SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Forsteo. For information on changes after approval please refer to module 8.

1. Introduction

Osteoporosis is a systemic disorder characterised by decreased bone mass and microarchitectural deterioration of bone tissue leading to bone fragility and increased susceptibility to fractures of the hip, spine and wrist. Osteoporosis affects an estimated 75 million people in Europe, United States and Japan combined. Osteoporotic fractures represent a major health problem. Within the past few years several antiresorptive therapies have been introduced. These include biphosphonates, hormone replacement therapy, selective oestrogen receptor modulators and calcitonin.

FORSTEO was developed to stimulate the bone formation. It contains teriparatide, a recombinant 1-34 N-terminal fragment of endogenous human parathyroid hormone (rhPTH(1-34)). 84-amino acid parathyroid hormone (PTH) stimulates the bone formation by direct effects on bone-forming cells (osteoblasts) increasing intestinal absorption of calcium and excretion of phosphate and increasing intestinal absorption of calcium via its effects on 1,25 dihydroxyvitamin D production.

It is indicated for the 'treatment of established osteoporosis in postmenopausal women. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated.' The recommended dose is 20 micrograms once daily administered subcutaneous.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

The finished product is formulated as a multi-dose small volume parenteral containing a 0.025 % w/v aqueous solution of teriparatide (20 µg/80 µl dose) in acetate buffer pH 4, preserved with 0.3 % w/v metacresol. It is presented in a 3 ml cartridge assembled into a disposable product-dedicated pen-injector that contains treatment for 28 days. The pen-injector is identical to that approved for Humalog-Pen™ in June 1997 (EU/1/97/0042/001), with the exception of injection volume and dose display. The product does not contain ingredients of animal or human origin.

Active substance

The active substance, teriparatide, is the 1-34 N-terminal fragment (4117.8 Da, as calculated) of endogenous human parathyroid hormone (rhPTH(1-34), produced in *E. coli* using recombinant DNA technology. The amino terminus is critical for G-protein linked stimulation of adenylate cyclase that catalyses the formation of second messengers such as cAMP that activates the desired biological effects by phosphorylation of critical intracellular proteins.

Development genetics and cell bank system

Teriparatide is produced in a transformed non-pathogenic *E. coli* K12 strain. Construction of the recombinant gene and production host/vector is described in detail.
Production of the Master Cell Bank (MCB) and Working Cell Bank (WCB) is adequately described. Characterisation testing of the cell banks was carried out in accordance with ICH Guideline Q5D. All test results demonstrate a pure and stable host/vector system through or beyond the end of production cycle.

Production and purification

The active substance is manufactured by Eli Lilly and Company, Indianapolis, USA.

Several process optimisations occurred during development, designated Process I, II, IIIa, IIIb and IIIc (commercial process), with no changes in manufacturing site. The consistency of the impurity profile of commercial lots (Process IIIc) compared to pre-clinical/clinical lots manufactured by earlier processes (Process I $\rightarrow$ IIIb) has been demonstrated by comparative RP-HPLC chromatograms. Moreover, the commercial process was used to manufacture batches used in late Phase III clinical trials.
The fermentation and isolation process have been adequately described in the application. The isolated materials are held at not more than -10°C until further processing. In-process controls assure appropriate cell growth, product synthesis and the absence of microbial or phage contamination. Specifications for raw materials and a description of cell culture media and equipment have been provided. No human or animal sourced raw materials are used in processing. The process has been validated and the data indicate that the manufacturing process consistently meets in-process specifications and control ranges. The rhPTH(1-34) purification process has been comprehensively described in the application and consists of several chromatographic separations, tangential flow filtrations, chemical reactions and a final freeze drying step. In-process controls assure appropriate purity. Specifications for raw materials have been provided. No human or animal sourced raw materials are used in processing. The process has been validated and the data indicate that the manufacturing process consistently meets in-process specifications and control ranges.
Additionally, validation addressed the removal of process and product related impurities and stability of process intermediates.

Characterisation of the active substance

rhPTH(1-34) is a single chain peptide containing 34 amino acids with a molecular mass of 4117.8 Da. The peptide is highly flexible, with transient helical regions. Full characterisation of the active drug substance has been performed on a primary in house reference standard (RS0265). Physico-chemical characteristics, primary, secondary, tertiary and quaternary structure of rhPTH(1-34) were evaluated and appropriately documented.

The biological potency is characterised by a cell-based assay which relies upon the ability of rhPTH (1-34) to stimulate cAMP production in a cell line expressing PTH receptors.

Analytical development
rhPTH(1-34) specific methods were developed at Eli Lilly and Company. Validation of all product specific analytical methods is described in detail, the reference standards used are fully documented.

Impurities
The data presented by the applicant demonstrate the capacity of the purification process to effectively remove product as well as process related impurities.

Batch Results
Batch data for all batches used in pre-clinical, toxicology and clinical trials and three recent validation lots manufactured according to the commercial process demonstrate compliance with the specifications.

Stability of the active ingredient

The company has provided updated drug substance stability data for three pilot-scale (primary stability lots) and three full-scale lots. The data provided indicates acceptable stability of the drug substance for the proposed shelf life.

Other ingredients

Excipients meet Ph. Eur. Monographs, where available (metacresol: USP). A certificate of analysis is provided for the 35% silicone emulsion. Water for injections is prepared by distillation and meets the requirements for Water for Injections in bulk, Ph. Eur. Standard microbial limits for raw materials used to prepare parenteral products are applied.

Product development and finished product

The manufacture of the finished product including batch release takes place at Lilly France S.A.S., Fegersheim, France
Briefly, the manufacturing process involves the following steps:

- Preparation of the excipient solution
- Preparation of a PTH intermediate solution. The pH is measured and adjusted if necessary. The intermediate solution is assayed by HPLC for rhPTH(1-34) content.
- Preparation of the final solution by diluting the PTH intermediate solution with additional excipient solution, based upon the in-process HPLC rhPTH(1-34) content assay. The pH is measured and may be adjusted.
- The solution is sterilized by filtration.
- The sterile solution is aseptically filled into sterile cartridges; then the cartridges are sealed, exterior washed and controlled for visual defects.
- The sorted cartridges are then finally assembled in the pen-injector.

Process validation

The manufacturing process steps and materials were validated using three validation lots. Commitment has been taken to provide stability data for any new reprocessing steps, besides the refiltration of the drug product, that are carried out.

Specification of the finished product

The release specifications limits were established based on experience with the manufacture of this product.

TSE and viral safety

The culture media are chemically defined and no Specified Risk Materials have been used to prepare or store Working Cell Banks (WCBs) or during routine manufacture of the finished product. Glycerol used in freezing menstruum of cell banks is of synthetic origin. Overall, the viral safety of the finished product has been adequately demonstrated.

Stability of the Product

Based on the stability data provided in the dossier, the proposed 24 months shelf-life at 2-8 °C (in a refrigerator) is accepted. The proposed in-use shelf-life is 28 days stored at 2 °C to 8 °C (in a refrigerator), in line with ICH requirements for in-use shelf life of aqueous preserved sterile injections (ICH/380/95).

Discussion on chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation are satisfactorily addressed. The development of the product went through several process changes; comparability of these processes has been validated by batch analysis and impurity and stability profiles for clinical batches manufactured by earlier processes compared to production-scale lots manufactured by the final process intended for marketing.
During the procedure, the characterisation of the strain, the cell bank system and its genetic stability has been further documented. Also, the batch definition has been further clarified, to ascertain that blending does not occur at any stage. The purity of the active substance and finished product relies on a single RP-HPLC assay. The company committed to validate and implement an additional method to support control of the purity of the active substance. Stability data support the 24 months shelf life of the product.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

The pharmacological effects of either teriparatide or a chemically synthesised PTH (1-34) were evaluated in four animal models: monkeys, rabbits, rats, and mice. Experimental models reproducing the characteristics and development of postmenopausal osteoporosis do not exist. Nevertheless, the pharmacodynamic studies performed in these preclinical species have provided essential information on the pharmacological properties of teriparatide. It should be noted, however, although monkeys and rabbits are remodelling species (similar to humans) their bone physiology does not mimic that seen in Man. Skeletal endpoints assessed in most of these studies included analyses of bone mass by quantitative computed tomography (QCT) or dual energy x-ray absorptiometry (DXA), assessment of bone architecture by histomorphometry and determination of bone quality by biomechanical testing. Bone mass data were collected for the proximal femur, mid-diaphysis, lumbar vertebra and proximals tibia.

The studies demonstrated that intermittent subcutaneous (*sc*) administration of teriparatide stimulated bone apposition and new bone formation in the rat, mouse, rabbit and monkey. In ovariectomised (OVX) monkeys, 1 and 5 µg/kg/day of teriparatide administered for 18 months improved bone mass, architecture and mechanical strength of trabecular and cortical bone without producing any adverse effects. In osteopenic OVX rat, the minimally efficacious dose was between 0.3 and 1µg/kg/day.
After treatment withdrawal in monkeys, beneficial changes in bone mass and biomechanical properties were sustained for about 6 months. Overall, teriparatide stimulated both modelling and remodelling of bone leading to improved bone quality.

- Pharmacodynamic drug interactions

Selective oestrogen receptor modulator (SERM) in association with teriparatide increased BMD in trabecular bone. Raloxifene did not modify teriparatide efficacy in osteopenic rats.

Estrogens prevented further increase of bone loss while PTH (1-34) alone or in combination with estrogens increased bone mass and strength above sham controls rats level.

Antiresorptive agents when associated with PTH (1-34) treatment neither blocked nor enhanced its skeletal effects on femoral neck, femur, vertebrae or tibia of intact males or osteopenic female rats.

1,25 dihydroxyvitamine D3 combined with PTH (1-34) did not significantly affect the skeletal efficacy of PTH (1-34).

Growth hormone (GH) alone increased trabecular and cortical bone mass, while a 30% to 50% greater bone mass was observed when (GH) was combined with PTH (1-34). This synergetic effect disappeared in aged female rats.

- General and safety pharmacology programme

Decreased blood pressure and increased heart rate were observed in conscious rat and dog models reflecting teriparatide-induced vasodilation. The no observed effect level (NOEL) for cardiovascular changes in the rat was 4.3 µg/kg of teriparatide. In female dog a decrease of arterial pressure and increase of left ventricular inotropic state and heart rate were observed after treatment with 6-µg/kg/day doses.

A quantitative assessment of ECG data after repeated-dose (toxicological studies) in monkey did not show any effects on cardiac conduction, re-polarisation (QTc) or production of cardiac arrhythmia.

In male adult mice, teriparatide at doses 100 µg/kg did not produce secondary pharmacology effect related to central nervous system and behavioural functions such as changes in body temperature,

ambulatory and non-ambulatory activity levels, central nervous system depression, and convulsive thresholds.

Pharmacokinetics

Pharmacokinetic studies after single dose and repeated doses were performed with teriparatide in Fischer 344 rats and Cynomolgus monkeys.
Clearance and volume of distribution, measured after 10 µg/kg of teriparatide intravenous administration were 67.5 ml/min/kg and 0.54 L/kg in rat and 6.18 ml/min/kg and 0.14 L/kg in monkey respectively. Minor sex differences were observed in rats with the higher parameters in male than in female (74.2 ml/min/kg and 62.1 ml/min/kg and 0.61 L/kg and 0.48 L/kg for clearance and a volume of distribution respectively).

The absolute bioavailability of the subcutaneous route for 10 µg/kg dose was 0.57 in rat (0.61 in male and 0.55 in female) and 0.36 in monkey (0.39 in male and 0.34 in female). The teriparatide bioavailability was lower in animals than in humans (57% in rat and 36% in monkey for 10 µg/kg dose against 95% in humans).

The kinetic profile of teriparatide was relatively simple with a short t_{max} and elimination half-life (both 15-40 min in the rat and monkey) after *sc* injection. AUC and C_{max} were dose-related. Minor differences in C_{max} and AUC between the rat toxicokinetic studies were observed, but no consistent pattern of increase or decrease and no consistent effect of gender could be noted. There were no changes in terminal elimination rates after repeated dosing; no serum accumulation or enzyme induction was detected following repeated administration. No notable gender differences were observed in both species, except in rats at high teriparatide doses (i.e. > 100 µg/kg for C_{max} and AUC values greater in female than in male).

Distribution, metabolism and excretion studies have not been studied, which was considered acceptable for a recombinant hormone. The Applicant has relied on literature information concerning metabolic clearance of PTH mainly by the liver and kidney.

No drug interaction study was performed. There was no induction of hepatic microsomal enzymes in male and female Cynomolgus monkeys given daily subcutaneous doses of teriparatide for 3 months.

Toxicology

The design of the experimental protocols for the toxicological studies were in agreement with that proposed with the route (sc.) and the frequency (daily) of study drug administration as well as duration for the clinical use. Animal species retained for toxicological studies (rat, rabbit and monkey) may be considered as relevant considering the bone responses observed in the pharmacological studies.

Acute toxicity in rat using subcutaneous (doses up to 1000 µg/kg) or intravenous (doses up to 300 µg/kg) administration of teriparatide did not reveal any functional toxic effects and the observable effects seemed to be related to the vasodilatation effects of the active substance.

Repeated dose toxicity studies were conducted in rat up to 6 months using doses up to 300 µg/kg/day and cynomolgus monkeys up to one year using doses up to 10 µg/kg/day subcutaneously.

Two chronic specific toxicity studies have been carried-out in Cynomolgus monkey, one evaluating special renal function (4 months of treatment with 3-months reversibility period) and one evaluating special histopathologic patterns (8 months of treatment or 12 months of treatment with 6-month reversibility period). Histological changes observed in renal function study are probably related to an exaggerated pharmacological effect induced by hypercalcaemia.

In summary, toxicity studies revealed a similar pattern of findings, which resulted from exaggerated pharmacological effects of high doses of teriparatide. The main target organs were the bone, liver spleen and kidney. Data suggest that the renal changes observed are secondary to increased calcium mobilisation. Since hypercalcaemia is not observed in patients at the intended clinical dose, the occurrence of kidney lesions seems unlikely. The changes are more evident in rat than in monkey. Absence of antigenic response is reported in the rodent and a weak antigenic potential is reported in the monkey.

Reproductive toxicity studies were generally uneventful indicating a low potential for effects on male and female fertility and embryo toxicity. However, there was some evidence for growth retardation and reduced motor activity in F_1 animals in the rat pre- and postnatal study. In addition, teriparatide was associated with a high level of embryolethality in the rabbit, probably associated with the foetal sensitivity of this species to hypercalcaemia. Given these uncertainties, it is considered prudent to avoid foetal exposure to teriparatide.

No mutagenic potential was detected in a standard battery of tests.

Carcinogenic potential has been evaluated in a 2-year rat bioassay. The main finding from this study was a pronounced treatment- and dose-related occurrence in malignant metastatic osteosarcoma in both males and females. Osteosarcoma was dependent upon dose and duration of treatment. The Applicant has provided a range of plausible explanations to account for these proliferative lesions, including chronic hormonal stimulation, virtual lifetime treatment duration spanning 25-30 bone turnover cycles, exposure during the rapid growth phase and exaggerated pharmacodynamic effects. Relative systemic exposure in the study ranged from *ca* 2 to 50 fold, although the expert's view that AUC-based exposure margins greatly underestimate the relative magnitude of the pharmacodynamic responses in rat and man is accepted.

A second rat oncogenicity study and a histopathological peer review of the results of this study were conducted. The data support the applicant's view, that the animal data indicate that teriparatide will likely not cause the formation of osteosarcoma in patients. It can be concluded:

- Teriparatide is not genotoxic.
- The NOEL relationship identified in the second carcinogenicity study is consistent with a threshold effect of dose and duration of treatment for non-genotoxic carcinogenesis.
- There is no evidence of carcinogenicity in the primate study (18 months dosing at 1 or 5µg/kg) or in the 12-month rat study (doses of 8 or 40µg/kg).
- The duration of treatment is the key factor in the development of bone neoplasms in the rat. Based on percentage of lifespan and bone turnover cycles, there are marked differences between the rat studies and intended human use.
- Increase in tumour incidence in mature female rats (6-12 months of age) is not seen at an 8x dose multiple (based on Cmax) and 3x dose multiple (based on AUC) for humans and following substantial increases in bone mass (↑BMC 87%) in treated rats.
- The dose and duration thresholds for development of bone neoplasms in rats are greater than the threshold for pharmacodynamic responses on rat bone.
- The rat is more sensitive than Man to the bone anabolic effects of PTH and AUC-based exposure margins greatly underestimate the relative magnitude of the pharmacodynamic response.
- The incidence of osteosarcoma in patients with chronic primary or secondary hyperparathyroidism is not increased despite increased osteoblast activity.
- There are no increases in bone malignancies in clinical trials with teriparatide or any other PTH hormone.

Furthermore, analysis of AUC values from all pharmacokinetic studies in rats estimate the AUC margin of exposure at 5µg/ml to be between 2 and 9 times that seen in patients given at 20µg/ml. These data indicate that an exposure multiple of 3 at the NOEL for osteosarcoma has now established for the formation of osteosarcomas.

4. Part IV: Clinical aspects

Eli Lilly has submitted a marketing authorisation application for FORSTEO (teriparatide) 250 µg/ml, solution for injection. Teriparatide (teriparatide) is identical to the 34 N-terminal amino acid sequence of endogenous human parathyroid hormone, and is manufactured using recombinant DNA technology. The indication approved for this product is 'treatment of established osteoporosis in postmenopausal women. A significant reduction in the incidence of vertebral, but not hip fractures has been

demonstrated'. The recommended dose of teriparatide is 20 µg administered once daily by subcutaneous injection in the thigh or abdomen.

Clinical pharmacology

Pharmacodynamics studies in relation with the claimed indication evaluate the teriparatide effects on bone and mineral metabolism in all patients receiving teriparatide and in healthy volunteers (men and postmenopausal women).

A safety pharmacological program includes specific studies of the teriparatide effects on calcium homeostasis in healthy postmenopausal women, on cardiac conduction, and on reporalisation in healthy volunteers. Additionally, a global analysis of ECG data obtained from 5 clinical studies in 118 subjects has been performed. Teriparatide pharmacodynamic properties were also evaluated in hypertensive women, in patients (men and women) with stable renal insufficiency, and in patients (men and women) with stable heart failure. Lastly, the effects of combination use of teriparatide with thiazid drug were assessed.

In December 1998 all ongoing clinical trials involving subcutaneous administration of teriparatide were discontinued by the applicant due to osteosarcoma finding in a 24-month rat ongogenicity study. A second rat oncogenicity study was performed and the findings support the applicants assertion that teriparatide will not cause the formation of osteosarcomas in patients (see 3.3. Toxicology).

The clinical programme intended to demonstrate efficacy of teriparatide in the proposed indication by the Company comprises:

- One dose-ranging study
- Three studies performed in woman: one placebo-controlled pivotal study and two comparative supportive studies (teriparatide versus alendronate, and teriparatide versus placebo in women receiving hormonal replacement therapy (HRT));
- One pivotal study performed in men.

Since the applicant decided due to osteosarcoma finding in a 24-month rat oncogenicity study (see 3.3. toxicology) to discontinue all clinical trials involving subcutaneous administration of teriparatide, an analysis of all the above-mentioned phase 3 studies has also been performed, including all safety data after discontinuation of studies and efficacy data as secondary objectives. This pooled data analyses, also included safety data, from three small supportive studies.

Pharmacodynamics

Mechanism of action

Dynamic studies:

Overall, a total of 6724 measurements from 1927 randomised patients who received either placebo or teriparatide were included in this analysis. Biomarkers from 623 patients were measured. The skeletal end-points of teriparatide were measured by bone mineral density (BMD) and by biochemical markers (urinary markers: Ca, N-telopeptide, free deoxypyridinoline and serum biological markers: calcium, bone specific phosphatase alcaline-BSAP, procollagen I carboxyterminal propeptide-PICP).
The analyses revealed a rapid BMD increase at lumbar site independent of the site of injection (abdominal wall or thigh). No gender differences were observed. The BMD response was not confounded by any of the following variables: body weight; body mass index, alcohol consumption, cigarette smoking and baseline serum concentrations of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. A rapid increase of bone formation markers (maximal increase of 45% in women and 23% in men for BSAP and of 41% for PICP) with a secondary increase of bone resorption markers (N-telopeptide-NTX and urinary deoxypyridinoline-DPD) was observed. Gender differences were observed in BSAP, NTX and DPD changes that were 25% to 50% lower in men than in women.
The effect of teriparatide on calcium homeostasis has been especially assessed in several clinical studies, especially in one open-label, partially randomised study performed in 23 healthy women aged from 48 to 75 years. A subcutaneous 40 µg teriparatide dose injection was administered for 14 days,

repeated dose combined with oral vitamin D supplementation. Overall results showed an increase in serum calcium at the therapeutic dose of 20 µg for a short period of time. When administered once daily, the serum total calcium increased transiently, beginning approximately 2 hours after dosing and reaching a maximum concentration between 4 and 6 hours. The serum calcium concentration began to decline approximately 6 hours after dosing and returned to baseline 16 to 24 hours after each dose. Teriparatide caused an increase in urine calcium excretion; however, a dose-response relationship between calcium intake and urine calcium excretion was not apparent during teriparatide administration. The results were similar with a 40 µg teriparatide dose.

The assessment of effects of an acute dose of teriparatide on blood pressure and heart rate (pulse rate) showed that teriparatide was safe and well tolerated in these subjects with mild or moderate heart failure. The drug was not associated with changed in supine or standing haemodynamic parameters, QT or other ECG abnormalities. Based on this study, the Applicant does not recommend adjustment for patients with heart failure.

In an open-label, non-randomised study performed in 14 women with hypertension, teriparatide 40µg was administered alone and in combination with atenolol or with a long-acting calcium channel antagonist. Results showed an increase in peak pulse rate and decrease in nadir blood pressure. Neither calcium channel antagonists nor atenolol potentiate the blood response associated with teriparatide.

In a single blind, randomised; two-period crossover study the effects of a 20 µg subcutaneous dose of teriparatide on cardiac conduction and re-polarisation was evaluated. Results showed that teriparatide was associated with a small but statistically significant decrease in average standing SBP compared to placebo, a slight increased in average pulse rate, relative to placebo, but approximately 3 and 2 bpm in the standing and supine positions, respectively and a small statistically significant decreases in RR and QT intervals but no changes in PR and QRS.

Additionally, a global analysis of ECG data obtained from 5 clinical studies in 118 subjects has been performed. Results did not show apparent adverse effects on ECG intervals with single subcutaneous doses of teriparatide in amounts of 20, 40 and 80 µg. No effect on the PR and QRS intervals was observed; however, dose-related shortenings in the RR, QT and QTc intervals were observed. A modest and not significant increase in heart rate was also observed.

In a single blind, randomised, two-arm crossover study performed in 24 subjects, 9 healthy subjects, 12 subjects with mild to moderate chronic renal insufficiency, and 5 subjects with severe chronic renal insufficiency, a 40-µg teriparatide dose was administered alone and with and without an infusion of furosemide (20 to 100 mg). An approximately decrease of 60 to 65% of the calcium excretion in 24 hours in subjects with renal insufficiency compared with healthy subjects was observed. The serum ionised calcium response to teriparatide was also significantly reduced in the renal insufficiency group suggesting that both the calcaemic and calciuric response was blunted.

Interaction with thiazides was assessed in, a single blind, partially randomised, placebo-controlled study, five-period crossover in 10 healthy men and 10 healthy women. The study evaluated the effect of hydrochlorothiazid on the serum and urine calcium in response to teriparatide 40 µg combined with 1000 mg/day calcium and 50 UI/day vitamin D. Results showed that the co-administration of HCTZ 25 mg with teriparatide did not result in a clinically significant pharmacodynamic drug interaction. However, the combined treatment was associated with a 15% reduction in the 24-hour urine calcium excretion compared with the response to teriparatide given alone.

Pharmacokinetics

The pharmacokinetics of teriparatide has been studied in healthy men and women, in patients with hypertension, renal insufficiency, heart failure, and in patients with osteoporosis. Pharmacokinetic data were obtained from approximately 200 healthy men and women who received at least one subcutaneous dose of teriparatide, ranging from 5 µg to 100 µg. For population pharmacokinetics, over 800 men and postmenopausal women with osteoporosis, who received teriparatide in the doses ranging 6 to 60 µg, were evaluated. Approximately, similar numbers of men and women were investigated and majority (90 %) of the subjects and patients were at least 50 years of age.

Following a subcutaneous injection, absorption of teriparatide was rapid with peak concentrations after 30 minutes and half-life was approximately 1 hour. Absolute bioavailability of teriparatide was 95 %. Pharmacokinetic results were consistent for studies carried out in 1995-1997. In the remaining 8 studies, performed after 1997, the teriparatide concentrations were significantly lower. The Applicant suggested that this could be due to the new batch of antibodies for the assay kit or to the change of the analytical site.

Systemic exposure (AUC) was approximately 20 % to 30 % lower in men than in women. In the population analyses, volume of distribution increased from 21 % to 30 % when teriparatide was injected into the thigh relative to the abdominal wall. This resulted in lower peak concentrations of teriparatide when injected into the thigh. There were no differences in pharmacokinetics with regard to age, smoking and alcohol consumption.

Serum total calcium concentration increased transiently reaching a maximum concentration between 4 and 6 hours, returning to baseline within 16 to 24 hours after injection. High concentrations of teriparatide were not associated with clinically relevant hypercalcaemia or hypercalcuria.

Studies in mild to moderate heart failure and in mild to moderate renal insufficiency suggested that the dose adjustment would not be required in these patients.

There was a marked increase in exposure to teriparatide in patients with severe renal impairment.

No pharmacokinetic data have been generated in patients with impaired hepatic function

There were no pharmacodynamic/pharmacokinetic interactions between teriparatide and furosemide or hydrochlorothiazide.

- Interaction studies:

No formal interaction studies were performed, however, the following combinations have been tested:

- With intravenous furosemide
- Co-administration of raloxifene
- With HRT in clinical phase 3 study

Results showed that furosemide did not seem to alter teriparatide pharmacokinetics, teriparatide did not seem to alter HRT pharmacological effects, however this study has been performed with 40-µg teriparatide.

Clinical efficacy

In December 1998, the applicant decided to discontinue all clinical trial involving subcutaneous administration of teriparatide, therefore none of the clinical studies in women and men succeeded in achieving their planed duration. This decision was based on the observation of osteosarcoma in a 24-month rat oncogenicity study. At this time a second rat oncogenicity study was ongoing. The findings from the second study supported the applicants assertion that teriparatide will not cause the formation of osteosarcoma in patients (see 3.3 Toxicology).
The following clinical studies were performed to demonstrate efficacy of teriparatide in the proposed indication by the company:

- One dose-ranging study in women only
- One placebo-controlled pivotal study
- Two comparative supportive studies in women: one study versus alendronate, the second study versus placebo in women receiving hormonal replacement therapy (HRT);
- One placebo-controlled pivotal study in men.

Additionally, a pooled analysis of all the above-mentioned phase 3 studies has been performed, including all safety data after discontinuation of studies and efficacy data as secondary objectives. The analyses also included safety data from three small supportive studies.

Dose-response studies and main clinical studies

Dose response study (ies)

Fifty-one ambulatory women, aged 42 years or older, postmenopausal for at least 2 years prior (with or without hysterectomy) with a vertebral T-score < 0 SD were enrolled in a double-blind, multicentre, randomised, placebo-controlled study. The primary objective of the study was to establish a range of safe and potentially effective doses of teriparatide in the treatment of postmenopausal osteoporosis. The primary endpoint for the efficacy evaluation was to characterise the dose dependent effect of teriparatide based on biochemical markers of bone formation (PCIP and serum BSAP) and resorption (urine NTX). Secondary endpoints included BMD and endogenous PTH (1-84) measurements. A safety analysis of data was performed including discontinuation percentage and incidence of adverse events by dose. The planned duration of the treatment phase and follow-up phase was both 6 weeks. Though not stated in the protocol, vitamin D was supplemented through the follow-up phase. The patients were randomised to receive either teriparatide 6 µg/day (n=4), teriparatide 15 µg/day (n=8), teriparatide 30 µg/day (n=9), teriparatide 40 µg/day (n=6), teriparatide 50 µg/day (n=8), teriparatide 60 µg/day (n=7) or placebo (n=9).

A response for the markers of bone formation serum PICP and serum bone-specific alkaline phosphatase (BSAP) between 15- and 40µg/day doses could be observed. Statistically significant differences from baseline were observed in both serum PICP and serum BSAP with doses as low as 15 µg/day, and 6 µg/day appeared to be a no-effect dose. BMD data indicated that out of 14 patients receiving teriparatide, 12 patients had an increase in lumbar spine BMD from baseline ranging from 0.52% (1 patient in the 15µg dose group) to 5.79% (1 patient in the 60µg dose group). There was an increase in the incidence of adverse events on doses above 40 µg/day.

The Applicant justifies the choice of the 20 µg/day dose as being an intermediate between the two efficacious doses of 15 µg/day and 30 µg/day. It is not possible to recommend a particular dose on the basis of the dose finding study. However, in women there is good evidence from Phase III studies that establishes the efficacy of both the 20µg and 40µg dose groups. The safety profile of the 20 µg dose is acceptable and therefore the risk/benefit of this dose is positive in women.

Main study(ies) (phase III = therapeutic confirmatory trials)

Pivotal study GHAC

1. Description of the study

A double blind, multicentre, randomised, placebo-controlled trial to evaluate the efficacy and safety of two doses of teriparatide 20 or 40 µg/day subcutaneous injection in postmenopausal women with established osteoporosis was performed. The patients were postmenopausal for at least 5 years. Each patient had a minimum of either one moderate or two mild non-traumatic vertebral fractures. In patients with fewer than two moderate fractures or in patients previously treated with biphosphonates or fluorides, the hip BMD or lumbar spine BMD measurement were required to be at least 1.0 SD below the average bone mass for young, healthy women (T score <–1.0).
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. As previously mentioned, due to safety concern in animal, the study was discontinued. Thus, data from 18 to 23 months (median time on study drugs, i.e. teriparatide exposure is 19.2 months) are only available.

The primary efficacy objective of the study was to demonstrate a reduction in the proportion of patients with new vertebral fractures following treatment with 20 and 40 µg/day of teriparatide plus calcium and vitamin D compared with calcium and vitamin D alone.

Secondary objectives include: efficacy on lumbar spine bone mineral density (BMD), on hip BMD, on total body and radial (forearm) BMD, on the rates of new nonvertebral fractures alone and of new nonvertebral and vertebral fractures combined, on height (via Harpenden stadiometer or other suitable stadiometer), on the iliac crest (histomorphometric effects), on biochemical markers of bone formation

and resorption (bone-specific alkaline phosphatase [BSAP], serum procollagen I C-terminal propeptide [PICP], urinary N-telopeptide [urinary NTX], and urinary free deoxypyridinoline); safety profile of chronic administration of teriparatide; pharmacokinetics data at selected sites; cost-effectiveness analysis; quality of life.

Primary endpoints/assays

The primary endpoint was occurrence of new vertebral fractures, determined by blinded, centralised evaluations of all spinal x-ray films. A patient was categorised as having a new vertebral fracture based on a reduction of at least 20% in anterior, mid or posterior height and for a minimum of one vertebra. The number of patients with new moderate or severe fracture or with multiple fractures was analysed separately. Worsening fractures were not included in the analysis.

Statistical analysis

The study was designed to enrol at least 1476 patients (492 in each treatment groups). It was planned that the total number of patients would be prospectively divided into two identical sub studies, sites were considered to be part of substudy 1 or 2 according to a size-based scheme.

Based on an anticipated fracture rate of approximately 60 new vertebral fractures per 1000 patient-years observation in the patients treated in the control group, and a 50% reduction in the patients treated with teriparatide, each substudy was to have over 75% to 80% power to detect a significant treatment effect using a two-tailed chi-square (χ^2) test of proportions at the 0.05 level, when comparing the pooled teriparatide groups with placebo after 3 years of treatment. Additionally, the two sub studies combined would have over 90% power to detect a significant treatment effect with either dose compared with placebo using these assumptions.

Primary analysis: intent-to-treat (ITT) analysis using data from all randomised patients with at least one baseline and one post baseline measurement (x-ray film). Based on the primary efficacy variable, analysis would compare the proportion of patients with new vertebral fractures in each teriparatide treatment group; and in the combined teriparatide treatment group with those in the control group using Pearson's chi-square (χ^2) test. Change and percent change of continuous variables (i.e. BMD and biochemical markers of bone metabolism), were assessed by an analysis of variance model (ANOVA). Missing values were imputed using Last Observation Carried Forward (LOCF).

RESULTS

4. Study populations/accountability of patients

A total of 1637 women, aged 30 – 85 years were randomised to receive teriparatide 20 µg (n=541), teriparatide 40 µg (n=552) or placebo (n=544), plus calcium and vitamin D. The three treatment groups were well balanced regarding demographic characteristics.
Regarding discontinuations of treatment, it must be pointed out that due to the Applicants decision to stop the study, the first reason for discontinuation was sponsor's decision. A total of 1295 (79.1%) patients discontinued due to this reason.

A total of 126 (7.7%) patients discontinued from the study because of an adverse event, 32 (5.9%) in the placebo group, 35 (6.5%) in the 20 g group, and 59 (10.7%) in the 40 µg group (p=0.005).

Seven (0.4%) patients discontinued from the study because of a lack of efficacy, progressive disease: 5 (0.9%) patients in the placebo group, no patients in the 20 µg group, and 2 (0.4%) patients in the 40 µg group.

Sixteen (1.0%) patients died during the study; none of the deaths were causally related to study drug or study conditions as assessed by the investigators. There was no significant difference in the number of death among the treatment groups.

5. Efficacy results

The efficacy analyses is on an 18 to 23 months (median 19 months) treatment-period with teriparatide 20 and 40 µg due to the premature stop of the study decided by the Applicant.
Overall, 1121 of the 1637 (68.5%) patients received placebo or teriparatide from 18 to 23 months.

Of the 1637 randomised patients, 1326 patients were evaluable with adequate baseline and endpoint x-ray films. A total of 105 of these 1326 patients experienced at least one new vertebral fracture.

Effect of teriparatide on risk of vertebral fractures

	Number (%) of patients with Fracture			Absolute Risk Reduction		Relative Risk Reduction	
	Placebo (N=448)	PTH20 (N=444)	PTH40 (N=434)	PTH20	PTH40	PTH20	PTH40
New fractures	64 (14.3)	22 (5.0)[a]	19 (4.4)[a]	9.3%	9.9%	65%	69%
Multiple new fractures	22 (4.9)	5 (1.1)[a]	3(0.7)[a]	3.8%	4.2%	77%	86%
New moderate or severe fractures	42 (9.4)	4(0.9)[a]	9 (2.1)[a]	8.5%	7.3%	90%	78%
New severe fractures	14 (3.1)	0 (0.0)[a]	3 (0.7)[b]	3.1%	2.4%	100%	77%

Abbreviations: PTH20 = teriparatide 20 µg/day; PTH40 = teriparatide 40 µg/day; N = number of patients with evaluated baseline and endpoint x-ray films.
[a] $p \leq 0.001$ compared with placebo
[b] $p=0.009$

Each teriparatide dose was statistically effective in reducing the frequency of vertebral fractures. No statistically difference was observed between the two dosage groups. The results demonstrated that 20 µg/day is statistically superior to placebo in reducing the frequency of new vertebral fractures.

Non-vertebral fractures occurred in 119 patients.

Summary of non-vertebral fragility and traumatic fractures

N Body site (n)	Placebo 544	PTH20 541	PTH40 552	Total 1637
Hip	4	2	3	9
Radius	13	7	10	30
Ankle	4	2	2	8
Humerus	5	4	3	12
Ribs	10	5	5	20
Foot	4	1	4	9
Pelvis	3	1	0	4
Other	16	14	9	39
Total [a] n (%)	53 (9.7%)	34 (6.3%)	32 (5.8%)	119 (7.3%)
Relative risk reduction compared with placebo	—	35%	40%	—
Relative risk (95% CI) compared with placebo	—	0.645 (0.426, 0.976)	0.595 (0.390, 0.908)	—
Pairwise comparison with placebo	—	p=0.036	p=0.015	—
Overall Treatment Comparison	—	—	—	p=0.024

Abbreviations: PTH20 = teriparatide 20 µg/day; PTH40 = teriparatide40 µg/day; N = number of patients randomly assigned to each treatment group; n = number of patients in each group with nonvertebral fractures; CI = confidence interval.

[a] The number of patients with nonvertebral fractures at each body site does not necessarily add up to the total number of patients with nonvertebral fractures. Of the 119 patients, 16 had two nonvertebral fractures, and in 11 of these 16 patients, both fractures occurred on the same date.

Treatment with teriparatide 20µg/day and 40µg/day resulted in a statistically significant reduction in the proportion of patients with non-vertebral fractures compared with placebo. Results on non-vertebral fractures were not conclusive for specific fracture sites, in particular hip fracture.

Treatment with teriparatide 20µg/day and 40µg/day for 18 to 23 months resulted in statistically significant dose-related increases in lumbar spine BMD, statistically significant increases in spine BMD were evident after 3 months of treatment, and at all subsequent visits.

Increases in femoral neck BMD for teriparatide 20µg/day and 40µg/day were observed at study endpoint).

There was a dose related decrease in BMD for the distal radius: in the placebo group there was a decrease of –1.28%, in the 20µg group –2.07%, and in the 40µg group –3.21%.

Summary of BMD

				P-Value (Treatment Comparison)	
Variable	Placebo (N=544)	PTH20 (N=541)	PTH40 (N=522)	Placebo vs PTH20	Placebo vs PTH40
Lumbar Spine (L-1 through L-4) (g/cm^2)					
n	504	498	497	-	-
Mean baseline ± SD	0.82 ± 0.17	0.82 ± 0.17	0.82 ± 0.17	NS	NS
Mean change ± SD	0.01 ± 0.04	0.07 ± 0.05	0.11 ± 0.07	<0.001	<0.001
Mean percent change ± SD	1.13 ± 5.47	9.70 ± 7.41	13.73 ± 9.69	<0.001	<0.001
Total Hip (g/cm^2)					
N	230	222	232	-	-
Mean baseline ± SD	0.71 ± 0.12	0.71 ± 0.12	0.71 ± 0.12	NS	NS
Mean change ± SD	0.01 ± 0.03	0.02 ± 0.03	0.02 ± 0.04	<0.001	<0.001
Mean percent change ± SD	-1.01 ± 4.25	2.58 ± 4.88	3.60 ± 5.42	<0.001	<0.001
Femoral Neck (g/cm^2)					
N	479	479	482	-	-
Mean baseline ± SD	0.64 ± 0.11	0.64 ± 0.11	0.064 ± 0.11	NS	NS
Mean change ± SD	-0.00 ±0.03	0.02 ± 0.04	0.03 ± 0.04	<0.001	<0.001
Mean percent change ± SD	0.69 ± 5.39	2.79 ± 5.72	5.06 ± 6.73	<0.001	<0.001

According to the protocol, investigators had the possibility to reduce permanently or not the doses of teriparatide in cases of AEs and/or increase in clinical laboratory serum calcium or urinary calcium values. No relation between the dose reduction (permanent or not) in each teriparatide groups and the reasoning for reduction was shown.

Regarding other secondary parameters such as BMC and height, results confirmed the activity of teriparatide on bone as well as measurement of biochemical markers of bone metabolism.

According to the protocol, investigators had the possibility to reduce permanently or not the doses of teriparatide in cases of AEs and/or increase in clinical laboratory serum calcium or urinary calcium values. No relation between the dose reduction (permanent or not) in each teriparatide groups and the reasoning for reduction was shown.

Due to the premature discontinuation of the study, long-term efficacy results are available for up to 24 months (median: 19 months) as opposed to 3 years required per CPMP guideline for Postmenopausal Osteoporosis in Women (CPMP/EWP/552/95 rev 1). This is reflected in the SmPC.

Two comparative studies have also been performed in postmenopausal women with osteoporosis:

- *Study in patients treated with Hormonal Replacement Therapy (HRT)*

A total of 247 postmenopausal women, aged 30-85, who were receiving HRT and had a hip or spine BMD measurements with T-score < - 1.0 SD, were randomized to receive teriparatide 40µg/day or placebo as subcutaneous injections.

Patients were stratified into two groups: 122 women received HRT for at least 1 year prior to the study and 125 women started HRT when enrolled to the study. All patients received calcium 1000mg/day and vitamin D 400-1200 IU/day.

The primary endpoints were BMD of the spine, and the secondary endpoints included BMD of hip, femoral neck and total body.

Patients completed up to 17 months (median 14 months) of the study at the time of study closure.

Mean percent change from baseline in total lumbar spine BMD (ITT-analyses)

	Previous use of HRT		No previous use of HRT	
	HRT	PTH40 / HRT	HRT	PTH 40 / HRT
n	58	58	58	56
Total lumbar spine BMD				
Mean baseline (g/cm^2)	0.91	0.92	0.89	0.88
Mean percent change from baseline	1.47 [ab]	11.19 [ab]	4.58 [ab]	16.93 [ab]

[a] within group comparisons versus no change ($p \leq 0.05$)
[b] between group comparison ($p \leq 0.05$)
Abbreviations: PTH40 / HRT = teriparatide 40 µg/day plus hormone replacement therapy; PTH40 = teriparatide 40 µg/day; N = number of patients; BMD = Bone Mineral Density.

Teriparatide 40 µg/day in combination with HRT significantly increased BMD (lumbar spine, the total hip and femoral neck) compared to that of the HRT only group. There were no differences between women treated with HRT or not treated with HRT before the study.

- *Study in patients treated with teriparatide or alendronate*

A double-blind, randomized study in postmenopausal women with osteoporosis to evaluate lumbar BMD. A total of 146 postmenopausal women, aged 30-85, who had a hip or lumbar BMD measurements with T score <-2.5 SD were randomized to teriparatide 40 µg/day or alendronate 10mg/day orally. All patients received additionally calcium 1000 mg/day and vitamin D 400-1200 IU/day. The primary endpoint was percent BMD change from baseline in total lumbar spine BMD, and the secondary endpoints included BMD of hip, radius and total body.
Patients completed up to 17 months (median 14 months) of the study at the time of study closure.

Analysis Mean percent change from baseline in total lumbar spine BMD (ITT analyses)

	ALN10	PTH40
n	66	62
Total lumbar spine BMD (L1 or L2 through L4)		
Mean baseline (g/cm^2)	0.80	0.80
Mean percent change from baseline	5.62 [ab]	12.21 [ab]

[a] within group comparisons versus no change ($p \leq 0.05$)
[b] between group comparison ($p \leq 0.05$)
Abbreviations: ALN10 = alendronate sodium 10mg/day; PTH40 = teriparatide 40 µg/day; N = number of patients; BMD = Bone Mineral Density.

There was a significantly increased BMD following teriparatide treatment when compared with the alendronate group at the lumbar spine, the total hip and femoral neck. The mean distal radius BMD in the teriparatide group was not statistically significantly different from the alendronate group.

The mean proximal radius BMD was lower in the teriparatide group then in the alendronate group.

Pivotal study in men

A double blind, randomized study, to demonstrate an increase in vertebral BMD in men with primary osteoporosis was performed. Male patients completed up to 14 months (median 11 months) of the study at the time of the study closure.
Four hundred thirty seven (437) men, aged 30-85, who had lumbar spine (L-1 to L-4 or L-2 to L-4) BMD or hip BMD measurement at least 2.0 standard deviations (SD) below the average bone mass for young, healthy men (T-score) were recruited.

Patients were randomized 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 primary endpoint for efficacy was vertebral BMD change from baseline at 3, 6 and 12 month. The secondary endpoints included change from baseline BMD in hip, total body, and radial (forearm).

Summary of bone mineral density for lumbar spine, total hip and femoral neck

Variable	Placebo (N=147)	PTH20 (N=151)	PTH40 (N=139)	Placebo vs PTH20	Placebo vs PTH40
Lumbar Spine (L-1 through L-4) (g/cm^2)					
N	143	141	129	—	—
Mean baseline ± SD	0.85 ± 0.14	0.89 ± 0.15	0.87 ± 0.14	0.005	NS
Mean change (g/cm^2) ± SD	0.01 ± 0.03	0.05 ± 0.04	0.07 ± 0.05	<0.001	<0.001
Mean percent change ± SD	0.54 ± 4.19	5.73 ± 4.46	8.75 ± 6.25	<0.001	<0.001
Total Hip (g/cm^2)					
N	137	135	125		
Mean baseline ± SD	0.83 ± 0.11	0.84 ± 0.10	0.83 ± 0.11	NS	NS
Mean change ± SD	0.00 ± 0.02	0.01 ± 0.02	0.02 ± 0.03	0.017	<0.001
Mean percent change ± SD	0.41 ± 2.77	1.14 ± 2.89	2.33 ± 4.51	0.040	<0.001
Femoral Neck (g/cm^2)					
N	137	135	125	—	—
Mean baseline ± SD	0.70 ± 0.11	0.71 ± 0.10	0.70 ± 0.11	NS	NS
Mean change ± SD	0.00 ± 0.03[a]	0.01 ± 0.03	0.02 ± 0.04	0.013	<0.001
Mean percent change ± SD	0.36 ± 3.95	1.44 ± 3.61	2.85 ± 6.07	0.038	<0.001

SD = standard deviation; n = maximum number of patients with a baseline and at least one post baseline measurement; NS = not significant.

Patients treated with teriparatide 20 µg/day and 40 µg/day had statistically significant increases in lumbar spine BMD of 5.7% and 8.8%, respectively, and significant increases in hip (femoral neck) BMD of 1.4% and 2.9%, respectively, at study endpoint. These increases were statistically significant compared with the placebo group. There was a dose response for BMD measurements, with greater increases in the 40 µg/day group.

Compared with the placebo group, the teriparatide treated patients had a statistically significant increase in total body BMD of approximately 0.5% in both the 20µg and 40µg groups compared with a decrease of 0.3% in the placebo group.

There were no statistically significant differences between the treatment groups in mean height changes.

There were significant increases in serum BSAP and serum PICP after the first month of treatment with teriparatide. All bone markers regressed to baseline at the end of the study.

Exploratory analysis performed across trials (pooled analyses and meta-analysis).

Not applicable

Supportive study(ies)

Since the efficacy studies were discontinued prematurely, the applicant initiated an observational follow-up study (non-blinded study) study to assess the effects of withdrawal of teriparatide treatment. All patients who received injectable study material during teriparatide studies were eligible to participate. The study was planned to be of two years duration. An interim report after 1 year has been submitted.

During the follow-up phase, all patients were offered calcium and vitamin D supplements. In addition, investigators could treat patients with any other drug treatments for osteoporosis. A patient was considered to be taking osteoporosis treatment if he or she reported any use of these drugs regardless duration of treatment. Moreover, patients may have taken multiple osteoporosis treatments.

A total of 1930 out of 2486 eligible patients were enrolled in the study from seven previous studies. 9 patients discontinued before the first visit (6 months following discontinuation of teriparatide) and

an additional 70 patients discontinued before the second visit (18 months following discontinuation of teriparatide).

After a median of 18 months following discontinuation of teriparatide, there was a 41% reduction (p=0.004) compared with placebo in the number of patients with a minimum of one new vertebral fracture.

Discussion on clinical efficacy

The Applicant submitted one small Phase 2 study. Data from this trial suggested that teriparatide in doses 15-40 µg/day could be safe and efficacious in the treatment of osteoporosis. However, the study did not allow for robust evaluation of a dose response.
In the pivotal Phase 3 studies, two doses of teriparatide were studied, 20 µg/day and 40 µg/day and over 500 women and 150 men received teriparatide 20 µg/day.

In the pivotal study postmenopausal women with osteoporosis were treated with teriparatide for up to 2 years. Teriparatide significantly decreased the incidence of vertebral and non-vertebral fractures (such as hip, radius, ankle, humerus) compared with placebo, and increased BMD in the total body, lumbar spine, and hip. Nevertheless, results on non-vertebral fractures were not conclusive for specific fracture sites, in particular hip fractures. The effect on vertebral fractures and BMD of the spine was more pronounced then the effect on nonvertebral BMD and fractures. The effect on BMD was observed after 3 months of treatment with teriparatide.

Over a median treatment period of 19 months, teriparatide 20 µg/day and 40 µg/day reduced the proportion of women who developed a new vertebral fracture by 65 % and 69 %, respectively, compared with placebo. The two doses of teriparatide did not differ significantly with respect to the reduction in risk of vertebral fracture. Treatment with teriparatide 20 µg/day or 40 µg/day resulted in statistically significant, dose-related increases in lumbar spine (BMD of approximately 10 % and 14 %, respectively, and hip BMD of approximately 3 % and 4 %, respectively, in postmenopausal women).

There was a decrease in BMD for distal radius (cortical bone), and this was statistically significant for the teriparatide 40 µg group.

In men with osteoporosis, treatment with teriparatide 20 µg/day or 40 µg/day for up to 14 months resulted in statistically significant increases in lumbar spine and hip BMD. No fracture data were available.

In the follow-up observational study, there was a reduction in the proportion of women and men with at least one new vertebral fracture during the 18 months after discontinuation of treatment with teriparatide. A significant reduction in non-vertebral fracture risk in postmenopausal women was maintained for 18 months.

Treatment with teriparatide 20 µg/day significantly reduced height loss in the subgroup of women who had suffered one or more new vertebral fractures.

Clinical safety

The application for marketing authorisation presents data from 24 clinical trials: 15 phase I studies, 1 phase II study (51 subjects) and 8 phase III (2573 subjects).

This assessment focuses on the results from all phase III clinical studies, especially the pivotal study. Among the phase III studies performed in postmenopausal women, approximately 84% of patients exposed were in the pivotal study. In addition, this is the only long-term study in postmenopausal women in which the 20-µg dose was administered.

It is to be noted that three studies were suspended prior to completing enrolment and the 4 other phase III clinical studies were terminated earlier due to sponsor decision. An observational study was performed to obtain additional information about the safety and the efficacy after discontinuation of teriparatide. A total of 1930 patients were enrolled in the observational study out of 2486 eligible from the 7 previous studies.

Patient exposure

Safety data derived from 23 clinical trials that enrolled over 2800 subjects. A total of 2032 subjects received teriparatide, including 800 subjects at 20 µg/day and 1107 subjects at 40 µg/day. 2486 subjects were randomised in the 6 phase 3 placebo controlled studies. Among these subjects, 1590 received teriparatide.
The four long-term phase III clinical trials included 2030 postmenopausal women and 437 men. 1137 patients were exposed to teriparatide for greater than one year (500 at 20 µg/day and 637 at 40 µg/day). Total exposure to teriparatide was more than 1967 patient-years.

Adverse events and serious adverse event/deaths

In the clinical pharmacology studies, orthostatic hypotension was observed in healthy subjects following administration of teriparatide at doses higher that 20 µg/day; teriparatide was associated with an increase in heart rate and a decrease in blood pressure in women with hypertension. Orthostatic hypotension did not occur in Phase 3 clinical trials. There were no significant changes in blood pressure or pulse rate, and no significant effects on other major cardiovascular adverse events were observed.
Out of 800 subjects, who received teriparatide at the proposed therapeutic dose of 20 µg/day, 500 patients received teriparatide 20 µg/day for one year. The most frequently reported AEs were leg cramps, nausea and headache.

Concerning all primary phase 3 studies (i.e. excluding studies GHAV and GHAU), a total of 418 patients (16.9 %) reported a minimum of one serious adverse effect (SAE). There was no significant difference in the number of patients reporting at least one SAE among treatment groups. No major concerns are raised by the SAE. However, there were some areas are of interest, such as dyspnea, cardiovascular adverse effects (palpitations and tachycardia, see SmPC), even though most patients have risk factors for cardiovascular disorders (age, history) and should be monitored.

Two cases of Paget's disease were diagnosed in patients receiving teriparatide, one of which being considered as related to treatment. No cases of osteosarcoma have been reported (follow-up less than 2 years), and the incidence of other malignancies in teriparatide patients was not different then in the placebo-treated patients.

A total of 20 patients (16 teriparatide group, 4 placebo group) died among the 2486 patients enrolled in the following phase III trials. No statistically significant treatment group difference was found.
The causes of death in the teriparatide groups were:

- Cardiovascular disorders (7 cases: cerebrovascular accident due to hypertension, myocardial infarction, possible myocardial infarction, cardiac failure, hypertensive crisis, cardiac arrest, possible cardiac arrhythmia),
- Pneumonia 4 cases (in 2 cases, the pneumonia was related to pre-existing lung cancer and in one case, the patient had a history of pulmonary emphysema since 1991),
- Carcinomas 3 cases (larynx neoplasm, lung cancer, bladder neoplasm),
- Pancreatitis 1 patient concomitantly treated with fenofibrate after 427 days of teriparatide therapy, the patient had slightly elevated calcium levels,
- Cardiopulmonary arrest as a direct consequence of suicide.

No cases of death were considered related to teriparatide by the investigators.

The four fatal cases in the placebo group involved cardiovascular system (heart attack, cardiogenic shock, myocardial infarction) and respiratory system (aspiration causing respiratory failure) respectively in 3 cases and one case.

In most of the cases of cardiovascular disorders, the patients had history of cardiovascular disease (hypertension, arteriosclerosis, myocardial infarction, coronary artery disease) and 5/7 received antihypertensive drugs.

In one case, the patient died of possible cardiac arrhythmia 3 months after teriparatide discontinuation because of a lack of efficacy. In 2 cases, the patients were found dead at home and the cause of death is only supposed (myocardial infarction, cardiac arrest). These 2 deaths appeared 450 and 313 days after therapy initiation and the data are too scarce to draw any conclusion.

The narratives do not allow suggesting a link between teriparatide and the fatal cases of carcinoma.

One fatal case of pancreatitis has been reported in a patient who experienced slightly elevated blood calcium levels. Hypercalcaemia (and hyperparathyroidism) is a known risk factor for pancreatitis. Even though this patient was also treated with fenofibrate, known to cause cholelithiasis, this case should be kept in mind. It is to be noted that another case of pancreatitis was reported in a patient, but no information is provided.

Discontinuation due to adverse events

Discontinuation due to adverse event was the second most common reason for discontinuation in the phase 3 studies.

A total of 215 patients (8.7 %) discontinued due to an adverse event.

Concerning the pivotal study (GHAC), 5.9%, 6.5% and 10.7% of the randomised patients discontinued from the studies earlier due to adverse event or death, in the placebo groups, in the teriparatide 20 µg/day and in the teriparatide 40 µg/day, respectively. In this study, nausea resulted in discontinuation by significantly more patients treated with teriparatide 40 µg/day than in patients treated with placebo. There were no events that caused discontinuation significantly more often in the teriparatide 20 µg/day group compared with placebo.

Concerning the observational study, discontinuations due to AEs were amnesia (1pt), asthma (1 pt), GI carcinoma (2 pts), breast carcinoma (1 pt).

Laboratory findings

There were small but statistically significant transient increases in 4- to 6-hour post dose serum calcium levels and in urinary calcium excretion. Serum calcium in all instances returned to baseline by 16 hours, and the 24-hour post dose serum calcium was not increased. There was no increase in urolithiasis or other clinical adverse effects related to increased urine calcium.

Teriparatide significantly increased serum uric acid with no other relevant clinical adverse outcomes.

In the 20 µg and 40 µg groups, there was a statistically significant increase in median serum uric acid while patients were on study drug, which decreased at endpoint, when most patients had been withdrawn from treatment for approximately 5 weeks. Analyses of urolithiasis and related events during and after treatment with teriparatide do not suggest that treatment for up to 2 years significantly increased the risk of these events.

In total, approximately 4% of patients developed anti-teriparatide antibodies. No effects were seen on BMD response or serum calcium concentrations. The clinical significance of this finding is not known.

Discussion on clinical safety

The safety data is based on the overall data provided from the clinical development program, which comprised 24 clinical studies including 2573 patients. A total of 2032 subjects received teriparatide, including 800 subjects at 20 µg daily.

FORSTEO treatment was well tolerated when administered for up to 2 years in postmenopausal women with osteoporosis and up to 14 months in men.

The major safety concern (pre-clinical) was raised due to the findings from evaluation of the carcinogenicity potential of FORSTEO in the 2-year rat bioassay. A pronounced treatment- and dose-related occurrence in malignant metastatic osteosarcoma in both males and females rats was observed. When this data became apparent the applicant discontinued all ongoing trial involving subcutaneous administration of FORSTEO. No cases of osteosarcoma have been reported in clinical studies. A second rat oncogenicity study as well as the review of clinical data leads to the conclusion that FORSTEO will be safe in this respect in clinical use. The applicant has established a comprehensive post-approval osteosarcoma surveillance program.

5. Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
"Viral Safety and Batch to batch consistency has been documented and the relevant test will be performed according to the agreed specifications".

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided adequate evidence that intermittent subcutaneous (*sc*) administration of teriparatide stimulated bone apposition and new bone formation in the rat, mouse, rabbit and monkey. After treatment withdrawal, beneficial changes in bone mass and biomechanical properties were sustained for about 6 months. Overall, teriparatide stimulated both modelling and remodelling of bone leading to improved bone quality. The general pharmacology studies showed that teriparatide posses vasopressor activity. Notwithstanding this, there were no ECG changes in animals indicative of adverse effects on conduction or repolarisation and no cardiac arrhythmias.
From the pharmacokinetic point of view, Fischer 344 rats and Cynomolgus monkeys were the most relevant species for preclinical efficacy and safety studies. The kinetic profile of teriparatide was relatively simple with a short T_{max} and elimination half-life after sc injection. AUC and C_{max} were dose-related, and no serum accumulation or enzyme induction was detected following repeated administration. The applicant has relied on literature information concerning metabolic clearance of PTH mainly by the liver and kidney.

Overall, the toxicology programme revealed a similar pattern of findings, which resulted from exaggerated pharmacological effects of high doses of teriparatide. The main target organs were the bone, liver spleen and kidney. Data suggest that the renal changes observed are secondary to increased calcium mobilisation. Since hypercalcaemia is not observed in patients at the intended clinical dose, the occurrence of kidney lesions seems unlikely. A weak antigenic potential is reported in the monkey.

Teriparatide produced no teratogenic effects in rats and mice. In pregnant rabbits, embryo/foetal mortality that was attributable to increases in blood ionised calcium occurred at doses >3 μg/kg and may occult an eventual teratogenic effect. Teriparatide had no effects on fertility of male or female rats at doses up to 300 μg/kg. This information has been included in the SPC.

Due to the results of a rat carcinogenicity study major objections were raised. In the initial carcinogenicity study the subcutaneous administration of 5, 30 or 75 μg/kg/day of teriparatide caused a highly significant increase in the incidence of osteosarcoma at all dose levels when administered for 24 months starting at age 6-7 week. However, in a second carcinogenicity study, there was no neoplastic bone lesions at a dose of 5 μg/kg/day, provided treatment did not commence until the rats were 6 months old. As such, the No-Observed-Adverse-Effect Level (NOAEL) was 5 μg/kg/day in full-grown rats. The applicant has now provided convincing toxico- and pharmacokinetic evidence that the exposure multiple – or safety margin – is 3, based on AUC measurements.

Efficacy

The intended indication is the treatment of established osteoporosis in postmenopausal women and men. The recommended dose is 20 μg/day administered by subcutaneous injection into the thigh or abdomen.

In the two pivotal studies in women and in men over 541 women and 151 men with osteoporosis received teriparatide 20 μg/day. Both trials were stopped early and the median duration of treatment in women was 19 months and for treatment in men was 11 months.

In women treatment with teriparatide 20 μg/day for 18 to 23 months resulted in a statistically significant reduction of the frequency of new vertebral fractures compared with placebo. The treatment also resulted in a statistically significant reduction of non-vertebral fractures compared with placebo, however results were not conclusive for specific fracture sites, in particular hip fracture. Regarding the secondary endpoints, treatment with teriparatide 20μg/day resulted in statistically significant dose-related increases in lumbar spine BMD.

The applicant was seeking an indication for the treatment of established osteoporosis in postmenopausal women and in men. An oral explanation was held on 20 November 2002. The company reviewed the outcome of the clinical program carried out in man and concluded that FORSTEO was an appropriate treatment for osteoporosis in men. The company stated that the ability of FORSTEO to reduce fractures had been established in women and a positive relationship between BMD and fracture reduction had been shown in women. This data had then been extrapolated to the studies in men, with bone mineral density used as a primary end point. The company stated, that if the indication in men is granted, a naturalistic outcomes study would be conducted in men.

Following this discussion, a number of members stated that anti fracture efficacy in men had not been shown, the data was based on a smaller overall database (compared with the antisorptive -alendronate) and there were difficulties in accepting extrapolation. The fact that the clinical programme had been shortened due to concerns of the outcomes of the pre-clinical studies was also highlighted. An orientation was sought among CPMP Members on whether the indication should include treatment of osteoporosis in men and a negative trend was observed (with the majority of members considering that such an indication could not be granted).

Safety

The safety data is based on the overall data provided from the clinical development program, which comprised 2573 patients included in 24 clinical studies. In general, teriparatide treatment was well tolerated when administered for up to 2 years in postmenopausal women with osteoporosis and up to 14 months in men. The most frequently reported AEs were leg cramps, nausea and headache. Two cases of Paget's disease were diagnosed in patients receiving teriparatide, one of which being considered as related to treatment.

No cases of osteosarcoma have been reported in clinical studies. However, it cannot be assessed that the duration of the observational study was sufficient to detect potential cases of osteosarcoma, and the possibility of a longer latency period cannot be excluded. The applicant commits to perform a Post-Approval Surveillance Study to identify newly diagnosed cases of osteosarcoma and to determine incident cases, if any, with a history of FORSTEO treatment.

Benefit/risk assessment

In women treatment with FORSTEO 20 μg/day for 18 to 23 months resulted in a statistically significant reduction of the frequency of new vertebral fractures compared with placebo. The treatment also resulted in a statistically significant reduction of non-vertebral fractures compared with placebo, however results were not conclusive for specific fracture sites, in particular hip fracture. Regarding the secondary endpoints, treatment with FORSTEO 20μg/day resulted in statistically significant dose-related increases in lumbar spine BMD

FORSTEO treatment was well tolerated when administered for up to 2 years in postmenopausal women with osteoporosis and up to 14 months in men.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus decision that the benefit/risk profile of FORSTEO was favourable in the treatment of established osteoporosis in postmenopausal women and therefore recommended the granting of the marketing authorisation.