London, 24 May 2007
Product name: **FORSTEO**
Procedure No: **EMEA/H/C/000425/II/0011**

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

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). At the time of the application for the initial Marketing Authorisation for Forsteo, the applicant was seeking an indication for the treatment of established osteoporosis in postmenopausal women and in men. The indication in men was based on a pivotal trial in men showing a significant increase in bone mineral density (BMD) after approximately 1 year of treatment and further extrapolation to men of the reduction in the incidence of fractures seen in women after approximately 2 years of treatment. The applicant reviewed the outcome of the clinical program carried out in men and concluded that Forsteo was an appropriate treatment for osteoporosis in men. Nevertheless, at that time the CPMP concluded that this extrapolation was not acceptable and the therapeutic indication for Forsteo should not include treatment of osteoporosis in men.

Since the review of the original Marketing Authorisation application for Forsteo, the scientific knowledge of osteoporosis in both postmenopausal women and men has been advancing rapidly, and the CHMP Guideline on the "Evaluation of medicinal products in the treatment of primary osteoporosis" has been updated. Specifically, the Marketing Authorisation Holder (MAH) referred to the CHMP draft Guideline on the "Evaluation of medicinal products in the treatment of primary osteoporosis" dated 14 December 2005 in order to introduce the following changes into the Product Information in the framework of this Type II variation:

- to revise the therapeutic indication from "established osteoporosis" to "osteoporosis at high risk of fracture" and to extend the treatment to non-vertebral fractures with consequential inclusion of clinical data on non-vertebral fractures in section 5.1 of the Summary of Product Characteristics (SPC);
- to extend the therapeutic indication to "osteoporosis in men at high risk for fracture", supported by study results that are already included in the current SPC (section 5.1);
- to change the Package Leaflet (PL) accordingly.

Nevertheless, the CHMP referred to the final version of the Guideline, dated 16 November 2006, which superseded the one the MAH was referring to. Namely, the wording for the therapeutic indication as expressed in the current version of the Guideline is "*women at increased risk of fracture*" which replaced the wording as stated in the previous version of the Guideline *"women at high risk of fracture"*.

The data to support the changes in this type II variation was already submitted with the original application for Forsteo and was already reviewed by the CHMP (Study B3D-MC-GHAC, the pivotal study in women, and B3D-MC-GHAJ, the pivotal study in men). The only new information submitted within this type II variation was the final report of study B3D-MC-GHBJ, which had been designed to collect safety data for up to 30 months following the withdrawal of the study drug. Additional objectives of this study were the evaluation of BMD and vertebral fractures; these data were submitted by the MAH in the form of a publication for the male cohort (Kaufman, 2005) as well as in an updated Clinical Study Report .

II. CLINICAL ASPECTS

2.1 Clinical pharmacology

The clinical pharmacology of teriparatide had been presented with the initial application for Forsteo. Thus, the MAH referred to the bioavailability of the already submitted study B3D-LC-GHBI ("Absolute bioavailability of teriparatide administered via subcutaneous injection") in order to assess the potential difference between genders and to pharmacodynamics analysis performed during clinical studies B3D-MC-GHAC and B3D-MC-GHAJ. The bioavailability of teriparatide has been shown to be lower in men than in women following subcutaneous injection (23% higher exposure in women; p=0.034); this produced a 25-50% lower response in bone turnover markers. The absolute bioavailability of teriparatide was not different between genders (p=0.679). The clinical consequence of the AUC differences has not been further investigated. However, the mechanism of action of teriparatide was not considered gender specific.

2.2 Efficacy data

To support the proposed extension of indication the MAH referred to the information extracted from the two pivotal trials in women (study B3D-MC-GHAC) and in men (study B3D-MC-GHAJ) to demonstrate that patients enrolled in these trials were at a high risk of fracture.

2.2.1 Pivotal study in women - study B3D-MC-GHAC (abbreviated GHAC)

The pivotal study GHAC was a double blind, multicentre, randomised, placebo-controlled trial to evaluate the efficacy and safety of two doses of teriparatide in postmenopausal women with established osteoporosis. The objective of this study was to demonstrate a reduction in the proportion of patients with new vertebral fractures following 3-year treatment with 20 and 40 µg/day of teriparatide plus calcium and vitamin D compared with calcium and vitamin D alone. This pivotal study included 1,637 postmenopausal women (mean age 69.5 years). The patients were postmenopausal women with cessation of ovarian function for a minimum of 5 years prior to randomisation; they had a minimum of either one moderate or two mild atraumatic vertebral fractures. In those with fewer than two moderate fractures or previously treated with therapeutic doses of bisphosphonates or fluorides, the hip or lumbar spine BMD measurement was required to be at least 1.0 standard deviation (SD) below the average bone mass for young, healthy women (T-score). The resultant annualized vertebral fracture rate in patients assigned to placebo was 8.3%.

The planned duration of the treatment phase of this study was 36 months, with possible interim analyses of safety after 12 months and of safety, efficacy and pharmacokinetics after 24 months. Due to safety concern in animal (observation of osteosarcoma in a 24-month oncogenicity study in rat), this clinical study was stopped in December 1998.

2.2.2 Efficacy results in non-vertebral fractures

A secondary objective of study GHAC in women was to determine the effect of treatment on the proportion of patients with new non-vertebral fractures alone, and with new vertebral and non-vertebral fractures combined. The non-vertebral fractures were assessed only when clinically indicated, and study site personnel were requested to confirm the fracture either by obtaining a radiologist's written report or by review of the x-ray film. New non-vertebral fractures were recorded as involving the hip, radius, ankle, humerus, ribs, foot, pelvis, or other body sites. In addition, investigators were asked to report whether the fractures were traumatic, defined per protocol as a fracture caused by a wound or injury that is severe enough to cause a fracture in an otherwise healthy person (for example, automobile accident or a fall from greater than standing height).

Overall, non-vertebral fragility and traumatic fractures were reported in 119 patients during study GHAC. Treatment with teriparatide at the dose of 20 µg resulted in a significantly lower proportion of patients with fracture (6.3%) compared with placebo (9.7%) the relative risk (RR 95% CI) being 0.65

[0.43, 0.98] ($p<0.05$). The reduction in fracture risk was not significantly different between the 40-µg group and the 20-µg group. An updated analysis of the major non-vertebral sites defined as hip, radius, humerus, ribs, and pelvis was provided by the MAH. The effect of treatment was also statistically significant compared with placebo with an RR of 0.52 [0.30, 0.90] and for fragility fractures an RR of 0.38 [0.17, 0.86].

Based on these results the MAH had initially proposed to delete the negative statement regarding hip fracture from the therapeutic indications (section 4.1 of the SPC) and to add a paragraph in section 5.1 of the SPC describing the results for all and major non-vertebral fractures.

2.2.3 Discussion on efficacy results in non-vertebral fractures

To support the wording for the new indication as expressed in the current version of the Guideline (i.e. "*women at increased risk of fracture*" which replaced the previous wording "*women at high risk of fracture"*), the MAH used information extracted from the pivotal trial to demonstrate that patients enrolled in this trial were at a high risk of fracture.

The CHMP noted that in the pivotal study GHAC, the new vertebral fracture rate was 14.3% over a median treatment duration of 19.2 months (range: 18-23), which yields an annualized rate of 8.3%.

The CHMP highlighted that the MAH did not actually try to characterise the study population with regard to the absolute fracture risk as recommended in the Guideline since they relied on the point-estimate of the risk found in the placebo group. In the last version of the Guideline, a 10-year probability range of 15-20% for spinal fracture and 10-15% for major non-vertebral fractures is considered a relevant inclusion criterion. Although a wide range of incertitude was to be expected when extrapolating a 10-year rate based on 2-year data (which would yield a rate of 58%), it was reasonable to conclude that this population was at increased risk of vertebral fracture. This was further supported by the main baseline characteristics of these women: mean age around 69 years with about 21 years since menopause; mean number of existing vertebral fractures of 2.3; mean lumbar spine BMD of 0.82 g/cm^2 (equivalent to a T-score = -2.6 SD). The concept of independent risk factors has not yet been translated into medical practice to promote a shift in focus towards a global assessment of future fracture risk. In order to be consistent with recently authorised applications for similar medicinal products, the CHMP recommended that the wording "*increased risk of fracture*" in section 4.1 of the SPC should be further qualified in section 5.1 "Pharmacodynamic properties" of the SPC by a description of the relevant risk factors.

Additionally, following the Request for Supplementary Information adopted at the December 2006 CHMP plenary meeting, the MAH presented a new analysis of the results of study GHAC showing the incidence of major non-vertebral fragility fractures as defined in the Guideline (i.e. pelvis, hip, ribs, humerus, and radius). The relative risk (95% CI) in the group treated with the recommended dose of teriparatide (20µg/kg) was 0.383 (0.171, 0.857); this corresponded to a relative risk reduction of 62%. The reductions in the incidence of both vertebral and non-vertebral fractures were highly significant ($p < 0.001$ and $p = 0.015$, respectively). Therefore, the CHMP concluded that the analysis of major non-vertebral fragility fractures in study GHAC showed significant risk reduction with an acceptable type I error level.

Thus, based on the evidence presented, the CHMP concluded that the extension of the indication to non-vertebral fractures could be endorsed. Nevertheless, as a non significant reduction in the incidence of hip fracture remained valid, the CHMP concluded that this information should be maintained in section 4.1 of the SPC and should also be mentioned in section 5.1 of the SPC.

2.2.4 Pivotal study in men - study B3D-MC-GHAJ (abbreviated GHAJ)

The pivotal study GHAJ was a double blind, randomised study, to demonstrate an increase in vertebral BMD in men with primary osteoporosis. Male patients completed up to 14 months (median 11 months) of this study at the time of the study closure. Four hundred thirty seven (437) men, aged 30-85, were recruited. Patients were randomised to receive one of the following treatments:

teriparatide 20 µg/day (151), teriparatide 40 µg/day (139), and placebo (147) as subcutaneous injections into the abdominal wall or thigh. All patients received additionally calcium 1000mg/day and vitamin D 400 IU/day orally.

The patients were men with primary osteoporosis defined as bone loss primarily attributable to either idiopathic or hypogonadal causes. They had at least one lumbar spine or proximal femur (neck or total hip) BMD at least 2 SD below the average for young, healthy men. Forty-one percent of the men had one or more prevalent vertebral fractures. Of the 437 men who participated in this study, 355 (81%) enrolled in the follow-up study B3D-MC-GHBJ already mentioned. The resultant annualized vertebral fracture rate in former GHAJ patients assigned to placebo was 4.9% according to the publication of Kaufman (2005).

The rates for vertebral fracture found in the placebo arm of each study were comparable to rates found in similar populations in other studies of osteoporosis therapies. In addition, the entry criteria for study GHAJ resulted in a male population which had an observed vertebral fracture rate within or greater than the range seen in prior studies in women.

Due to safety concern in animal (observation of osteosarcoma in a 24-month oncogenicity study in rat), this study was stopped in December 1998.

2.2.5 Efficacy results in men with osteoporosis

The study GHAJ was a double-blind randomised study to demonstrate an increase in vertebral BMD in men with primary osteoporosis. Four hundred thirty seven men, aged 30-85, who had lumbar spine or hip BMD measurement at least 2.0 SD below the average bone mass for young healthy men, were recruited. The primary endpoint for efficacy was the change from baseline in vertebral BMD. The planned duration of the trial was 24 months but it was prematurely stopped in December 1998. As a result, the median observation time was 11.6 months; approximately 25% of the men received treatment for more than 12 months with the longest duration of treatment at 14 months.

The comparison of lumbar spine BMD results between men and women is shown in the following table for the recommended daily dose (20 µg).

CHANGE IN LUMBAR SPINE BMD BASELINE TO STUDY END MEN (GHAJ) AND WOMAN (GHAC)

	GHAJ	**GHAC 12-month visit**
	TPTD20 (N = 151)	TPTD20 (N = 541)
Variable		
Lumbar Spine (L-1 through L-4)		
n	141	466
Mean baseline (g/cm²)	0.89±0.15	0.82 ± 0.17
Mean change (g/cm²) from baseline	0.05±0.04	0.06 ± 0.04
Mean percent change from baseline	5.73%±4.46	8.26% ± 6.11

Abréviations: TPTD20 = teriparatide 20 µg injection.
Source: Part IV, v20, page 10 (Table GHAC.11.18); Part IV, v61, page 133 (Table GHAJ.11.9).

In addition, the MAH extracted data on the incidence of vertebral fractures from the publication of Kaufman (2005), which reported the results of the male cohort followed after drug withdrawal in study GHAJ. A subset of 279 patients had adequate spine radiographs at baseline and at the 18-month visit of the follow-up study; the incidence of new vertebral fractures in patients that had been treated with teriparatide (both doses combined) was reduced by 51% compared with placebo (p = 0.07) and by

83% for moderate/severe fractures (p = 0.01). In the 114 men who had a prevalent vertebral fracture at baseline the risk reduction was more significant. In addition, results were quite similar for both doses (20 and 40 µg daily).

Based on these data the MAH had proposed to extend of the therapeutic indication to "osteoporosis in men at high risk for fracture" (section 4.1 of the SPC).

2.2.6 Discussion on efficacy results in men with osteoporosis

According to the CHMP Guideline on the "Evaluation of medicinal products in the treatment of primary osteoporosis", once an initial marketing authorisation has been granted for the treatment of osteoporosis in postmenopausal women, a separate bridging study can be sufficient to support a claim of treatment of osteoporosis in men provided that the following prerequisites are fulfilled:

- the duration of the study is at least one year;
- the dosage is justified;
- the applicant justifies that the cut-off of BMD, age and any other risk factor chosen for the inclusion of men in the pivotal study will generate a fracture risk of a similar magnitude compared with postmenopausal women that were recruited in the studies used to obtain the indication;
- the magnitude of the changes in BMD versus placebo is similar to that observed in postmenopausal osteoporotic women treated with the same compound and is proportional to the decreased incidence of fractures in treated women.

The pivotal study GHAJ in men with primary osteoporosis, which was submitted with the initial application for the Marketing Authorisation for Forsteo, was presented by the MAH as a bridging study.

Thus, the CHMP discussed whether the four criteria for defining a bridging report, as established by the Guideline, were fulfilled.

a) Duration of the study

The CHMP acknowledged that the duration of the trial was less than one year due to premature discontinuation of the trial as already mentioned. Actually, about 80% of the patients completed at least 10 months in the trial while about 45% (approximately 70 patients) completed 12 months.

Although limited, the study duration was considered acceptable by the CHMP as compared to the minimum of 12 months required in the Guideline.

b) Justification of the dose

The magnitude of the changes in lumbar spine BMD appeared slightly smaller in men than in women. BMD results of the femoral neck were not provided. They were less favourable than lumbar spine BMD results for both genders at the end of the trials and were similarly slightly better in women than in men. Although this difference seemed marginal it may be explained by the lower bioavailability of the product in men. BMD results showed a dose response in both women and men but this did not translate into significant differences with regard to fracture rates.

Therefore, the CHMP concluded that the same daily dose of 20 µg was adequate for men.

c) Risk factors

Of the 437 men who participated in study GHAJ, 355 (81%) enrolled in the follow-up study GHBJ after study GHAJ was prematurely stopped. A subgroup of 279 subjects (64%) had adequate lateral radiographs at GHAJ baseline and also at the 18-month follow-up visit of study GHBJ, which

occurred in average 30 months from treatment study GHAJ baseline. The incidence of vertebral fractures over this 30-month period was estimated in this subgroup. Although this was not an endpoint in the initial study GHAJ, it was the specific reason for a prospective amendment to the follow-up study GHBJ, which was implemented in a majority of centres. Furthermore, the methodology, quality assurance coordination and central reading of these x-rays were the same for studies GHAC, GHAJ and GHBJ as well as the vertebral fracture assessment which was performed by the same laboratory. Finally, the baseline characteristics of the subjects who participated in this analysis were representative of the original GHAJ cohort.

The annualized vertebral fracture rate in former GHAJ patients assigned to placebo was estimated at 4.9% based on the observation that 12/103 men (11.7%) developed a new vertebral fracture after an average follow-up of 30 months. The MAH argued that this fracture rate was within or greater than the range seen in prior published studies in women. However, the Guideline recommends that this risk should be "of a similar magnitude" compared with the postmenopausal women recruited in study GHAC, which was used to obtain the indication (annualized risk of 8.3%). It should be noted that 25% of these male subjects received an osteoporosis drug after the end of the controlled trial, which means that this possibly underestimates the fracture risk slightly.

Thus, considering the annualized fracture rates in men and women (respectively, 4.9% and 8.3%), the MAH was requested to justify the similarity of the magnitude of the fracture risk in men and in women through a Request for Supplementary Information and in an oral explanation.

Thus, an oral explanation was held by the MAH on 23 May 2007. The MAH compared the rate of incident radiographic vertebral fractures in the placebo groups of women and men. Although the annualised fracture rate was lower in men (4.9% *vs* 8.3%) than in women, the MAH highlighted that there was an overlapping of the Confidence Intervals. Additionally, considering that women were enrolled primarily based on the presence of a radiographic vertebral fracture, whereas men were enrolled based on the presence of low bone mineral density, the MAH compared vertebral fracture incidence in men and women with prevalent vertebral fractures. The MAH highlighted that the annualized vertebral fracture rates were of a similar magnitude in men and women after accounting for prevalent vertebral fractures (1.9% *vs* 2.4% in the group with "no prevalent vertebral fracture" and 9.4% *vs* 9.5% in the group with "at least one prevalent vertebral fracture"). Likewise, BMD changes were comparable in men and women regardless of the baseline vertebral fracture status.

The CHMP acknowledged that, while the overall risk for new incident vertebral fracture was higher in women than in men, these new analyses suggested that the risk was similar after accounting for prevalent vertebral fractures.

d) Correlation of changes in BMD and fracture risk

A recently published manuscript by Chen et al (2006) described a post-hoc correlation analysis of spine bone density and vertebral fracture data from study GHAC. This analysis demonstrated that in postmenopausal women treated with teriparatide, increases in lumbar spine BMD were significant determinants of vertebral fracture risk reduction, accounting for about 30-40% of the risk reduction.

Having considered that this relationship was as strong as or stronger than has been demonstrated for anti-resorptive treatments, the CHMP concluded that this last criterion was met.

2.2.7 Conclusion on efficacy data

Based on the assessment of the efficacy data, the CHMP concluded that the wording of the indication could be revised to osteoporosis "at increased risk of fracture", and to include the treatment of non-vertebral fractures in women. Nevertheless, as a non significant reduction in the incidence of hip fracture remained valid, the CHMP concluded that this information should not be deleted from section 4.1 of the SPC and should be mentioned also in section 5.1, as well as an updated table reflecting the data on non-vertebral fragility fractures. Furthermore, considering the overall evidence of clinical

efficacy in men, including BMD results as well as limited but favourable fracture data, the CHMP concluded that the therapeutic indication for Forsteo could be extended to the treatment of osteoporosis in men.
In addition, the CHMP recommended that section 5.1 of the SPC should include a description of the relevant risk factors of fracture in osteoporotic patients.

2.3 Safety data

Study B3D-MC- GHBJ (abbreviated GHBJ)

The MAH submitted the final report on serious adverse events for study GHBJ which was completed in October 2004. A total of 1,943 patients formerly treated in teriparatide studies were enrolled in GHBJ, including 1,263 women from study GHAC and 355 men from study GHAJ; 31% reported serious adverse events during a median of 4.5 years of follow-up after stopping teriparatide treatment.

There were no significant differences between groups (teriparatide 20 µg vs. teriparatide 40 µg vs. placebo) in any preferred terms in ≥1.0% of the study population in any system organ class. There was no increase in bone cancers, in cardiovascular disease, and in vertebral fractures. There were no instances of osteosarcoma. Although an overall statistical comparison between groups showed statistical difference in three serious adverse events (chronic lymphocytic leukemia, inguinal hernia, and asthma), there were no differences in the incidences of these adverse events in pair wise comparisons. Moreover, the three events of lymphocytic leukaemia were evaluated by two internal experts, independently, concluding that one patient was suspected to have had leukemia prior to entering the treatment study and a second patient was possibly misdiagnosed because of a history of lymphadenopathy. In addition, the adverse event "colon cancer" showed a trend towards significance and greater numbers in the teriparatide-treated groups than in placebo but when considering all related colorectal cancers the occurrence was the same in all groups.

Risk Management Plan

The first Risk Management Plan (RMP) for Forsteo was submitted.

As of 14 June 2006, teriparatide has been approved in 70 countries and marketed in approximately 57 countries. The cumulative patient exposure to teriparatide worldwide (since its first marketing through 26 May 2006) was estimated to be approximately 400,500 patients. Since launch (9 December 2002), the gender distribution for teriparatide prescriptions was 90% women and 10% men. This post marketing exposure was sufficiently large to permit the detection of rare and very rare events.

Based on this experience, the safety specification summary of the RMP was essentially focused on the potential risk for osteosarcoma since no new important risks have been identified for teriparatide. In June 2006, the MAH identified the first confirmed case of osteosarcoma (after 14 months of treatment). However, causality between Forsteo and the osteosarcoma could not be established, taking into account this was a single case, the patient had a complex medical history, and the background incidence (1 per 250,000 per year in the general population over 60 years of age).

Apart from standard pharmacovigilance activities, including targeted surveillance terms and early signal detection, a specific study was initiated to address the osteosarcoma issue.

Study GHBX (Teriparatide Post-Approval Osteosarcoma Surveillance Study) is an ongoing case-finding surveillance study designed to identify documented cases of osteosarcoma among men and women 40 years of age and older and determine which cases, if any, have a history of teriparatide treatment. This study is conducted both in the US and in Europe. The protocol has been appended to the RMP.

2.3.1 Discussion on safety data

The safety profile in both postmenopausal women and men had been evaluated as part of the original assessment at the time of the initial Marketing Authorisation for Forsteo and the data from the female and male population had already been reflected in the Product Information.

In the last PSUR covering the period from 27 May 2005 to 26 May 2006, one case of osteosarcoma and one case of bone tumor (undetermined nature), both with a fatal outcome have been reported. More recently, one case of extraskeletal osteosarcoma was reported at the end of September 2006. In addition, ten cases of Paget's disease of the bone have been reported: 3 of these were considered possibly related to teriparatide by the reporter.

During the long-term carcinogenicity studies, focal cellular proliferative lesions, including osteosarcomas, were observed in the bone of rats in all rhPTH (recombinant human parathyroid hormone) groups. Malignant bone neoplasms occurred in rats (males and females) in a dose responsive manner. Even though no such cases were observed during the phase III clinical studies, this was considered as a matter of concern, due to the fact that no such risk could be ruled out in human. Moreover, the lack of events in human was not considered as reassuring given the duration of the studies, the small number of patients who received teriparatide (n= 2032), and the fact that osteosarcoma was a rare disease.

Study GHBJ did not involve study drug and was designed as safety follow-up study, following the completion of several clinical studies. The interim study report had been submitted in the original application for the Marketing Authorisation and included data up to 18 months of follow-up.

The CHMP noted that the analysis of serious adverse events with thorough analysis of neoplasms provided reassuring conclusions. Nevertheless, when considering deaths, which occurred at a similar rate in the 3 treatment groups, the number of cases without specified cause seems high for a clinical trial (13/66, i.e. about 20%) raising a concern about the quality of the monitoring. Thus, the CHMP reinforced the conclusion endorsed with the assessment of the last PSUR on the need to obtain complete follow-up information and to fully assess spontaneous cases.

With regard to the RMP, the MAH submitted a revised one upon request from the CHMP (Request for Supplementary Information adopted at December 2006 CHMP plenary meeting).

The safety specification summary of the RMP was essentially focused on the potential risk for osteosarcoma. The report of a new long term toxicity study in ovariectomised female cynomolgus monkeys was submitted by the MAH with its responses to the Request for Supplementary Information. No concerns of toxicity arose in monkeys treated daily for a prolonged period (18 months), with a high dose (5 µg/kg) and with a 3-year follow-up period after treatment cessation. The CHMP noted that the effects observed were consistent with the pharmacological action of the drug. This study can be considered a test of the hypothesis that teriparatide would not produce the same type of effect in monkeys as it did in rats. Indeed, humans and monkeys are osteonal remodelling species, which is not the case of rats. In addition, longitudinal skeletal growth continues throughout rodent life, whereas in primates, growth plates close and longitudinal growth ceases. Thus, extreme gains in bone mass can be induced in rats by daily injections of teriparatide throughout their life. In contrast, comparable changes are not possible in osteonal remodelling species (i.e., humans and monkeys) given teriparatide for a relatively short (2 – 3%) portion of the normal life span.

A comprehensive assessment of the risk of osteosarcoma has been performed. Background incidence data have been provided by gender and age category for adults aged 60 years and older. The incidence rate was approximately 4 per 1,000,000 people in the general population >60 years of age. Thus, the 2 reports of osteosarcoma in the estimated 400,500 patients who have received teriparatide were not unexpected.

An assessment of the risk of Paget's disease of the bone has also been performed upon request of the CHMP. A single case report of Paget's disease was diagnosed in clinical trials (prevalence = 0.04%) and 24 spontaneous reports have been received through 30 November 2006 (prevalence = 0.005%). These rates were compared with the overall age- and sex-standardized prevalence rate of Paget's

disease (0.3%); however, this background rate was based on screening of abdominal x-rays while most of the cases in the spontaneous Adverse Event (AE) reports were symptomatic (when this information was available). The disease may have been pre-existing but an acceleration of the process due to the treatment cannot be ruled out. Furthermore, since Paget's disease of the bone is a contraindication, this may reveal insufficient screening before starting treatment with teriparatide. Therefore, the RMP should be updated to include Paget's disease.

Apart from standard pharmacovigilance activities, including targeted surveillance terms and early signal detection, the CHMP noted that a specific study was initiated to address the osteosarcoma issue.

The CHMP concluded that the current version of the RMP should be amended. The MAH committed to performing all Pharmacovigilance activities as per the current Pharmacovigilance Plan agreed by the CHMP, as well as to updating the current RMP to address a few outstanding issues.

2.3.2 Conclusion on safety data

Having considered the safety profile in both postmenopausal women and men which was evaluated as part of the original assessment at the time of the initial Marketing Authorisation for Forsteo, the assessment of recent PSURs and of study GHBJ, the CHMP concluded that no new safety issues have been identified which would change the positive benefit/risk balance of Forsteo.

With regard to the RMP the CHMP concluded that the current version of the RMP should be amended to address some outstanding issues.

2.4 Overall conclusion

The changes proposed by the MAH in this Type II variation were not supported by new data but were justified referring to the current CHMP Guideline on the "Evaluation of medicinal products in the treatment of primary osteoporosis" with some re-analysis of data submitted with the original application and of the follow-up study.

Based on the review and discussion of the efficacy data from the pivotal trials in postmenopausal women and in men, the CHMP concluded that the update of the therapeutic indication to osteoporosis in postmenopausal women at increased risk of fracture as well as the extension to the treatment of osteoporosis in men at increased risk of fracture were approvable. Furthermore, since the results showed a significant decrease in the risk of major fragility non-vertebral fractures, the CHMP concluded that a significant reduction in non-vertebral fractures has been demonstrated in women.

Furthermore, the CHMP concluded that this Type II variation was approvable provided that the MAH will amend the RMP to address some outstanding issues.

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

As requested by the CHMP, the MAH agreed to address some outstanding questions on the RMP and to submit an updated RMP, as well as to submit any variation application which would be necessary in the light of compliance with these commitments. The MAH has submitted the response to the outstanding questions and an updated RMP on 14 June 2007.

IV. CHANGES TO THE PRODUCT INFORMATION

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

SUMMARY OF PRODUCT CHARACTERISTICS

SECTION 4.1 "THERAPEUTIC INDICATIONS"

The MAH had initially proposed to revise the therapeutic indication from "established osteoporosis" to osteoporosis in postmenopausal women "at high risk of fracture" in line with the CHMP draft Guideline on the "Evaluation of medicinal products in the treatment of primary osteoporosis" dated 14 December 2005. Nevertheless, the CHMP noted that the final version of the Guideline has been released on 16 November 2006 and superseded the one the MAH was referring to. Namely, the wording for the therapeutic indication as expressed in the current version of the Guideline is "*women at increased risk of fracture*" which replaced the wording as stated in the previous version of the Guideline *"women at high risk of fracture"*. Thus, based on the assessment of the data presented by the MAH, the CHMP concluded that the wording of the indication could be revised according to the current Guideline and the extension of the indication to non-vertebral fractures could be endorsed. As a non significant reduction in the incidence of hip fracture remained valid, the CHMP concluded that this information should be maintained in section 4.1 of the SPC. The MAH agreed to update this section as recommended by the CHMP.

The therapeutic indication for Forsteo was revised to extend the treatment of osteoporosis in men

SECTION 5.1 "PHARMACODYNAMICS PROPERTIES"

As a non significant reduction in the incidence of hip fracture remained valid, the CHMP concluded that this information should also be mentioned in section 5.1 of the SPC, as well as an update of the existing table to include results of non-vertebral fragility fractures. In addition, the CHMP recommended that section 5.1 of the SPC should include a description of the relevant risk factors for fractures in osteoporotic patients. Furthermore, with regard to the men population, the CHMP requested the MAH to include the main baseline characteristics of the patients treated in the trial.

The MAH agreed to update this section as recommended by the CHMP.

PACKAGE LEAFLET

Section 1 "What Forsteo is and what it is used for" of the PL has been updated in accordance with the changes implemented in the SPC.

Finally, the complete set of Annexes has been updated in line with the EMEA/QRD template version 7.2, including the addition of the two new EU Member States (Bulgaria and Romania) in the list of local representatives in the PL.

V. CONCLUSION

On 24 May 2007 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 Labelling and Package Leaflet based on the observations and the appropriate conclusions.

The CHMP adopted on 24 May 2007 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation, as amended.

VI. REFERENCES

Kaufman J-M, Orwoll E, Goemaere S, San Martin J, Hossain A, Dalsky GP, Lindsay R, Mitlak BH. 2005. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. Osteoporos Int 16:510-516.

Chen P, Miller PD, Delmas PD, Misurski DA, Krege JH. 2006. Change in lumbar spine BMD and vertebral fracture risk reduction in teriparatide-treated postmenopausal women with osteoporosis. J Bone Miner Res 21:1785-1790.