first 18 months of treatment.

Two reasons for discontinuation were significantly different between treatment groups. “Patient decision” was the most common reason for alendronate and was twice as frequent as for Forsteo (30 vs. 16 subjects); the MAH clarified that “withdrawal of consent” was the most frequent reason, other reasons including that the patient did not wish to continue in the study, moving away from investigative site, and not wishing to continue with injections. “Adverse events” was the most common reason for Forsteo and was twice as frequent as for alendronate (25 vs. 13 subjects). However, when these “Adverse events” were combined with “Deaths”, the difference was not significant any more because there were more deaths in the alendronate group (12) then in the Forsteo group (7).

Upon CHMP’s request, the MAH also clarified that 103 patients discontinued their glucocorticoid therapy (56 [26.2%] alendronate, 47 [22.0%] teriparatide). Of these 103 patients, 95 had both a baseline and postbaseline lumbar spine BMD measurement and were included in the FAS lumbar spine efficacy analyses. Compliance with study drugs and maintenance in the trial for patients who discontinued glucocorticoid therapy were consistent with the results in the overall population. Of the 103 patients who discontinued glucocorticoid therapy, 77 (74.8%) completed and 26 (25.2%) discontinued the study. There was no statistically significant difference between treatment groups in the number of patients who completed or discontinued the study.

g) Baseline characteristics
Patient demographics, GC therapy, prevalent vertebral fractures, and baseline BMD measures are shown in Table 1. The groups were comparable for baseline characteristics.

The study population consists of 277 postmenopausal women (65%), 67 premenopausal women (16%), and 83 men (19%). More than 80% of the postmenopausal women had over 5 years of menopause at study entry. Based on the median daily dose of prednisone equivalent, the mean T scores, the prevalence of vertebral and non vertebral fragility fractures, this study population adequately qualifies as suffering from GIO and being at increased risk for fracture.
Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Alendronate 10 mg/d (n = 214)</th>
<th>Teriparatide 20 mcg/d (n = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SE</td>
<td>59.1 ± 1.5</td>
<td>57.9 ± 1.5</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>148 (69%)</td>
<td>153 (72%)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>173 (81%)</td>
<td>172 (80%)</td>
</tr>
<tr>
<td>Prior bisphosphonate use, n (%)</td>
<td>20 (9%)</td>
<td>20 (9%)</td>
</tr>
<tr>
<td>Prednisone equivalent daily dose (mg, median)</td>
<td>7.8</td>
<td>7.5</td>
</tr>
<tr>
<td>Duration glucocorticoid use (years, median)</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Radiographically confirmed vertebral fracture, n (%)</td>
<td>53 (25%)</td>
<td>62 (30%)</td>
</tr>
<tr>
<td>Non vertebral fracture, n (%)</td>
<td>89 (42%)</td>
<td>93 (44%)</td>
</tr>
<tr>
<td>Non vertebral fragility fracture, n (%)</td>
<td>43 (20%)</td>
<td>42 (20%)</td>
</tr>
<tr>
<td>Lumbar spine T-Score, mean ± SE</td>
<td>-2.5 ± 0.1</td>
<td>-2.4 ± 0.1</td>
</tr>
<tr>
<td>Total hip T-Score, mean ± SE</td>
<td>-2.0 ± 0.1</td>
<td>-2.0 ± 0.1</td>
</tr>
<tr>
<td>Femoral neck T-Score, mean ± SE</td>
<td>-2.1 ± 0.1</td>
<td>-2.2 ± 0.1</td>
</tr>
</tbody>
</table>

Underlying glucocorticoid-requiring disorders at baseline

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Alendronate 10 mg/d (n = 214)</th>
<th>Teriparatide 20 mcg/d (n = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint disorders, n (%)</td>
<td>120 (56%)</td>
<td>110 (52%)</td>
</tr>
<tr>
<td>Other musculoskeletal disorder, n (%)</td>
<td>37 (17%)</td>
<td>45 (21%)</td>
</tr>
<tr>
<td>Respiratory, n (%)</td>
<td>30 (14%)</td>
<td>29 (14%)</td>
</tr>
<tr>
<td>Other disorders, n (%)</td>
<td>26 (12%)</td>
<td>29 (14%)</td>
</tr>
</tbody>
</table>

h) Treatment compliance

The treatment compliance was calculated based on the amount of drug dispensed and returned at each study visit in those subjects where these data were available for all visits. The percentage of compliant patients (compliance > 70%) was similar for the oral study drug but lower for the injection of Forsteo (86%) as compared with the placebo (92%) (p = 0.077).

The mean baseline calcium doses were around the recommended dose and similar in both alendronate and Forsteo groups (1048 and 1042 mg/d, respectively); they decreased slightly during the trial with endpoint mean doses of 977 and 988 mg/d, respectively. No data were recorded on vitamin D supplementation.

i) Efficacy results

- Bone Mineral Density

The results of the primary analysis (change in lumbar spine BMD) are shown in Table 2.

Table 2  Change from baseline in lumbar spine BMD (g/cm²)

<table>
<thead>
<tr>
<th>Lumbar Spine</th>
<th>Alendronate 10 mg/d</th>
<th>Teriparatide 20 mcg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SE</td>
<td>N</td>
</tr>
<tr>
<td>Month 3</td>
<td>0.014 ± 0.004</td>
<td>184</td>
</tr>
<tr>
<td>Month 6</td>
<td>0.018 ± 0.004</td>
<td>173</td>
</tr>
<tr>
<td>Month 12</td>
<td>0.029 ± 0.004</td>
<td>159</td>
</tr>
<tr>
<td>Month 18</td>
<td>0.033 ± 0.005</td>
<td>148</td>
</tr>
<tr>
<td>End point</td>
<td>0.028 ± 0.006</td>
<td>195</td>
</tr>
</tbody>
</table>

The change in lumbar spine BMD from baseline to endpoint was significantly greater in patients treated with Forsteo than with alendronate (p< 0.001) and corresponded to a percent increase of 7.2% vs. 3.4%, respectively. For those patients completing 18 months of treatment, the figures were 8.2% and 3.9%, respectively. Similar results were obtained in the females-only dataset. The analysis in the
Per Protocol Set showed similar results to that in the FAS. Furthermore, sensitivity analyses using other imputation techniques confirmed the robustness of the primary analysis.

Although less important, the increases in total hip and femoral neck BMD were still significantly greater with Forsteo in the combined male/female dataset (respectively 0.026 vs. 0.017 g/cm²; p=0.006 and 0.024 vs. 0.014 g/cm²; p=0.011); the corresponding percent increases were 3.6% vs. 2.2% and 3.7% vs. 2.1%, respectively. However, in the females-only dataset, the difference did only reach statistical significance for the total hip.

Upon CHMP’s request, sub-group analyses were presented by the MAH. These showed a significantly greater increase from baseline to endpoint (primary study objective) and at 6, 12, and 18 months in lumbar spine BMD in the teriparatide compared with the alendronate group in postmenopausal women, premenopausal women, and men plus premenopausal women. In the men-only subgroup, there was a significantly greater increase in lumbar spine BMD in the teriparatide versus the alendronate group at 18 months (see Figure).

Figure: Mean percent change in lumbar spine BMD

> *Biochemical markers*

Changes in biochemical markers of bone formation (PICP, PINP, BSAP) and resorption (CTX) in a subset of patients during therapy with Forsteo and alendronate were consistent with their antagonist
pharmacodynamic properties, anabolic effects for teriparatide and antiresorptive effects for alendronate.

- **Vertebral and non vertebral fractures**

Although no analysis of vertebral fracture was initially planned at the end of the primary phase, it was performed in the subgroup of patients with both baseline and post-baseline radiographs (78% of the study population).

The fracture results are shown in Table 3.

**Table 3  Vertebral and non vertebral fractures**

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Alendronate 10 mg/d n/N (%)</th>
<th>Teriparatide 20 mcg/d n/N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral radiographic</td>
<td>10/165 (6.1)</td>
<td>1/171 (0.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Non vertebral</td>
<td>8/214 (3.7)</td>
<td>12/214 (5.6)</td>
<td>0.362</td>
</tr>
</tbody>
</table>

During the primary phase of the trial, 17 patients in the alendronate group and 13 patients in the Forsteo group experienced vertebral and/or non vertebral fracture(s); one patient in the alendronate group experienced both a vertebral and a non vertebral fracture.

Ten patients in the alendronate group had new vertebral fractures (1 new vertebral fracture in each patient) that were mild (n=4), moderate (n=2), and severe (n=4); one patient in the Forsteo group had 1 new vertebral fracture that was moderate in severity. The 10 fractures in the alendronate group occurred in 6 postmenopausal women and 4 men, and the 1 fracture in the teriparatide group occurred in a postmenopausal woman (see Table 4).

**Table 4  Incident radiographic vertebral fractures in sub-groups**

<table>
<thead>
<tr>
<th>Category</th>
<th>Fracture Type</th>
<th>ALN10 n(%)</th>
<th>PTH20 n(%)</th>
<th>P-value(a)</th>
<th>P-value(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>None</td>
<td>165 (100)</td>
<td>171 (100)</td>
<td>0.004</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Vertebral fracture</td>
<td>155 (93.9)</td>
<td>170 (99.4)</td>
<td>0.004</td>
<td>0.005</td>
</tr>
<tr>
<td>Post-Menopausal</td>
<td>None</td>
<td>105 (63.6)</td>
<td>105 (61.4)</td>
<td>0.048</td>
<td>0.120</td>
</tr>
<tr>
<td></td>
<td>Vertebral fracture</td>
<td>6 (3.6)</td>
<td>1 (0.6)</td>
<td>0.048</td>
<td>0.120</td>
</tr>
<tr>
<td>Pre-Menopausal</td>
<td>None</td>
<td>23 (13.9)</td>
<td>33 (19.3)</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td></td>
<td>Vertebral fracture</td>
<td>23 (13.9)</td>
<td>33 (19.3)</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Male only</td>
<td>None</td>
<td>31 (18.8)</td>
<td>31 (18.1)</td>
<td>0.048</td>
<td>0.113</td>
</tr>
<tr>
<td></td>
<td>Vertebral fracture</td>
<td>27 (16.4)</td>
<td>31 (18.1)</td>
<td>0.048</td>
<td>0.113</td>
</tr>
<tr>
<td>Male+Menopausal</td>
<td>None</td>
<td>54 (32.7)</td>
<td>64 (37.4)</td>
<td>0.038</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td>Vertebral fracture</td>
<td>50 (30.2)</td>
<td>64 (37.4)</td>
<td>0.038</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Note: ALN10 = Alendronate; PTH20 = Teriparatide. Full analysis set (FRS) =Randomized and treated patients. (a)Percentages compared between treatment groups using a region-stratified Cochran Mantel Haenszel Test. (b)Percentages compared between treatment groups using Fisher’s Exact test.

New non vertebral fractures were reported in a similar number of patients from both groups: 12 (5.6%) in the Forsteo group and 9 (4.2%) patients in the alendronate group (this includes one additional patient for whom a hip fracture was reported as a serious TEAE (treatment emergent adverse events)).

Most of the non vertebral fractures occurred in postmenopausal women in both treatment groups (see Table 5).
2.3 Discussion on efficacy data

The objective of this type II variation was to extend the therapeutic indications for Forsteo to include the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.

The MAH submitted the results of the primary phase of a randomised double-blind comparative trial vs. alendronate, which is in line with the current recommendations of the GREES for the registration of agents in this indication.

At the dose recommended for PMO (20 µg/d), Forsteo produced significant effects on BMD that were comparable to those reported in the PMO pivotal trial after a similar follow-up duration (approximately 18 months). The increase in lumbar BMD, the primary endpoint, was substantial, twice as large as that achieved by alendronate (10 mg/d) (p<0.001). Although still statistically significant, much smaller differences were observed at the level of the hip and the femoral neck; their clinical significance is unknown.

The trial is continuing - blinded – for an additional 18 months of treatment. Compliance will obviously become an issue. Already, 24% of patients have stopped taking glucocorticoids and 31% have withdrawn from the trial at the end of the first phase. Preliminary fracture data, a secondary endpoint at the end of the continuation phase, are supportive of the BMD findings; a significant benefit of Forsteo over alendronate was observed on the spinal column with a lower incidence of vertebral fractures but not on the appendicular skeleton. The MAH committed to provide the complete results of the GHBZ trial by September 2008 (see Letter of Undertaking). This study should provide further information on the effect of Forsteo over time.

The CHMP requested the MAH to further justify the use of Forsteo in premenopausal women given the absence of a clear definition of risk factors for this population.

The MAH highlighted that many of the disorders that require long-term use of glucocorticoids including systemic lupus erythematosus, rheumatoid arthritis, respiratory disorders (chronic obstructive pulmonary disease, asthma), and gastrointestinal disorders (Crohn’s) affect both younger and older adults. Analyses of the effects of underlying disease and use of glucocorticoids in these
populations have been published and indicate that younger adults with disorders requiring sustained glucocorticoid therapy have decreased BMD and/or are at increased risk for fracture (Ramsey-Goldman et al. 1999, van Staa et al. 2006 and Klaus et al. 2002).

The MAH highlighted that BMD is a strong predictor of fracture risk in patients with osteoporosis not taking glucocorticoids. This is not the case in patients with GIOP where glucocorticoids treatment influences the occurrence of fracture by a mechanism independent of BMD. For patients with glucocorticoids treatment, BMD is one of several risk indicators of fracture (van Staa et al. 2003 and 2005). Studies have shown that patients with GIOP have a risk of fracture exceeding that predicted by BMD values alone; postmenopausal patients taking glucocorticoids had a higher risk of vertebral fracture at the same level of BMD compared with controls (van Staa et al. 2003). These types of analyses have led to recommendations for treating patients with current or previous glucocorticoid use at higher levels of BMD than individuals of the same age with osteoporosis not associated with the use of glucocorticoids (Kanis et al. 2004; van Staa et al. 2003).

The MAH highlighted that although there is less information available on the role of risk factors in predicting fracture risk in patients with GIOP than with postmenopausal osteoporosis, studies have shown that factors such as age, gender, fall history, fracture history and indication for glucocorticoid therapy independently contribute to fracture risk in patients with GIOP (van Staa et al. 2005).

The CHMP highlighted that although information from the literature is sparse, it shows that women less than 50 years of age (a proxy for premenopausal status) suffering from lupus erythematosus or rheumatoid arthritis are 2-3 times more likely to have a fracture as compared to age and gender-matched controls; this is attributable to a combination of disease activity and use of glucocorticoids although their respective relative contribution remains unclear. Risk factors include sustained high dose GC therapy (cumulative dose and duration), low BMD, history of fractures or falls, low BMI, disease activity, no use of oral contraceptives.

A number of these factors were present at baseline in the premenopausal cohort of study GHBZ. The underlying diseases requiring glucocorticoid therapy were mainly rheumatologic diseases, essentially rheumatoid arthritis and lupus erythematosus. Patients were taking a median dose of glucocorticoid (prednisone equivalent) of 10 mg/d in the alendronate group and 8 mg/d in the teriparatide group with a median duration of glucocorticoid use of 0.8 and 1.2 years, respectively. The mean lumbar spine T-score at baseline was $-2.2\pm0.2$ in the alendronate group and $-2.1\pm0.2$ in the teriparatide group. Finally, 1/3 of the premenopausal women reported a clinical fracture at baseline and about 1/10 had already a prevalent vertebral fracture.

Based on these data, the majority of the CHMP agreed with the MAH’s proposal to include a statement in section 5.1 to describe more specifically the factors that increase the risk of fracture in premenopausal women which are consistent with the literature and study GHBZ. The majority of the CHMP considered acceptable to assume that a history of osteoporotic fracture reflects an increased risk of fracture or, failing that, the combination of several factors (e.g., low bone density, sustained high dose glucocorticoid therapy, high underlying disease activity, low sex steroid levels). The majority of the CHMP recommended that the MAH should further specify thresholds to define low bone density (T score $\leq -2$) and sustained high dose GC therapy ($\geq 7.5$ mg/d for at least 6 months).

The majority of the CHMP also recommended that the description of the study results in section 5.1 should include a description of the baseline characteristics (risk factors) in the three patient subgroups (post- and premenopausal women, and men) as well as a separate description of the efficacy results in premenopausal women.

Based on the efficacy data submitted, the majority of the CHMP concluded that the MAH has justified the use of Forsteo in the new indication. Nevertheless, 4 CHMP members highlighted that the population of the pivotal study GHBZ consisted mainly of postmenopausal women and men with low BMD which corresponded to the population Forsteo is already indicated for. The number of premenopausal women was low, only 16% of the included patients. This is too small a data base to support a positive benefit/risk balance. The clinical relevance of an increase in BMD might be
2.4 Safety data

*Safety results in study GH62Z*

Overall, there were no significant differences between both treatment groups in the frequency of TEAEs, in TEAEs possibly related to medication or possibly related to device, in serious TEAEs, in TEAEs leading to discontinuation, or in TEAEs resulting in death (see Table 7).

Table 7  Overview of TEAEs

<table>
<thead>
<tr>
<th>Type of TEAE</th>
<th>ALN10 (FAS = 214)</th>
<th>PTH20 (FAS = 214)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-emergent AE (TEAE)</td>
<td>170 (79.4)</td>
<td>182 (85.0)</td>
<td>0.107</td>
</tr>
<tr>
<td>Possibly-related TEAE (b)</td>
<td>28 (13.1)</td>
<td>38 (17.0)</td>
<td>0.193</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>39 (18.2)</td>
<td>45 (21.0)</td>
<td>0.157</td>
</tr>
<tr>
<td>Serious possibly-related TEAE (b)</td>
<td>2 (0.9)</td>
<td>3 (1.4)</td>
<td>0.657</td>
</tr>
<tr>
<td>TEAE resulting in discontinuation</td>
<td>25 (11.7)</td>
<td>31 (14.5)</td>
<td>0.363</td>
</tr>
<tr>
<td>TEAE resulting in death</td>
<td>12 (5.6)</td>
<td>8 (3.7)</td>
<td>0.371</td>
</tr>
<tr>
<td>Device-related TEAE</td>
<td>14 (6.5)</td>
<td>24 (11.2)</td>
<td>0.088</td>
</tr>
<tr>
<td>Clinical fractures</td>
<td>11 (5.1)</td>
<td>12 (5.6)</td>
<td>0.824</td>
</tr>
</tbody>
</table>

- Treatment emergent adverse events (TEAEs)
  - The most frequent TEAEs were infections in both groups; this is not unexpected in patients on glucocorticoid therapy and a causal relationship with the study drugs is unlikely.
  - Gastrointestinal complaints were more frequent in the Forsteo group, especially nausea (twice as frequent: 14% vs. 7%; p=0.016). Nausea is listed in the SPC.
  - In the SOC of Nervous System Disorders, headache and dizziness were slightly more frequent in the Forsteo group; they are listed in the SPC.
  - In the SOC of General Disorders, asthenia and fatigue were slightly more frequent in the Forsteo group; they are listed in the SPC.
  - In the SOC of Cardiac Disorders, palpitations were reported slightly more frequently in the Forsteo group; this is listed in the SPC.
  - Symptoms related to the SOC of Psychiatric disorders were significantly more frequent in the Forsteo group, mainly due to insomnia (5.1% vs. 0.9%; p= 0.011) and anxiety (3.7% vs. 1.4%) whereas the rate of depression was similar (5.6% vs. 5.1%). These events are not listed in the SPC.

- Possibly related TEAEs and device-related TEAEs
  - Those TEAEs that led to withdrawal were more frequent in the Forsteo group (5% vs. 2%; p=0.065); these were mainly GI symptoms and dizziness.
  - Injection site reactions, whether considered related to the medication or the device, were more frequent with Forsteo than with the placebo injection. These local reactions are listed in the SPC.

- Serious TEAEs, deaths, and TAEs leading to study withdrawal
  - There were more deaths in the alendronate group (12) than in the Forsteo group (8). There was no notable difference in the SAEs; most of them were infections.
Two pregnancies were reported, one in each treatment group. The patient in the alendronate group delivered an infant with low birth weight, while otherwise no anomaly was reported.

Serious renal events and study withdrawals due to renal events occurred more frequently in the Forsteo group than in the alendronate group (6 patients vs. 1). According to the narratives provided in the study report, these were unlikely to be related to the study drug.

Laboratory tests

- The laboratory results demonstrated the known effects of teriparatide and antiresorptive agents on serum calcium. Small decreases in predose serum calcium occurred in the alendronate group whereas small increases occurred in the Forsteo group; one patient reported a TEAE of hypercalcemia that was mild in severity and considered by the investigator as possibly related to study drug. This effect is listed in the SPC.
- The increase from baseline to endpoint in serum uric acid was significantly greater in the Forsteo group compared with the alendronate group. In the Forsteo group, 3 patients reported TEAEs of hyperuricemia that were mild (1) and moderate (2) in severity, and 1 patient reported a TEAE of gout that was mild in severity. The effect of hyperuricemia is listed in the SPC.
- There was a significant decrease in serum alkaline phosphatase in the alendronate group that was likely due to the antiresorptive effects of the drug.
- Mean 24-hour urinary calcium concentrations decreased slightly in each treatment group with the decrease being significant in the alendronate group. However, there was no difference between groups in the change from baseline to endpoint in 24-hour urinary calcium.

Post-marketing data

Following the assessment of PSURs no 5 and 6 (covering the period from 27 May 2005 to 26 May 2006), the MAH was requested to review and closely monitor, amongst other events, the event of “back pain”. In addition, in December 2006, Swissmedic requested the addition of “muscle cramps in the back/lumbar region in the sense of ischias syndrome” to the adverse event section of the Swiss SPC. This request was based on their assessment of a single report from a patient in Switzerland who had the non-serious adverse event report of “… cramps from neck to pelvis and cramps radiating from vertebral column …” with a positive dechallenge and rechallenge.

A comprehensive review of the Lilly Safety System revealed:
- 14 serious reports of muscle spasms, 10 of which specifically involved the back
- 67 serious reports of back pain, 13 of which specifically described muscle spasms.

Based on the fact that 10 of these 23 serious adverse event reports occurred shortly after the first dose of Forsteo and that 7 reports included a positive rechallenge for “muscle spasm of the back”, the MAH has determined that muscle spasm of the back is an adverse reaction to Forsteo.

Muscle cramps, predominantly in the legs, were identified as a reaction with teriparatide during clinical trials. The current SPC incorporates muscle cramps as a common adverse reaction of teriparatide in Section 4.8, Table 2.

The MAH proposed adding “serious back cramp” as a “very rare” adverse reaction to Section 4.8, post-marketing experience, to more clearly distinguish for prescribers the rare observation of this unusual form of muscle cramp. The “very rare” designation is based on the fact that these 23 cases were reported from the estimated 400,500 cumulative teriparatide new patient starts worldwide through November 2006 (for a reporting rate of 0.57 per 10,000 or <0.01%).

Risk Management Plan

The Risk Management Plan initially submitted by the MAH (dated 5 April 2007) did not address the new proposed indication. No additional data with regard to the new target population were provided.
and the MAH had not discussed the potential impact for the treatment in this specific population, in particular the risk of potentiating the side-effects of GC therapy. Furthermore, no long-term safety data had been obtained in patients with GIO on sustained systemic corticoid therapy and no discussion was included about the impact of the immusupression status of such patients and the potential risk of bone cancers including osteosarcoma.

An updated Risk Management Plan was submitted by the MAH in October 2007; it was further updated in January 2008 (dated 17 January 2008 – version n. 2.5). Upon request from the CHMP, the MAH included a section referring to the epidemiology of GIOP. Furthermore, the pharmacovigilance plan for teriparatide was revised to include a provision to analyse post-marketing safety data using gender and age of female patients <50 years as a proxy for premenopausal status. The MAH agreed to modify the Statistical Analysis Plan of Study GHBX in osteosarcoma to take into account regional differences in expected response rates. However, it is clearly specified in the current protocol that the study aims at identify approximately 40% of newly diagnosed cases of osteosarcoma among men and women 40 years and determine which cases, if any, have a history of teriparatide treatment. No distinction in this objective has been provided despite the ability to identify a higher number of osteosarcoma cases in the European component of the study thanks to Scandinavian registries. It is of crucial importance that agreement between the Scandinavian Sarcoma Group Registry, the Coordinating Epidemiology Unit and the MAH take into account that the identification of 40% of osteosarcoma cases corresponds to the American's goal and not to the EU’s one. If this agreement is in line with the EU objective, it could be acceptable to amend only the statistical plan and not the protocol of the study GHBX but only on this condition.

The MAH has also committed to reformat their RMP in accordance with the latest template and to include the amendments to the statistical plan for study GHBX by Q3 2008 (see Letter of Undertaking).

2.5 Discussion on safety data

The CHMP acknowledged that there were no significant differences between the alendronate and teriparatide groups in the frequency of TEAEs, in TEAEs possibly related to medication or possibly related to device, in serious TEAEs, in TEAEs leading to discontinuation, or in TEAEs resulting in death.

Nevertheless, considering that the use of Forsteo would be extended to premenopausal women, the CHMP requested the MAH to address the issue of the potential risks of Forsteo in women of childbearing age.

In Study GHBX the number of patients reporting TEAEs at the system organ class and preferred term levels in the alendronate and teriparatide groups was consistent among subgroups of postmenopausal women, premenopausal women, men, and men plus premenopausal women. The incidence of TEAEs in these subgroups both within and between the alendronate and teriparatide groups was also consistent with those in the overall study population. Therefore, the safety profile of teriparatide in patients with GIOP did not differ in women based on menopausal status.

In order to address the management of women of childbearing age the CHMP agreed with the MAH’s proposal to include “pregnancy and lactation” as a contraindication and to include that women of childbearing potential should use effective methods of contraception during use of Forsteo. Moreover the Product Information should state that if pregnancy occurs, Forsteo should be discontinued.

The Pharmacovigilance Plan for teriparatide has been revised to include a provision to analyse post-marketing safety data using gender and age of female patients <50 years as a proxy for premenopausal status. This will enable the MAH to discern any unique features of the safety profile of teriparatide in this patient population. Section 4 of the RMP has been revised to include the changes to the SPC described above.
An additional question was raised by the CHMP whether sufficient safeguards were in place to prevent long term use of Forsteo, which is currently limited to 18 months. The MAH argued that the current SPC with statements in sections 4.2 and 4.4 was sufficient to prevent long term use of the product. Supportive evidence was provided by the results of an observational study (EFOS) conducted in a community setting in 8 EU countries. The protocol was submitted and the MAH has committed to submit the full results when available (see Letter of Undertaking). Out of 1649 postmenopausal women, 78% effectively discontinued treatment before 18 months and the maximum duration was 21 months. These results are reassuring although it is not clear whether the conditions of this study were fully representative of the usual clinical practice and how they can be extrapolated to premenopausal women. Therefore, the mention in section 4.2 of the SPC of 18 months as the maximum treatment duration has been reinforced by a statement that the 18-month course of Forsteo should not be repeated over a patient’s lifetime.

The MAH committed to reformat their RMP in accordance with the latest template and to include the amendments to the statistical plan for study GHBX by Q3 2008 (see Letter of Undertaking).

Most TEAEs that occurred in the Forsteo group are known ADRs listed in the current SPC, with the exception of insomnia and anxiety. These are well known ADRs of GC therapy. They were mild/moderate in all cases but one and did not lead to treatment discontinuation. Although a potentiation of the side-effects of glucocorticoids cannot be completely ruled out, the relationship of these events to the test drug appeared highly questionable in a number of cases (e.g. implausible chronology, other possible causes).

Upon request by the CHMP, the MAH provided a comprehensive review of the serious reaction “back cramp”. Unfortunately, the information is very scarce. From the listing submitted, it can only be inferred that it is an injection reaction, since it usually occurred within minutes of the injection; furthermore, six patients (out of 23) were administered narcotic analgesics. The mechanism of this reaction has not been elucidated. The MAH confirmed that it had not been reported in clinical trials.

The CHMP agreed that “back cramp” is an ADR to Forsteo. However, in line with the Guideline on SPC (2005), frequencies for ADRs should not be based on post-marketing sales and therefore the frequency “not known” should be used. Furthermore, additional details should be included in the SPC in order to better describe for prescribers the nature and chronology of this ADR. In addition, the CHMP recommended to include the term “back pain”.

2.6 Overall conclusion

The objective of this type II variation was to extend the therapeutic indications for Forsteo to include the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.

The MAH submitted the results of the primary phase of a randomised double-blind comparative trial vs. alendronate, which is in line with the current recommendations of the GREES for the registration of agents in this indication.

At the dose recommended for PMO (20 µg/d), Forsteo produced significant effects on BMD that were comparable to those reported in the PMO pivotal trial after a similar follow-up duration (approximately 18 months). The increase in lumbar BMD, the primary endpoint, was substantial, twice as large as that achieved by alendronate (10 mg/d) (p< 0.001). Although still statistically significant, much smaller differences were observed at the level of the hip and the femoral neck; their clinical significance is unknown.

The trial is continuing – blinded – for an additional 18 months of treatment. Compliance will obviously become an issue. Already, 24% of patients have stopped taking glucocorticoids and 31% have withdrawn from the trial at the end of the first phase. Preliminary fracture data, a secondary endpoint at the end of the continuation phase, are supportive of the BMD findings; a significant
benefit of Forsteo over alendronate was observed on the spinal column with a lower incidence of vertebral fractures but not on the appendicular skeleton. The MAH committed to provide the complete results of the GHBZ trial by September 2008 (see Letter of Undertaking). This study should provide further information on the effect of Forsteo over time.

Upon CHMP’s request, further analysis of BMD data was presented in the subgroups of postmenopausal women, premenopausal women, and men. The greatest difference between alendronate and Forsteo was observed in premenopausal women. However, it is acknowledged that the relationship between BMD and fracture risk is less well established in GIO than in PMO with vertebral fracture occurring at a higher BMD. The MAH provided additional supporting evidence from literature that women less than 50 years of age (a proxy for premenopausal status) suffering from lupus erythematosus or rheumatoid arthritis are 2-3 times more likely to have a fracture as compared to age and gender-matched controls. Several risk factors have been identified, which the MAH proposed to introduce in section 5.1 of the SPC. Additional information has been added in the SPC regarding the management of women of childbearing potential and the recommendation of a maximum treatment duration of 18 months has been reinforced. The majority of the CHMP also recommended that the description of the study results in section 5.1 should include a description of the baseline characteristics (risk factors) in the three patient subgroups (post- and premenopausal women, and men) as well as a separate description of the efficacy results in premenopausal women.

The MAH committed to reformat their RMP in accordance with the latest template and to include the amendments to the statistical plan for study GHBX by Q3 2008 (see Letter of Undertaking).

Thus, the majority of the CHMP concluded that the new indication is approvable provided that the Product Information will be amended as outlined in section VI of this assessment report.

Nevertheless, 4 CHMP members highlighted that the population of the pivotal study GHBZ consisted mainly of postmenopausal women and men with low BMD which corresponded to the population Forsteo is already indicated for. The number of premenopausal women was low, only 16% of the included patients. This is too small a data base to support a positive benefit/risk balance. The clinical relevance of an increase in BMD might be different in this population and bridging using BMD data is doubtful. Therefore these CHMP members did not agree to extend the indication for Forsteo to the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in premenopausal women.

As far as the addition of a new ADR to section 4.8 is concerned, this change is also approvable.

III. FOLLOW-UP MEASURES UNDERTAKEN BY THE MARKETING AUTHORISATION HOLDER

As requested by the CHMP, the MAH agreed to submit the final study reports of two clinical studies upon their completion, to re-format the RMP and to submit any variation application which would be necessary in the light of compliance with these commitments.

IV. CHANGES TO THE PRODUCT INFORMATION

The majority of the CHMP and the MAH agreed to change the Product Information for Forsteo as follows.

SUMMARY OF PRODUCT CHARACTERISTICS

The majority of the CHMP requested to include in section 4.2 “Posology and method of administration” that the 18-month course of Forsteo should not be repeated over a patient’s lifetime.
In order to address the management of women of child-bearing age the majority of the CHMP recommended to include “pregnancy and lactation” as a contraindication in section 4.3 “Contraindications” of the SPC and to include in sections 4.4 “Special warnings and precautions for use” and section 4.6 “Pregnancy and lactation” of the SPC that women of childbearing potential should use effective methods of contraception during use of Forsteo. Moreover if pregnancy occurs, Forsteo should be discontinued.

With regard to section 4.8 “Undesirable effects”, as the frequencies for ADRs should not be based on post-marketing sales, the CHMP recommended to use the frequency “not known” for back cramp. Furthermore, the CHMP recommended to include the description that this ADR has been reported within minutes of the injection and to include the term “back pain”.

The majority of the CHMP recommended that the description of the study results in section 5.1 “Pharmacodynamic properties” should include a description of the baseline characteristics (risk factors) in the three patient subgroups (post- and premenopausal women, and men) as well as a separate description of the efficacy results in premenopausal women. The majority of the CHMP also recommended to include a statement in section 5.1 of the SPC to further specify thresholds to define low bone density (T score ≤ -2) and sustained high dose GC therapy (≥ 7.5 mg/d for at least 6 months).

The majority of the CHMP recommended including in section 5.3 “Preclinical safety data” of the SPC a description of studies in rabbits which are mentioned in section 4.6.

ANNEX II
The Annex II should be updated to reflect the last version and date of the RMP.

PACKAGE LEAFLET
The majority of the CHMP recommended updating section 2 “Before you use Forsteo” of the PL to include that women of child-bearing potential should use effective methods of contraception during the use of Forsteo and that Forsteo should be discontinued if pregnancy occurs.

The majority of the CHMP recommend updating section 3 “How to use Forsteo” of the PL to include that patients should not receive more than one treatment course of 18 months over your lifetime.

The Product Information includes also the changes from variation EMEA/H/C/000425/II/0017 which received a positive opinion by CHMP at the February CHMP plenary meeting (To include the adverse reaction “alkaline phosphatase increase” in section 4.8 “Undesirable effects” of the SPC and to amend section 4 “Possible side effects” of the PL accordingly).

The MAH agreed with the changes in the SPC, Annex II and PL as recommended by the majority of the CHMP and submitted a revised Product Information.

V. CONCLUSION
On 21 February 2008 the majority of the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet subject to the additional commitments undertaken

VI. REFERENCES


