Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Teriparatide

Proprietary Product Name: Forteo

Sponsor: Eli Lilly Australia Pty Ltd

December 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Major variation — Extension of treatment duration
Decision:	Withdrawn
Date of Decision:	7 September 2010
Active ingredient(s):	Teriparatide
Product Name(s):	Forteo
Sponsor's Name and Address:	Eli Lilly Australia Pty Ltd 112 Wharf Rd, West Ryde, NSW 2114
Dose form(s):	Solution for injection;
Strength(s):	250 µg/mL
Container(s):	2.4 mL cartridge
Route(s) of administration:	Subcutaneous (SC) injection
Dosage:	20 µg/day

Product Background

Teriparatide is recombinant human parathyroid hormone (rhPTH), identical in sequence to the active fragment, the 34 N-terminal amino acids (1-34), of the natural endogenous 84 amino acid human parathyroid hormone (PTH). The pharmacological mechanism of action in treatment of osteoporosis is considered to be via preferential stimulation of osteoblastic activity over osteoclastic activity. It is currently registered for the treatment of osteoporosis in postmenopausal women and the treatment of primary osteoporosis in men when other agents are considered unsuitable and when there is a high risk of fractures. Teriparatide is also indicated for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at high risk of fracture. Eli Lilly Australia Pty Ltd has applied for an extension of treatment duration for teriparatide (Forteo) to 24 months. Currently, the maximum lifetime exposure to teriparatide for an individual patient is limited to 18 months.

There have been 3 previous Applications relating to teriparatide. All were considered by the Australian Drug Evaluation Committee (ADEC, now succeeded by the Advisory Committee for Prescription Medicines (ACPM)) as per follows:

(1) ADEC Minutes 6-7 February 2003, 226th Meeting

The ADEC recommended registration of the new chemical entity teriparatide for the treatment of postmenopausal osteoporosis and the treatment of primary osteoporosis in men when other agents are considered unsuitable and when there is a high risk of fractures. In addition, the Committee recommended that the maximal lifetime duration of treatment should be limited to 18 months and that the Australian Product Information should include the information contained within the US boxed warning regarding the risk of osteosarcoma.

(2) ADEC Minutes 3-4 April 2003, 227th Meeting

The ADEC reviewed a submission from Eli Lilly Australia Pty. Ltd. requesting the Committee reconsider the condition of registration requiring a patient registry. The ADEC resolution was:

'In the matter relating to reconsideration of point 2 (i) regarding the ADEC's request for a patient registry, the Committee concluded that, provided the sponsor agrees to carry out all the actions detailed in its letter of 7 March 2003, then a patient registry would not be warranted. '

(3) ADEC Minutes 2-3 April 2009, 263rd Meeting

The ADEC considered a submission from Eli Lilly Australia Pty Limited to register Forteo solution for injection, containing the new chemical entity, teriparatide 250 µg [rbe] for an extension of indications. The proposed indication was 'For the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at high risk for fracture'.

This dossier included a single double blind, randomised, multicentre study, B3D-US-GHBZ, comparing the effects of teriparatide subcutaneously versus oral alendronate, both at the recommended doses, in 214 patients with corticosteroid associated osteoporosis randomised to each group. The ADEC agreed that efficacy and safety were demonstrated in this new indication, and that current limitations in place regarding the use of this product should stand, particularly since greater numbers of subjects are likely to receive teriparatide. The ADEC resolution was:

1. There should be no objection to approval of the submission from Eli Lilly Australia Pty Ltd to register Forteo solution for injection containing teriparatide 250 µg/mL for the new indication:

   For the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at high risk for fracture.

Regulatory Status

The application for Forteo extended treatment duration has been submitted in the following countries (see Table 1 below) and granted approval in the EU and Canada.

Table 1.

Country	Submission Date	Status (pending; approved; deferred; withdrawn; rejected)
EU	15 October 2008	EMA centralized approval 25 February 2009
Canada	12 March 2009	Approved 09 February 2010
New Zealand	24 July 2009	Approved 16 September 2010

EU=European Union, EMA=European Medicines Agency.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

No new quality data were submitted with the current Australian submission.

III. Nonclinical Findings

Introduction

No new nonclinical data were submitted with the current Australian submission.

Currently, the maximum lifetime exposure to teriparatide for an individual patient is 18 months, and the sponsor is applying to extend this to 24 months. The reason that the lifetime

exposure is limited is to minimise the potential risk of osteosarcoma, as seen in treated rats (discussed under *Toxicology* below).

Pharmacology

No new data were submitted with the current Australian submission.

Pharmacokinetics

No new data were submitted with the current Australian submission.

Toxicology

The carcinogenicity of teriparatide has been examined in two rat carcinogenicity studies which were submitted in the original application for the drug's registration. Teriparatide caused a dose-dependent increase in the incidences of both benign and malignant bone tumours (osteoma, osteoblastoma and osteosarcoma). A no observed effect level (NOEL) was not established for a treatment duration in the rat of 24 months; the lowest dose tested (5 µg/kg/day SC) was associated with a serum area under the concentration versus time curve (AUC) value of only 1.8 times that anticipated in patients. Treatment with teriparatide did not increase the incidence of neoplasms in non-osseous tissues. A second rat study was undertaken to determine the effect of treatment duration and the age of the animals on the development bone tumours. There was no difference between mature and immature rats in susceptibility to teriparatide-induced bone tumours, but there was a dependence on the duration of exposure. Thus, female rats that received 30 mg/kg/day teriparatide SC for 6 months from the age of 6 months had close to a background level of osteosarcomas at 26 months, whereas when the treatment period was 20 months, the incidence of osteosarcomas was significantly increased.

Animals maintain bones in two different ways. Mice and rats are bone-modelling species, in which bone resorption and formation occur at different sites. In contrast, rabbits, monkeys and humans are bone-remodelling species, in which bone undergoes a continuous, coordinated process of bone resorption followed by new bone formation at the same site. Because of this difference in the bone formation process between rats and humans, the relevance to humans of the positive findings in the carcinogenicity studies may be questioned. In order to address this, the sponsor has conducted a long-term monkey study. This study is not of sufficient size or duration to be described as a true carcinogenicity study, as such studies need to have large group sizes (50/group) and be conducted for the lifespan of the animals. However, the study does give some information on the tumourigenicity of teriparatide in monkeys.

The final report for this monkey study was submitted as post-registration data, and was evaluated by the TGA in a report dated 1st February 2007. The results of this study have now been published in the literature[1]. Ovariectomised female cynomolgus monkeys (30/group, 2 groups) received vehicle or teriparatide (5 µg/kg) SC daily for 18 months. The dose selection was based on it being the maximum dose that did not result in hypercalcaemia in a previous monkey study. Six animals/group were sacrificed at the end of the treatment phase; the remaining animals were assigned for observation for a further 3 years before necropsy. Eighteen treated monkeys survived until scheduled termination at 4.5 years.

Plain film radiographs were obtained of the entire monkey (lateral and dorsal-ventral views) pre-treatment, at 18 months, and at the end of the 3 year observation period. These radiographs were examined by the staff veterinarian, a consulting radiologist and the pathologist conducting the necropsies. Histopathology was performed on the tibia, femur,

[1] Vahle *et al*., 2008; *J. Bone Min*. Research 23: 2033–2039.

humerus, L-2 and L-3 lumbar vertebra, rib, sternum, iliac crest and any other significant bone lesions. No bone neoplasms were found. In addition, histopathological evaluation did not detect any microscopic foci of cellular atypia, focal hyperplasia or other preneoplastic lesions.

Given that the current application is to extend treatment duration from 18 months to 24 months, it would have been preferable for the monkeys to have been treated for 24 months. However, when taking into account bone turnover rates (number of complete resorption and formation cycles/year), a treatment period of 18 months in cynomolgus monkeys is comparable to about 4 years in humans. In addition, if this period of time is considered as percentage of lifetime, 18 months in cynomolgus monkeys is about 5% of lifespan (31 years[2]), whereas 24 months is about 2.7% of a human lifespan (75 years). Therefore, in terms of both bone turnover and percentage of lifespan, the monkeys were exposed to teriparatide for about twice as long as humans will be when exposed for 24 months. Exposure to teriparatide in the monkeys was 5- to 6-fold the levels of teriparatide observed clinically, which is an adequate exposure margin. The total duration of the study (4.5 years) is considered adequate given that hyperplastic and pre-neoplastic lesions were considered in addition to tumours. In the 2-year rat study by comparison, osteosarcomas were observed in ~6% of animals at an animal: human exposure ratio of 1.8 and ~28% at an exposure ratio of ~14. This study is therefore considered to be designed sufficiently to give useful—but not definitive—information about the potential of teriparatide to cause osteosarcoma or other bone neoplasms in a bone remodelling species. It indicates reduced susceptibility in such species compared with bone modelling species such as the rat.

The TGA clinical evaluator (5th December 2009) has stated that the post-marketing information relating to reports of osteosarcoma provides some reassurance, but that the animal studies are of central importance. In the context of existing reassuring postmarketing information, the nonclinical evaluator considers that the results of the monkey studies are sufficient to support an extension of treatment duration to 24 months on safety grounds, so long as the benefit increases with a longer duration of treatment. Osteosarcoma formation in rats was clearly dependent on treatment duration, and without fully understanding the mechanism of tumour formation, an extension in clinical treatment duration still increases the risk of osteosarcoma formation.

The Risk Management Plan (RMP) summarises the nonclinical data in a number of places. However, it is noted that the description of the second rat carcinogenicity study omits the positive results obtained for osteosarcomas. In addition, the sponsor has used phrases such as: "the clinical relevance of these findings is not known and most likely minor" and "the observations in the rat study are poorly predictive of human risk for osteosarcoma". As discussed above, the clinical relevance of the results of the rat studies is still unknown, and will remain unknown until sufficient clinical data have been collected for a sufficient period of time post-treatment. It is important and appropriate that osteosarcoma remains classified as an important potential risk to patients treated with Forteo. All animal studies have limitations in the assessment of risk to humans, and ultimately it will be post-marketing data that establishes the extent of the risk of osteosarcomas to humans treated with teriparatide.

Nonclinical Summary and Conclusions

Currently, the maximum lifetime exposure to teriparatide for an individual patient is limited to 18 months to minimise the potential risk of osteosarcoma, as seen in treated rats in

[2] Cawthon Lang KA. 2006 (January 6). Primate Factsheets: Long-tailed macaque (Macaca fascicularis) Taxonomy, Morphology & Ecology . <http://pin.primate.wisc.edu/factsheets/entry/long-tailed_macaque>. Accessed 2010 January 14.

long-term carcinogenicity studies. The frequency of osteosarcoma in rats was dependent on treatment duration.

No new nonclinical data were submitted in the current application.

In a previously submitted study in monkeys, animals received teriparatide SC for 18 months (equivalent to 4 years in humans if bone turnover rates or percentage lifespan are considered) at an exposure ratio of between 5 and 6, and were observed for a subsequent 3 year period. In this study, which was specifically designed to find bone tumours, no bone neoplasms or preneoplastic lesions were observed.

In the context of existing reassuring post-marketing information, the results of the monkey study are considered sufficient to support an extension of treatment duration to 24 months on safety grounds, provided that clinical benefit, like risk, also increases with a longer duration of treatment.

The sponsor's Risk Management Plan is highly dismissive of the importance of the positive findings of the rat carcinogenicity studies. The relevance of these rodent findings remains unclear, and until sufficient post-marketing data exist, osteosarcoma should remain classified as an important potential risk for humans.

IV. Clinical Findings

Introduction

A single new study, B3D-EW-GHCA, was submitted in support of the application. Tabulated individual patient data were included. The protocol was not included; in particular, no statistical analysis plan was included.

Apart from this new study, the application also relied specifically on 2 studies submitted to TGA previously: B3D-US-GHBZ (Clinical Evaluation Report (CER) dated December 2008) and B3D-MC-GHAC (CER dated February 2002). The clinical evaluator found it confusing that Study B3D-EW-GHCA was also referred to as Study B3D-US-GHCA. In different documents, Study B3D-MC-GHAC was referred to as Study B3D-US-GHAC.

Pharmacokinetics

No new data submitted.

Drug Interactions

No new data submitted.

Pharmacodynamics

No new data submitted.

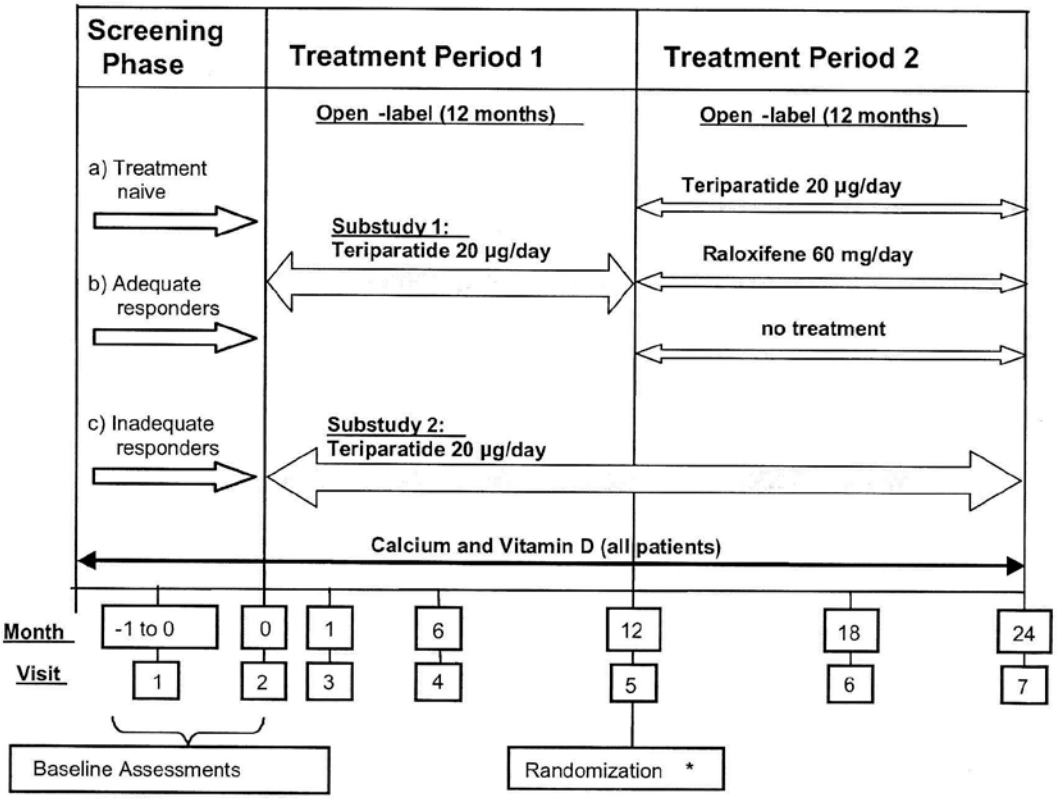
Efficacy

Study B3D-EW-GHCA

Description of study

This was a phase 3/4, multicentre, open trial in postmenopausal women with severe osteoporosis, comprising 2 substudies. The structure of the trial is shown in Figure 1.

Figure 1. Structure of Study B3D-EW-GHCA



* Randomisation applies to Substudy 1 only. Note: After enrolment for Substudy 2 was closed, inadequate responders were also allowed to enter Substudy 1.

Primary objectives

- To compare the effect of 24 months continuous treatment with 20 µg of teriparatide per day in combination with calcium and Vitamin D, with a treatment regimen of teriparatide, calcium and Vitamin D for 12 months followed by 12 months of calcium and Vitamin D alone.
- To compare the effect of a sequential treatment regimen of teriparatide, calcium and Vitamin D for 12 months followed by 12 months of raloxifene 60 mg/day, calcium and Vitamin D, with a treatment regimen of teriparatide, calcium and Vitamin D for 12 months followed by 12 months of calcium and Vitamin D alone.

Secondary objectives

- To compare the effect of 24 months continuous treatment with 20 µg of teriparatide per day, calcium and Vitamin D, with a treatment regimen of teriparatide, calcium and Vitamin D for 12 months, followed by 12 months of calcium and Vitamin D alone, on changes in total hip and femoral neck bone mineral density (BMD).
- To compare the effect of a sequential treatment regimen of teriparatide, calcium and Vitamin D for 12 months followed by 12 months of raloxifene, calcium and Vitamin D, with a treatment regimen of teriparatide, calcium and Vitamin D for 12 months, followed by 12 months of calcium and Vitamin D alone, on change in total hip and femoral neck BMD.
- To compare the effect of 24 months continuous treatment with teriparatide, calcium and Vitamin D, with a sequential treatment regimen of teriparatide, calcium and Vitamin D for

12 months, followed by 12 months of raloxifene, calcium and Vitamin D, on change in lumbar spine, total hip, and femoral neck BMD.

· To assess the effect on BMD of continuous treatment with teriparatide over 24 months, calcium and Vitamin D in severely osteoporotic women who previously failed to respond to treatment with antiresorptive agents (Substudy 2).

Further objectives

· To analyse the change over time in the incidence rate of clinical (vertebral and nonvertebral) fragility fractures in treatment arm 1 of Substudy 1 (teriparatide for 24 months), in all 3 treatment arms of Substudy 1 combined, in both substudies combined, and in all patients receiving continuous teriparatide over 2 years (treatment arm 1 of Substudy 1, and Substudy 2).

· To analyse the change over time in back pain and frequency of falls.

· To compare the safety of the 3 treatment regimens in Substudy 1 and to assess the safety of 2 years of therapy with teriparatide in Substudy 2, as determined by physical examinations, vital signs, clinical laboratory measurements, and reports of adverse events (AEs).

Enrolment criteria

Inclusion criteria for Substudy 1 included:

· Ambulatory, postmenopausal women aged 55 years or above, whose last menstrual period occurred ≥ 2 years prior to entry into the trial. Women < 57 with indeterminate menopause due to premenopausal hysterectomy had to have their postmenopausal status confirmed with a serum follicle stimulating hormone (FSH) level >30 IU/L and a serum oestradiol level < 20 pg/ml or <73 pmol/L.

· Free of severe or chronically disabling conditions other than osteoporosis.

· Posterior-anterior lumbar spine (L-1 through L-4) BMD and/or femoral neck BMD and/or total hip BMD measurement at least 2.5 standard deviations (SDs) below the average bone mass for young women (T-score ≤ -2.5).

· At least 2 of the 3 lumbar vertebrae L-2, L-3, and L-4 had to be without artifacts, vertebral fractures, osteophytes, or other abnormalities that would interfere with the analysis of the posterior-anterior lumbar spine BMD measurement.

· Presence of at least one known and documented preexisting clinical fragility fracture, either vertebral or nonvertebral, in the past 3 years.

· Normal or clinically insignificant abnormal laboratory values including serum calcium and PTH (1-84) levels and alkaline phosphatase (ALP).

Patients were eligible for enrolment into Substudy 2 if they met any 1 of the following additional criteria:

· Had sustained at least 1 new clinical fragility fracture (vertebral or nonvertebral), despite prescription of antiresorptive therapy (includes all bisphosphonates, raloxifene, estrogen replacement therapy (ERT)/ and hormone replacement therapy (HRT), calcitonin, and Vitamin D metabolites) during the 12 months prior to the last new fracture.

Or

· At least 2 years after initiating antiresorptive therapy, either had a lumbar spine, femoral neck, or total hip BMD of at least 3 SDs below the average bone mass for young women (T-score ≤ -3), or showed a decrease of at least 3.5% in BMD at any one of these sites.

Exclusion criteria included:

· History of diseases which affect bone metabolism, other than postmenopausal osteoporosis, in the one year prior to Visit 2 such as Paget's disease, renal osteodystrophy,

osteomalacia, any secondary causes of osteoporosis, hypoparathyroidism, hyperparathyroidism, or hyperthyroidism.
- History of sprue, inflammatory bowel disease, or malabsorption syndrome.
- History of radiation therapy involving the skeleton.
- Abnormal thyroid function.
- Significantly impaired hepatic function, as documented by an alanine transaminase (ALT) value above the 2.5-fold upper normal range according to the local clinical laboratory, or a bilirubin of >2.0 mg/dL.
- Severely impaired renal function, as documented by a serum creatinine of >2.5 mg/dL.
- Subjective postmenopausal symptoms which were severe enough, in the investigator's opinion, to justify hormone therapy (HT).
- Restrictions relating to treatment within stipulated periods before the study with androgens; fluorides; calcitriol; Vitamin D; Vitamin D analogs; systemic corticosteroids; warfarin; cholestyramine or other anion-binding resins.

Treatments and assessments

See Figure 1. As well as lumbar spine and hip BMD measurements (by dual energy x-ray absorptiometry (DEXA) scan), the following information was collected at stipulated visits:

- Incidence of vertebral and non-vertebral clinical fragility fractures.
- Number of falls.
- Back pain assessed through a horizontal scale.
- Routine clinical and laboratory data.

Patient disposition

Reasons for discontinuing the study in the first and second years, respectively, are shown Tables 2 and 3.

Table 2. Study B3D-EW-GHCA − Reasons for discontinuation in the first year.

	Number (%) of patients		
	Substudy 1	**Substudy 2**	**Total**
Total enrolled	634 (100.0%)	234 (100.0%)	868 (100.0%)
Total discontinuations	127 (20.0%)	35 (15.0%)	162 (18.7%)
Reasons for discontinuation			
Patient decision	49 (7.7%)	12 (5.1%)	61 (7.0%)
Adverse Events	34 (5.4%)	17 (7.3%)	51 (5.9%)
Entry criteria not met	26 (4.1%)	5 (2.1%)	31 (3.6%)
Death	4 (0.6%)	0 (0.0%)	4 (0.5%)
Sponsor decision	4 (0.6%)	0 (0.0%)	4 (0.5%)
Physician decision	3 (0.5%)	1 (0.4%)	4 (0.5%)
Lost to follow-up	2 (0.3%)	0 (0.0%)	2 (0.2%)
Noncompliance	2 (0.3%)	0 (0.0%)	2 (0.2%)
Protocol violation	2 (0.3%)	0 (0.0%)	2 (0.2%)
Moved away	1 (0.2%)	0 (0.0%)	1 (0.1%)

Table 3. Study B3D-EW-GHCA − Reasons for discontinuation in the second year.

	Number (%) of patients				
	Substudy 1			Substudy 2	Total
	Teriparatide	Raloxifene	No active		
Total included in the second year	305 (100.0%)	100 (100.0%)	102 (100.0%)	199 (100.0%)	706 (100.0%)
Total discontinuations	20 (6.6%)	10 (10.0%)	10 (9.8%)	8 (4.0%)	48 (6.8%)
Reasons for discontinuation					
Adverse Events	6 (2.0%)	7 (7.0%)	1 (1.0%)	4 (2.0%)	18 (2.5%)
Patient decision	9 (3.0%)	1 (1.0%)	5 (4.9%)	2 (1.0%)	17 (2.4%)
Physician decision	1 (0.3%)	1 (1.0%)	2 (2.0%)	0 (0.0%)	4 (0.6%)
Death	2 (0.7%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	3 (0.4%)
Protocol violation	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.5%)	2 (0.3%)
Moved away	1 (0.3%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	2 (0.3%)
Noncompliance	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Other	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)

Outcomes

Analyses are for the Full Analysis Population, defined as follows:

Substudy 1. All 503 who were randomised at 12 months and had at least 1 dose of study medication and 1 follow-up visit after randomisation.

Substudy 2. All 234 enrolled patients who had at least 1 dose of teriparatide and 1 follow-up visit after randomisation.

1st and 2nd secondary objectives

See Table 4.

Table 4. Study B3D-EW-GHCA (Substudy 1) − 1st & 2nd secondary objectives: Treatment A or B versus treatment C, assessed by change in total hip and femoral neck BMD

Treatment	Time point	Results	
		Total hip BMD (g/cm^2)	**Femoral neck BMD (g/cm^2)**
A (N=304)	Baseline (N=294)	Mean 0.699 (SD 0.107)	Mean 0.626 (SD 0.109)
	Changes		
	at 6 months	LS mean -0.002 (-0.005, 0.001)	LS mean -0.002 (-0.006, 0.002)
	at 12 months	LS mean 0.004 (0.001, 0.008)	LS mean 0.006 (0.002, 0.010)
	at 18 months	LS mean 0.010 (0.006, 0.013)	LS mean 0.014 (0.009, 0.018)
	at 24 months	LS mean 0.017 (0.013, 0.021)[1]	LS mean 0.022 (0.017, 0.026)[3]
B (N=97)	Baseline (N=96)	Mean 0.711 (SD 0.106)	Mean 0.634 (SD 0.124)
	Changes		
	at 6 months	LS mean 0.000 (-0.005, 0.005)	LS mean 0.003 (-0.003, 0.010)
	at 12 months	LS mean 0.006 (0.000, 0.012)	LS mean 0.010 (0.003, 0.017)
	at 18 months	LS mean 0.015 (0.009, 0.022)	LS mean 0.020 (0.012, 0.027)
	at 24 months	LS mean 0.016 (0.009, 0.024)[2]	LS mean 0.019 (0.012, 0.027)[4]
C (N=102)	Baseline (N=97)	Mean 0.708 (SD 0.109)	Mean 0.626 (SD 0.111)
	Changes		
	at 6 months	LS mean -0.004 (-0.009, 0.002)	LS mean -0.006 (-0.013, 0.000)
	at 12 months	LS mean 0.001 (-0.005, 0.007)	LS mean 0.001 (-0.006, 0.008)
	at 18 months	LS mean 0.006 (0.000, 0.013)	LS mean 0.013 (0.005, 0.020)
	at 24 months	LS mean 0.004 (-0.004, 0.001)[1,2]	LS mean 0.008 (0.000, 0.016)[3,4]

[1] Statistically significant difference, p=0.001. [2] Statistically significant difference, p=0.012. [3] Statistically significant difference, p=0.002. [4] p=0.044.

3rd secondary objective

Relevant measurements are reproduced below (Table 5).

Table 5.

Treatment	Time point	Lumbar spine BMD (g/cm^2)	Total hip BMD (g/cm^2)	Femoral neck BMD (g/cm^2)
A	Baseline	Mean 0.736 (SD 0.108)	Mean 0.699 (SD 0.107)	Mean 0.626 (SD 0.109)
	Change at 24 m	LS mean 0.079 (0.073, 0.084)	LS mean 0.017 (0.013, 0.021)	LS mean 0.022 (0.017, 0.026)
B	Baseline	Mean 0.751 (SD 0.121)	Mean 0.711 (SD 0.106)	Mean 0.634 (SD 0.124)
	Change at 24 m	LS mean 0.058 (0.049, 0.068)	LS mean 0.016 (0.009, 0.024)	LS mean 0.019 (0.012, 0.027)
Comparison between treatments		Significant at 0.001	NSS	NSS

4th secondary objective

Substudy 2. See Table 6.

Table 6. Study B3D-EW-GHCA (Substudy 2) – 4th secondary objective: Substudy 2: effect of teriparatide over 24 months, in patients who had previously failed to respond to antiresorptive agents.

Time point	Results		
	Lumbar spine BMD (g/cm^2)	**Total hip BMD (g/cm^2)**	**Femoral neck BMD (g/cm^2)**
Baseline	Mean 0.715 (SD 0.119) (N=233)	Mean 0.685 (SD 0.107) (N=229)	Mean 0.611 (SD 0.120) (N=229)
Changes			
at 6 months	LS mean 0.024 (0.015, 0.033)	LS mean -0.008 (-0.014, -0.002)	LS mean -0.002 (-0.009, 0.004)
at 12 months	LS mean 0.040 (0.031, 0.050)	LS mean -0.002 (-0.008, 0.005)	LS mean 0.005 (-0.002, 0.011)
at 18 months	LS mean 0.058 (0.048, 0.068)	LS mean 0.009 (0.002, 0.016)	LS mean 0.016 (0.009, 0.023)
at 24 months	LS mean 0.067 (0.057, 0.078)	LS mean 0.018 (0.011, 0.025)	LS mean 0.030 (0.022, 0.038)

Clinical outcomes

Numbers of patients with clinical fragility fractures diagnosed during the study were tabulated (see Tables 7 and 8). Similarly, data on reported back pain were presented (see Tables 9 and 10).

Table 7. Study B3D-EW-GHCA. Number of patients with clinical fragility fractures in the total study population. Enrolled and treated population.

Type of fracture Time interval	Total Patients	Number of clinical fragility fractures		
		Number (%) of patients with clinical fragility fracture	Per given interval	Per 10000 patient years
All Fractures				
0 to 6 months	866	29 (3.3%)	38	953
7 to 12 months	735	20 (2.7%)	24	658
13 to 18 months	699	11 (1.6%)	12	347
19 to 24 months	666	16 (2.4%)	19	590
0 to 24 months	866	70 (8.1%)	93	650
Vertebral Fractures				
0 to 6 months	866	8 (0.9%)	13	326
7 to 12 months	735	3 (0.4%)	4	110
13 to 18 months	699	1 (0.1%)	1	29
19 to 24 months	666	3 (0.5%)	3	93
0 to 24 months	866	15 (1.7%)	21	147
Non-vertebral Fractures				
0 to 6 months	866	21 (2.4%)	25	627
7 to 12 months	735	17 (2.3%)	20	548
13 to 18 months	699	10 (1.4%)	11	318
19 to 24 months	666	13 (2.0%)	16	497
0 to 24 months	866	57 (6.6%)	72	503

Table 8. Study B3D-EW-GHCA. Number of patients with clinical fragility fractures in the total continuous teriparatide group. Enrolled and treated population.

Type of fracture Time interval	Total Patients	Number of clinical fragility fractures		
		Number (%) of patients with clinical fragility fracture	Per given interval	Per 10000 patient years
All Fractures				
0 to 6 months	503	15 (3.0%)	20	795
7 to 12 months	501	12 (2.4%)	14	559
13 to 18 months	501	10 (2.0%)	11	442
19 to 24 months	478	14 (2.9%)	17	734
0 to 24 months	503	46 (9.1%)	62	631
Vertebral Fractures				
0 to 6 months	503	5 (1.0%)	8	318
7 to 12 months	501	2 (0.4%)	2	80
13 to 18 months	501	1 (0.2%)	1	40
19 to 24 months	478	3 (0.6%)	3	130
0 to 24 months	503	11 (2.2%)	14	143
Non-vertebral Fractures				
0 to 6 months	503	10 (2.0%)	12	477
7 to 12 months	501	10 (2.0%)	12	479
13 to 18 months	501	9 (1.8%)	10	402
19 to 24 months	478	11 (2.3%)	14	605

0 to 24 months	503	37 (7.4%)	48	489

Table 9. Study B3D-EW-GHCA. Back Pain measured by visual analog scale after 24 months. Full analysis population.

Time point-statistic	Substudy 1			Substudy 2
	Teriparatide (N=304)	Raloxifene (N=97)	No active treatment (N=102)	(N=234)
Baseline				
N	302	96	98	230
Mean	47.6	48.8	42.7	54.1
Median	50.3	49.8	44.8	55.0
SD	24.4	24.0	24.9	22.9
Minimum	0.0	0.5	0.0	0.0
Maximum	100.0	100.0	95.0	100.0
24 months (Visit 7)				
N	285	94	94	191
Mean	32.5	34.5	34.5	36.2
Median	30.0	30.0	30.0	30.0
SD	24.4	25.4	28.2	24.9
Minimum	0.0	0.0	0.0	0.0
Maximum	100.0	95.0	100.0	95.0
Change from baseline at 24				
N	285	94	94	190
Mean	-15.2	-13.9	-8.6	-17.2
Median	-15.0	-10.8	-7.3	-18.0
SD	27.1	28.3	26.3	24.0
Minimum	-77.0	-93.0	-86.0	-68.5
Maximum	52.0	54.0	63.5	56.0
p-value	<0.001	<0.001	0.001	<0.001

N = Number of available patients; SD = Standard deviation. Note: Score ranged from 0 mm ("No back pain") to 100 mm ("Worst possible back pain"). P-value derived from a 1-sample t-test testing the hypothesis of no change.

Table 10. Study B3D-EW-GHCA. Treatment Arm Comparison in Back Pain measured by Visual Analog Scale. Full analysis population.

	Difference in the change from baseline at			
Comparison	6 months[a]	12 months[a]	18 months	24 months
Teriparatide-Teriparatide vs. Teriparatide-No active treatment				
LS mean	-3.746	-2.155	-2.941	-5.334
95%-CI	-8.885 to 1.393	-7.591 to 3.281	-8.882 to 3.000	-11.58 to 0.914
p-value	0.152	0.436	0.331	0.094
Teriparatide-Raloxifene vs. Teriparatide-No active treatment				
LS mean	-1.854	0.915	-1.012	-4.474
SE	3.244	3.427	3.739	3.921
95%-CI	-8.227 to 4.519	-5.818 to 7.648	-8.359 to 6.334	-12.18 to 3.230
p-value	0.567	0.789	0.786	0.254
Teriparatide-Teriparatide vs. Teriparatide-Raloxifene				
LS mean	-1.892	-3.070	-1.928	-0.859
SE	2.666	2.816	3.062	3.209
95%-CI	-7.129 to 3.345	-8.602 to 2.462	-7.944 to 4.087	-7.166 to 5.447
p-value	0.478	0.276	0.529	0.788

Note: Mixed-model repeated measures analysis. [a]All patients were treated with teriparatide during the first 12 months.

Comment

The study was not adequately powered to detect differences in clinical outcomes between treatment groups. However, the clinical evaluator doubted that simply increasing the numbers studied would have been worthwhile, as the sort of study needed to settle reliably the question central to the present application – that is, the medium to long-term clinical benefits (if any) of a 24 month course of teriparatide compared to an 18 month course– would have required much longer follow-up, with treatment arms which included restoration of antiresorptive treatment at the end of teriparatide treatment.

An aspect which is of considerable interest is the extent to which efficacy of teriparatide is influenced by prior treatment (whether effective or not) with antiresorptives. The Substudy 2 data are suggestive of a reduced response to teriparatide in patients who had sustained a new clinical fragility fracture despite previous treatment with antiresorptive therapy. During evaluation, the sponsor was asked whether the data from Substudy 1 had been, or could be, analysed for evidence of an effect of previous antiresorptive therapy. The sponsor responded that the study was not designed to look at the causal effect of previous antiresorptive treatment and was not suitable to address whether the differences seen amongst these groups was due to the prior treatment or other characteristics specific to these patients.

Comment

The clinical evaluator notes the following provisions of the relevant guideline (European medicines Evaluation Agency (EMEA) 2006):

"Aim of treatment

The aim of the pharmacological intervention is to reduce the incidence of fractures. The applicant will be requested to demonstrate the effect of the investigated medicinal product on both spinal and non-spinal fractures.

Criteria of efficacy and their assessment

All endpoints to assess efficacy in clinical trials must be defined prior to the start of the trial and included in the study protocol.

Bone Mineral Density (BMD)

BMD may be the primary end point in exploratory studies but it is not an appropriate surrogate for fracture reduction. The current usual method for assessing BMD is dual energy X-ray absorptiometry. For all techniques, instrument precision and accuracy are very important. Careful quality control and assurance are required. The use of central BMD quality assurance centres is recommended. "

Regarding the first of these: A significant effect on fractures was not demonstrated in the new study included in the present dossier (B3D-EW-GHCA) (see second paragraph below).

Regarding the second of these: Compliance could not be verified for the new study, as the trial protocol was not included in the dossier.

Regarding the third of these: The provisions relating to BMD accuracy appear to have been met. However, the primary efficacy variable in the new study was change in BMD. The study was not powered to use fracture incidence as a primary end point.

Studies evaluated previously (B3D-US-GHBZ & B3D-MC-GHAC)

As the greater part of the previous CER (dated December 2008) focused on Study B3D-US-GHBZ, the clinical evaluator suggests that CER should be included for review with the present CER.

Numbers of patients treated with teriparatide for various periods are given under *Safety* below. For use > 18 months, the efficacy data for Study B3D-US-GHBZ (patients with glucocorticoid-induced osteoporosis (GIOP)) and Study B3D-MC-GHAC were favourable.

Efficacy summary

The new study report shows that teriparatide continues to have a beneficial effect on BMD in postmenopausal osteoporosis to 24 months. Studies submitted and evaluated previously provide supporting evidence, in patients with postmenopausal osteoporosis and patients with GIOP.

However, the present application is deficient, in that extended use of Forteo is not compared to the currently approved maximum treatment period followed by reintroduction of antiresorptive therapy.

Comparison with Preotact[3]

As part of the rationale for extended treatment duration, the sponsor claims that "Comparable safety and greater gains in BMD than demonstrated with 24-months treatment with Preotact". The sponsor also makes an efficacy comparison as follows:

"The BMD increases between 18 and 24 months at the lumbar spine, total hip, and femoral neck in Study GHCA (postmenopausal women with severe osteoporosis previously treated with antiresorptives) were +1.2%, +1.3% and +2.1%, respectively, and in Study GHBZ (patients with GIOP) were +1.7%, +0.9% and +0.4%, respectively.

[3] Preotact contains the active substance parathyroid hormone and is marketed in the EU by Nycomed Danmark ApS.

Although no head-to-head trial was performed by the Marketing Authorisation Holder (MAH) to compare teriparatide with Preotact, as reported in the European Preotact Summary of Product Characteristics (SmPC) the increases in lumbar spine and femoral neck BMD between 18 and 24 months were +0.3% and +0.4%, respectively in postmenopausal women with osteoporosis treated with Preotact."

Comment

Apart from the fact that there was no direct comparison, the claim is unjustified, because:

- the Preotact study has not been submitted for evaluation; and
- the results from Study GHCA come in fact from Substudy 2, for which an inclusion criterion was failure of antiresorptive therapy.

Safety

Study B3D-EW-GHCA

Exposure to teriparatide in the study is summarised below (Table 11).

Table 11.

	Number exposed (N=868)
Number of exposed patients	866[a]
Number of patients with exposure duration of	
≤ 3 months	829[c]
3 to < 6 months	757
6 to < 9 months	730
9 to < 12 months	715
12 to < 15 months	587
15 to < 18 months	485
18 to < 21 months	478
21 to < 24 months	468
≥ 24months[b]	194
Number of patient years	1216
Number of patient years (post 18 months)	232

[a]Two patients did not receive any teriparatide. [b]Maximum was 26.2 months. [c]Not computable for 37 patients, due to missing data.

An AE was defined as "treatment-emergent" (TEAEs) in a given period if it was reported for the first time or with greater severity within that period. TEAEs are tabulated in Tables 12 and 13.

Table 12. Study B3D-EW-GHCA. Teriparatide TEAEs by SOC. Safety population

	Number (%) of patients by 6-month intervals									
	<6 Months (N=866)		6 to 12 Months (N=743)		12 to 18 Months (N=504)		>18 Months (N=486)		0 to 24 Months (N=866)	
Preferred term	n	%	n	%	n	%	n	%	n	%
Any TEAE	508	58.7	306	41.2	193	38.3	166	34.2	631	72.9
No TEAE	358	41.3	437	58.8	311	61.7	320	65.8	235	27.1
Musculoskeletal and connective tissue disorders	173	20.0	89	12.0	63	12.5	33	6.8	277	32.0
Gastrointestinal disorders	180	20.8	64	8.6	26	5.2	38	7.8	255	29.4
Infections and infestations	136	15.7	76	10.2	53	10.5	44	9.1	230	26.6
Nervous system disorders	107	12.4	45	6.1	22	4.4	12	2.5	163	18.8
General disorders and administration site	87	10.0	18	2.4	13	2.6	12	2.5	118	13.6
Vascular disorders	48	5.5	23	3.1	15	3.0	25	5.1	102	11.8
Injury, poisoning and procedural complications	35	4.0	29	3.9	21	4.2	18	3.7	98	11.3
Metabolism and nutrition disorders	56	6.5	27	3.6	10	2.0	8	1.6	92	10.6
Skin and subcutaneous tissue disorders	44	5.1	23	3.1	7	1.4	11	2.3	73	8.4
Respiratory, thoracic and mediastinal disorders	33	3.8	17	2.3	10	2.0	14	2.9	64	7.4
Cardiac disorders	36	4.2	18	2.4	5	1.0	9	1.9	62	7.2
Psychiatric disorders	31	3.6	18	2.4	8	1.6	3	0.6	56	6.5
Investigations	20	2.3	12	1.6	7	1.4	10	2.1	44	5.1
Ear and labyrinth disorders	18	2.1	13	1.7	8	1.6	5	1.0	43	5.0
Eye disorders	21	2.4	14	1.9	6	1.2	6	1.2	39	4.5
Renal and urinary disorders	16	1.8	8	1.1	6	1.2	5	1.0	34	3.9
Neoplasms benign, malignant and unspecified	12	1.4	5	0.7	8	1.6	4	0.8	28	3.2
Reproductive system and breast disorders	11	1.3	1	0.1	3	0.6	1	0.2	16	1.8
Blood and lymphatic system disorders	2	0.2	7	0.9	4	0.8	3	0.6	14	1.6
Surgical and medical procedures	4	0.5	2	0.3	1	0.2	5	1.0	12	1.4
Hepatobiliary disorders	2	0.2	2	0.3	3	0.6	4	0.8	11	1.3
Immune system disorders	8	0.9	3	0.4	0	0.0	0	0.0	11	1.3
Endocrine disorders	7	0.8	4	0.5	0	0.0	0	0.0	10	1.2

Table 13. Study B3D-EW-GHCA. Teriparatide TEAEs reported by ≥ 0.5% of patients. Safety population

	Number (%) of patients by 6-month intervals									
	<6 Months (N=866)		6 to 12 Months		12 to 18 Months (N=504)		>18 Months (N=486)		0 to 24 Months (N=86	
Preferred term	n	%	n	%	n	%	n	%	n	%
Any possibly related TEAE	223	25.8	53	7.1	34	6.7	23	4.7	269	31.1
Nausea	62	7.2	5	0.7	3	0.6	2	0.4	69	8.0
Headache	34	3.9	1	0.1	2	0.4	2	0.4	38	4.4
Muscle cramp	28	3.2	8	1.1	2	0.4	1	0.2	37	4.3
Hypercalcaemia	19	2.2	6	0.8	2	0.4	1	0.2	27	3.1
Dizziness	19	2.2	5	0.7	1	0.2	1	0.2	25	2.9
Arthralgia	10	1.2	5	0.7	5	1.0	0	0.0	15	1.7
Vertigo	9	1.0	1	0.1	2	0.4	1	0.2	13	1.5
Injection site erythema	10	1.2	0	0.0	0	0.0	1	0.2	11	1.3
Pain in extremity	6	0.7	5	0.7	1	0.2	1	0.2	11	1.3
Vomiting	9	1.0	1	0.1	1	0.2	0	0.0	11	1.3
Diarrhoea	8	0.9	2	0.3	0	0.0	0	0.0	10	1.2
Back pain	8	0.9	1	0.1	1	0.2	1	0.2	9	1.0
Hyperhidrosis	5	0.6	2	0.3	0	0.0	1	0.2	7	0.8
Asthenia	5	0.6	0	0.0	0	0.0	1	0.2	6	0.7
Palpitations	6	0.7	0	0.0	0	0.0	0	0.0	6	0.7
Syncope	3	0.3	1	0.1	2	0.4	0	0.0	6	0.7
Blood AP increased	1	0.1	2	0.3	2	0.4	1	0.2	5	0.6
Blood calcium increased	2	0.2	3	0.4	0	0.0	0	0.0	5	0.6
Constipation	4	0.5	2	0.3	0	0.0	0	0.0	5	0.6
Fatigue	5	0.6	0	0.0	0	0.0	0	0.0	5	0.6
Feeling abnormal	5	0.6	0	0.0	0	0.0	0	0.0	5	0.6
Hot flush	4	0.5	0	0.0	0	0.0	1	0.2	5	0.6
Muscle spasms	5	0.6	0	0.0	0	0.0	0	0.0	5	0.6
Post procedural nausea	3	0.3	1	0.1	1	0.2	0	0.0	5	0.6
Abdominal pain	4	0.5	0	0.0	0	0.0	0	0.0	4	0.5
Abdominal pain upper	4	0.5	0	0.0	0	0.0	0	0.0	4	0.5
Bone pain	4	0.5	0	0.0	0	0.0	0	0.0	4	0.5
Depression	2	0.2	2	0.3	0	0.0	0	0.0	4	0.5
Hypertension	3	0.3	1	0.1	0	0.0	0	0.0	4	0.5
Myalgia	2	0.2	1	0.1	2	0.4	0	0.0	4	0.5

Deaths

8 deaths occurred during the study:

First year: 1 cerebral ischaemia; 1 acute dextropopoxyphene toxicity; 1 lower respiratory tract infection; 1 cerebral haemorrhage.

Second year (Substudy 1, teriparatide arm): 1 metastatic neoplasm, primary unknown; 1 neoplasm lung.

Second year (Substudy 1, raloxifene arm): 1 neoplasm pancreas.

Second year (Substudy 2): 1 chronic obstructive airway disease.

AEs leading to discontinuation

First year (Substudy 1): 34 patients

First year (Substudy 2): 17 patients

Second year (Substudy 1, teriparatide arm): 6 patients

Second year (Substudy 1, raloxifene arm): 7 patients

Second year (Substudy 1, no active treatment arm): 1 patient

Second year (Substudy 2): 4 patients

The Preferred Terms for AEs leading to discontinuation in the first year were: abdominal pain, abdominal pain upper (2 reports), atrial fibrillation, back pain, bipolar disorder, bone pain, Bowen's disease, cardiac failure congestive, convulsion, depression, diabetes mellitus, diarrhoea, disorientation, drug hypersensitivity, feeling abnormal, femoral neck fracture, flushing, gastric cancer stage ii, gastric ulcer, headache (3 reports), hypercalcaemia (2 reports), hypersensitivity, hypertension, injection site erythema (2 reports), injection site rash, malaise, multiple myeloma, muscle cramp, myalgia, nausea (8 reports), pancreatic carcinoma, phlebitis, pruritus, renal pain, sarcoidosis, transient ischaemic attack, vertigo (2 reports), vomiting.

The Preferred Terms for AEs leading to discontinuation in the second year were: bone pain, breast cancer, cerebrovascular accident, colon cancer stage iii, gastric cancer, headache (2 reports), myocardial ischaemia, nausea (2 reports), nephrolithiasis, pain in extremity, pancreatic carcinoma, papillary thyroid cancer, post procedural nausea, rectal adenoma, syncope, visual acuity reduced.

Laboratory monitoring

Samples for assessment of serum calcium, ALP and albumin were taken at 1, 6, 12, and 18 months before injection of study drug. However, values were not routinely reported or analysed. The study report stated "Individual patient laboratory data was not routinely collected. Where results were considered abnormal, the data has been captured as part of the adverse event report."

Safety summary

Exposure to teriparatide in the relevant studies submitted previously (B3D-US-GHBZ and B3D-US-GHBZ) is tabulated below (Tables 14 and 15).

Table 14.

B3D-US-GHBZ

Number of Patients Remaining	Time point, months						
	Total	3	6	12	18	24	36
ALN10	214	184	176	159	144	138	118
PTH20	214	189	183	167	150	138	123

Table 15.

B3D-MC-GHAC

	No. of months completed						
Number of Patients	0 to 5	6 to 11	12 to 17	18 to 20	21 to 23	24 to 26	Total
Placebo	41	23	94	257	127	2	544
PTH20	48	30	86	250	125	0	539
PTH40	61	34	93	235	127	2	552
Total	150	87	273	742	379	4	1635

The safety data from the new study do not appear to add substantially to those from the studies evaluated previously.

As is made clear in the current Australian PI (under *Precautions*), the reason for the limitation in lifetime exposure to Forteo is to "minimise the potential risk of osteosarcoma". In the present application, no new human trial data have been provided which could alleviate this specific safety concern. Information which is in the evaluator's opinion is relevant comprises:

- any information on relevant animal studies and
- the following information, provided in the *Risk Management Plan*:
  "Lilly has identified five reports for which a diagnosis of osteosarcoma was included in at least one pathology report out of an estimated 747000 patients and approximately 2.1 million patient years (PY) of observation as of April 2009. Details of these cases have been reported to regulatory agencies. The reporting rate does not exceed the expected incidence rate in the patient population for teriparatide use ... ."

  Comment

  Details of the osteosarcoma cases mentioned above should be reviewed.

A flaw in all 3 studies relied upon was lack of formal long-term follow-up, after the end of the study treatment.

Post marketing experience

No Periodic Safety Update Report (PSUR) was submitted. The sponsor states that in a report submitted 18 July 2008, worldwide exposure to Forteo was estimated at 1.4 million patient years.

Clinical Summary and Conclusions

Regarding efficacy, the present application is deficient, as explained above. However, the clinical evaluator believed that if the current trial data had been submitted at the time of initial application, 24 months of therapy would have been approved, but for the concern (arising from nonclinical data) about osteosarcoma.

The post-marketing information relating to reports of osteosarcoma provide some reassurance, but the clinical valuator believed the animal studies are of central importance. The clinical evaluator recommended approval of the application, subject to expert review of the relevant nonclinical data.

V. Pharmacovigilance Findings

The sponsor submitted a Risk Management Plan (summarised in Tables 16 and 17 below) with their submission which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM).

Table 16. Proposed pharmacovigilance activities, other than routine.

	Pharmacovigilance Activities (Routine and Additional)	
Safety Concern	**Activity**	**Milestone**
Important Identified Risk of Hypercalcemia	Routine pharmacovigilance Targeted surveillance	Report data in PADER/PSUR.
Important Identified Risk of Orthostatic Hypotension	Routine pharmacovigilance Targeted surveillance	Report data in PADER/PSUR.
Important Potential Risk of Osteosarcoma	Routine pharmacovigilance Targeted surveillance Study GHBX (Teriparatide Post-Approval Osteosarcoma Surveillance Study)	Submit analysis of cumulative data, including GHBX data, in PADER/PSUR, or if appropriate, other communication venues will be used.
Important Missing Information Concerning Limited Clinical Trial Experience in Pre-Menopausal Women	Routine pharmacovigilance, including close monitoring and follow-up of all reports of pregnancy. Analysis of post-marketing safety data using age of patient <50 years as a proxy for menopausal status.	Report data in PADER/PSUR.

PADER=Periodic Adverse Drug Experience Report (FDA). Periodic Safety Update Report (EU).

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 17. Proposed Risk Minimisation Plan

Safety Concern	Routine Risk Minimization Activities
Important Identified Risk of Hypercalcemia	Prescribing information includes: • contraindication concerning pre-existing hypercalcemia (SPC section 4.3) • special warning and precaution concerning the potential for hypercalcemia (SPC section 4.4)
Important Identified Risk of Orthostatic Hypotension	Prescribing information includes: • special warning and precaution concerning the potential for orthostatic hypotension (SPC section 4.4)
Important Potential Risk of Osteosarcoma	Prescribing information includes: • contraindication excluding patients with a history of skeletal radiation or malignancy or Paget's disease of the bone • information regarding the animal study observations MAH publications of case report in the medical literature.
Important Missing Information Concerning Limited Clinical Trial Experience in Pre-Menopausal Women	Prescribing information includes: • contraindication concerning pregnancy and lactation (SPC section 4.3) • special warning and precaution concerning limited experience in premenopausal women (SPC section 4.4) • discussion of pregnancy and lactation (SPC section 4.6) • dosing instructions that the 18-month course of treatment should not be repeated over a patient's lifetime (SPC section 4.2)

SPC refers to the United Kingdom equivalent to the Australian PI.

Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Teriparatide was first approved in Australia on 22 May 2003 for the treatment of established osteoporosis in postmenopausal women and for the treatment of osteoporosis in men when other agents are unsuitable, for a maximum treatment period of 18 months. It is also indicated for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at high risk for fracture.

Exposure was restricted to a lifetime maximum of 18 months due to a potential risk of osteosarcoma identified in nonclinical animal studies. In these studies, there was a clear dose and time dependent relationship between teriparatide exposure and the development of osteosarcoma. The clinical significance of these findings, and whether this risk applies to humans, is unknown.

In this application, the sponsor is seeking to extend the maximum treatment duration from 18 months to 24 months. The major safety concern associated with an increase in treatment duration is the potential for an increased risk of developing osteosarcoma. The nonclinical evaluator has concluded that this is an important safety issue of unknown clinical significance, and due to the low background rate of this condition, ultimately only post market data will establish whether there is a true association. In the opinion of this OMSM

evaluator, this highlights the importance of having a robust pharmacovigilance system to adequately monitor and investigate this potential risk.

Internationally, teriparatide is approved for a maximal treatment duration of 24 months in the European Union (EU) and 24 months in the United States (US). In the US, the FDA and Sponsor have implemented a patient registry as part of the Risk Evaluation and Mitigation Strategy (REMS) to mitigate the potential risk of osteosarcoma.[4]

For the monitoring and management of the potential risk of osteosarcoma, the sponsor proposes routine pharmacovigilance (PhV), targeted surveillance, warning information in the PI and study GHBX (post approval surveillance study GHBX). In addition, it is a condition of registration that patients sign a consent form warning of the potential risk of osteosarcoma, but this is not included in the RMP. Post approval surveillance study GHBX is a case-series post approval study being conducted in the US and EU. The aim of this study is to identify approximately 40% of newly diagnosed cases of osteosarcoma among men and women 40 years and older, starting 90 days after the first marketed use of teriparatide, and to determine incident osteosarcoma cases and any cases where there is a history of teriparatide treatment or other osteosarcoma risk factors. Completion is expected in 2018. To date, no cases of osteosarcoma have been identified in patients who have taken teriparatide in the GHBX study. In addition to osteosarcoma, the following safety issues have been included:

- Identified risks: hypotension and hypercalcaemia
- Important area of missing information: use in premenopausal females.

For these safety issues, the Sponsor proposes routine Pharmacovigilance Findings (PhV), targeted surveillance and including information in the PI. These are considered acceptable.

The following issues have been identified and require comment from the Sponsor:

1. The sponsor has committed to a voluntary patient registry in the US. However, this is not included in the RMP. The sponsor should be requested to provide a detailed description of this registry, including recruitment of subjects, data collection, outcome measures and frequency and duration of follow up.
2. As the extended time of use (from 18 to 24 months) of teriparatide may be associated with an increased risk of developing osteosarcoma it is recommended a patient registry be implemented in Australia or Australian patients are added to the existing US registry and that regular reports are provided to the TGA. The final details of these should be agreed with the TGA.
3. For all of the additional EU requirements, the sponsor should confirm that they will conduct an analysis of the additional EU requirements and these analyses will be presented in each Periodic Safety Update Report (PSUR).

In summary, the proposed RMP for the potential risk of osteosarcoma requires additional PhV activities, in the form of a patient registry. The proposed activities outlined for the safety issues of hypercalcaemia, hypotension and missing information on use in premenopausal women are acceptable.

[4] Proposed Risk Evaluation and Mitigation Strategy (REMS), Forteo NDA: 21-318/S-012. Teriparatide (rDNA origin) Injection Osteoporosis. United States Food and Drug Administration Division of Reproductive and Urologic Products. Eli Lilly and Company. http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM173371.pdf

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

No new data submitted were submitted with the current Australian submission.

Nonclinical

No new data were submitted with the current Australian submission. The nonclinical submission consisted of a published report of a previously evaluated long-term monkey study. The sponsor confirmed that no further nonclinical data existed, stating that this more recent peer review publication provides further discussion on duration of treatment (see Nonclinical evaluation above).

Ovariectomised female cynomolgus monkeys (30/group, 2 groups) received vehicle or teriparatide (5 µg/kg) SC daily for 18 months. Six animals/group were sacrificed at the end of the treatment phase; the remaining animals were assigned for observation for a further 3 years. Eighteen treated monkeys survived until scheduled termination at 4.5 years. Plain film radiographs were obtained pre-treatment, at 18 months, and at 3 years, and histopathology was performed. No bone neoplasms were found. In addition, histopathological evaluation did not detect any microscopic foci of cellular atypia, focal hyperplasia or other pre-neoplastic lesions.

The nonclinical evaluator noted that the monkey study is not of sufficient size or duration to be regarded as a true carcinogenicity study, as such studies need to have large group sizes, (50/group) and be conducted for the lifetime of the animals. The nonclinical evaluator considered the study design could give useful, but not definitive, information about the potential of teriparatide to cause osteosarcoma or other bone neoplasms in a bone-remodelling species, and indicates reduced susceptibility compared to bone-modelling species such as the rat. When bone turnover rates are taken into account 18 months treatment is comparable to about 4 years in human, and the exposure was 5 to 6-fold levels observed clinically, an adequate exposure margin.

The evaluator concluded that the results of the monkey studies were sufficient to support an extension of treatment duration to 24 months on safety grounds, so long as the benefit increases with a longer duration of treatment. Osteosarcoma remains classified as an important potential risk to patients treated with Forteo. A new paragraph was recommended under *Carcinogenicity* in the PI describing the 4.5 year monkey study.

Clinical

Study B3D-EW-GHCA was submitted in support of the application. The study enrolled postmenopausal women aged 55 years or above with lumbar spine, femoral neck or total hip T scores < -2.5 There were 2 substudies (see Figure 1 above). Exclusion criteria included diseases of bone metabolism or any secondary cause of osteoporosis, impaired hepatic function, severe renal impairment, abnormal thyroid function and history of skeletal radiation therapy.

The primary objective was to compare the effect of 24 months continuous treatment with 20 µg of teriparatide per day with a treatment regimen of teriparatide for 12 months only. The primary outcome variable was change in lumbar spine BMD at 24 months. A "co-primary objective" was to compare the effect of a sequential treatment regimen of teriparatide for 12 months followed by 12 months of raloxifene 60 mg/day, with a treatment regimen of teriparatide for 12 months only. All patients received calcium and Vitamin D throughout.

Secondary objectives included comparisons of changes in total hip and femoral neck BMD, changes in women who previously failed to respond to antiresorptive agents (Substudy 2) change over time in the incidence rate of clinical (vertebral and nonvertebral) fragility fractures, safety comparisons in Substudy 1 and safety assessments in Substudy 2.
In ***Substudy 1*** 632 women received study medication: mean age 69.9 (SD 7.6); mean BMI (619 patients) 25.3 (SD 4.4); mean time since menopause (630 patients) 271.7 months (SD 115); all were Caucasian. Treatment in Period 1, Months 1-12 was teriparatide 20 µg/day. In Period 2, months 13-24, the 507 patients remaining were randomised to treatments in the ratio 3:1:1.

In ***Substudy 2*** there were 234 women enrolled, and all patients received teriparatide 20 µg/day in Period 1 and 2; there was no control arm.

Efficacy

Table 18. ***Substudy 1***

Subjects, treatments	Time points	Results Lumbar Spine BMD g/cm^2
(A) Teriparatide 20 µg/day 304: mean age 69.2 (SD 7.2)	Baseline (n = 300)	Mean 0.736 (SD 0.108)
	Changes at	
	6 mo	LS mean 0.031 (0.027, 0.035)
	12 mo	LS mean 0.052 (0.048, 0.057)
	18 mo	LS mean 0.066 (0.061, 0.071)
	24 mo	LS mean 0.079 (0.073, 0.084)
(B) Raloxifene 60 µg/day 97: mean age 69.4 (SD 7.0)	Baseline (n =96)	Mean 0.751 (SD 0.121)
	Changes at	
	6 mo	LS mean 0.037 (0.029, 0.044)
	12 mo	LS mean 0.060 (0.052, 0.068)
	18 mo	LS mean 0.058 (0.049, 0.067)
	24 mo	LS mean 0.058 (0.049, 0.068)[2]
(C) No active treatment 102: mean age 69.1 (SD 8.6)	Baseline (N=97)	Mean 0.746 (SD 0.109)
	Changes at	
	at 6 mo	LS mean 0.031 (0.024, 0.038)
	at 12 mo	LS mean 0.048 (0.040, 0.057)
	at 18 mo	LS mean 0.037 (0.028, 0.046)
	at 24 mo	LS mean 0.028 (0.018, 0.038)[1,2]

[1] Statistically significant difference at 0.001 level (first primary objective). [2] Statistically significant difference at 0.001 level (second primary objective).

Table 19. ***Substudy 2***

Subjects, treatments	Time points	Results Lumbar Spine BMD g/cm^2
Teriparatide 20 µg/day n =234:	Baseline (n = 214)	Mean 0.716 (SD 0.119)
	Changes	
	6 mo	LS mean 0.024 (0.015, 0.033)
	12 mo	LS mean 0.040 (0.0431, 0.050)
	18 mo	LS mean 0.058 (0.048, 0.068)
	24 mo	LS mean 0.067 (0.057, 0.078)

The table below (Table 20) summarises the data in Tables 7 and 8 of the CER. It shows patients with clinical fragility fractures diagnosed during the study in the total study population and in the teriparatide-treated group, in the last 6 months of the study and over the full study duration.

Table 20.

Type of fracture Time interval	total study population	teriparatide continuous treatment
All fractures		
19 -24 months	16/666 (2.4%)	14/478 (2.9%)
0-24 months	70/866 (8.1%)	46/503 (9.1%)
vertebral		
19 -24 months	3/666 (0.5%)	3/478 (0.6%)
0-24 months	15/866 (1.7%)	11/503 (2.2%)
non-vertebral		
19 -24 months	13/666(2.0%)	11/478 (2.3%)
0-24 months	57/866(6.6%)	37/503 (7.4%)

The clinical evaluator noted that the study was not adequately powered to detect differences in clinical outcomes between treatment groups. The clinical evaluator considered that a study would have required much longer follow-up to answer 'the question central to the present application – that is, the medium to long-term clinical benefits (if any) of a 24 month course of teriparatide compared to an 18 month course', with treatment arms which included restoration of antiresorptive treatment at the end of teriparatide treatment.

In summary, B3D-EW-GHCA shows that teriparatide continues to have a beneficial effect on BMD in postmenopausal osteoporosis to 24 months.

The application also relied on 2 studies submitted to TGA previously.

B3D-US-GHBZ and B3D-MC-GHAC were included in previous Australian submissions. The clinical evaluator noted that for use > 18 months, the efficacy data from these studies were favourable.

Safety

The evaluator summarises safety/adverse effects in the CER. The number of patient-years of exposure in GHCA was 1216, of which 232 were post 18 months. There were 8 deaths, including 2 neoplasms in the teriparatide arm in Year 2, 1 in the raloxifene arm, and 1 COPD

in Year 2 in Substudy 2. The discontinuations were described in the CER. The TEAEs reported by > 0.5% of the safety population are shown in Table 13. The clinical evaluator considers safety data from the new study do not appear to add substantially to those from the studies evaluated previously. The exposure in studies GHBZ and GHAC is tabulated in the CER. The clinical evaluator considered that a flaw in all 3 studies relied upon was lack of formal long-term follow-up, after the end of the study treatment.

The clinical evaluator states that in the present application, no new human trial data have been provided which could alleviate the specific safety concern of the potential risk of osteosarcoma, the reason for the current limitation in lifetime exposure to Forteo. The clinical evaluator notes that 5 reports of osteosarcoma in approximately 2.1 million PY of observation are reported in the RMP by the sponsor. These were described in the pre-ADEC response to the previous submission for extension of indications, and discussed by ADEC at the 263rd meeting.

Clinical Evaluator Conclusion

The evaluator recommended approval of the application, subject to expert review of the relevant nonclinical data.

Risk Management Plan

See part *V. Pharmacovigilance Findings*. The evaluator states that for the potential risk of osteosarcoma, the sponsor proposes routine pharmacovigilance, warning information in the PI, targeted surveillance, and the post approval case-series surveillance study GHBX. The aim of GHBX is to identify approximately 40% of newly diagnosed cases of osteosarcoma among patients ≥ 40 years, starting 90 days after first marketed use of teriparatide, and to determine incident osteosarcoma cases and any cases where there is a history of teriparatide treatment or other sarcoma risk factors. No cases have been identified in patients who have taken teriparatide.

The US Risk Evaluation and Mitigation Strategy (REMS) is focussed on alerting and warning healthcare providers about the potential risk of osteosarcoma, highlighting the maximum two year duration, and advising prescribers of a voluntary patient register to monitor for this risk, using a Dear Healthcare Provider Letter (DHCP) letter and an additional direct mail letter mailed once a year for two years to all prescribers who newly prescribe teriparatide.

Teriparatide was reviewed by The Adverse Drug Reactions Advisory Committee (ADRAC) in June 2007. In May 2009 it was listed on the Pharmaceutical Benefits Scheme (PBS); 947 items were dispensed to December 2009. Adverse events reported in Australia are summarised in the RMP evaluation report.

It was considered that a pharmacovigilance system capable of exploring the potential association between teriparatide and osteosarcoma required a patient register. The evaluator noted that the Australian requirement for patient consent to the osteosarcoma warning is not included in the RMP. The OMSM evaluator found the proposed RMP for the potential risk of osteosarcoma was not acceptable, and identified issues about a patient register.

Additional Safety Information

PSUR 13, covering May-November 2009, was submitted to the TGA on 21 January 2010. There were no reports of osteosarcoma. Unlisted serious events included 2 cases of pancreatitis and there were 2 reports of lumbar spine stenosis.

In the European Summary of Product Characteristics (SPC) and the US label, patients with skeletal malignancies are excluded from treatment with teriparatide.

Sponsor Response to Reports.

The protocol for study B3D-EW-GHCA was supplied by the sponsor after receiving the CER. In answer to the clinical evaluator's request for the source of the proposed paragraph under Clinical Trials, it was described as a combination of data from Substudy 1 and Substudy 2 of GHCA. Such analyses were presented in the clinical part of the Australian submission, see Table 21 below.

Table 21.

Table GHCA.14.2.1.1.5. Bone Mineral Density (g/cm²)
Lumbar Spine
(PRIMARY ENDPOINT)
Summary Statistics of changes between 18 and 24 Months - by country
(substudy two plus teriparatide - teriparatide patients of substudy one)
B3D-EW-GHCA

		Austria	Belgium	Denmark	France	Germany	Greece	Iceland	Portugal	Spain	United Kingdom	All Teriparatide Patients
18 to 24 Months	N	14	27	27	39	180	15	7	19	43	98	469
	Mean	0.015	0.007	0.013	0.007	0.009	0.010	0.009	0.020	0.009	0.016	0.011
	CI	-0.002 to 0.033	-0.002 to 0.016	0.006 to 0.020	-0.003 to 0.016	0.005 to 0.012	-0.002 to 0.022	-0.002 to 0.019	0.005 to 0.035	-0.003 to 0.021	0.011 to 0.021	0.009 to 0.013
	Median	0.013	0.011	0.015	0.005	0.011	0.018	0.009	0.011	0.007	0.016	0.013
	Std. Dev.	0.030	0.022	0.017	0.030	0.024	0.021	0.012	0.032	0.038	0.025	0.026
	Std. Err.	0.008	0.004	0.003	0.005	0.002	0.005	0.004	0.007	0.006	0.002	0.001
	Min	-0.064	-0.053	-0.026	-0.070	-0.064	-0.024	-0.006	-0.028	-0.053	-0.044	-0.070
	Max	0.056	0.041	0.038	0.078	0.063	0.049	0.025	0.083	0.160	0.089	0.160
	p-value	0.083	0.106	<0.001	0.176	<0.001	0.086	0.101	0.013	0.127	<0.001	<0.001

1. p-value: one-sample t-test testing the hypothesis of no change
2. Missing data are excluded

The sponsor responded to issues raised by the RMP evaluator with details of the voluntary US patient registry, an addendum to study GHBX that followed the US approval of the use of Forteo in glucocorticoid induced osteoporosis. The registry enrols patients aged ≥ 18 years who receive Forteo for a 5 year period from July 2009, and will follow patients annually through US cancer registries for 12 years. In the US there would be sufficient patients to have an appropriate sample size, and the linkage is with participating US state cancer registries. The sponsor also noted that GHBX commenced in 2002 in the US and was expanded to include Scandinavia in 2003, and in the US has been extended to 2018. Spontaneous report data and an update on GHBX are summarised in each PSUR.

Risk-Benefit Analysis

- The evaluation of GHCA (see CER) did not explicitly support the claims of statistical and clinically significant BMD increase between 18 and 24 months contained in the letter of Application, namely that the BMD increase doubled between 18 and 24 months in post-menopausal women who were treated with antiresorptives before starting teriparatide. The sponsor's clinical overview, prepared for the European application to extend the treatment duration, refers only to data from GHCA Substudy 2. The Australian letter of application appears to refer to the published paper, provided after the CER was received, which reported results of a post-hoc subgroup analysis of Substudy 1 and Substudy 2 patients who completed 2 years of study (4).

Sponsor's (Eli Lilly) comment:

In the initial submission to the TGA, a statement was made regarding changes in BMD that applies only to the total hip BMD changes observed in GHCA Substudy 2 (where the increase in total hip BMD through 18 months was 1.3% and through 24 months was 2.6%).

In the initial submission to the European Medicines Agency (EMA), Eli Lilly included only the results from GHCA Substudy 2 rather than pooled data from Substudies 1 and 2. The Substudy 2 results were based on a predefined secondary objective of the study protocol. However, during the review, the EMA requested that Eli Lilly present the whole cohort of women treated with teriparatide for 24 months in Study GHCA to produce a more accurate estimate of the BMD gains observed between 18 and 24 months in postmenopausal women. Eli Lilly complied, providing the results of a post-hoc analysis that combined data from Substudies 1 and 2[5]*. The results from the combined analysis are included in both the European and Canadian labels. The changes in BMD at all skeletal sites are quite similar in Substudy 2 compared with the pooled data set. Thus, Eli Lilly proposes that the pooled analysis be considered for inclusion in Australian labelling to be consistent with the European and Canadian labels. However, if this post hoc analysis is unacceptable to the TGA, Eli Lilly proposes to include the results from only Substudy 2 in the Australian labelling. The two options are shown below:*

> *<u>Post-hoc analysis of GHCA Substudies 1 and 2:</u> In an open-label study, 503 postmenopausal women with severe osteoporosis and a fragility fracture within the previous 3 years (83% had received previous osteoporosis therapy) were treated with Forteo for up to 24 months. At 24 months, the mean increase from baseline in lumbar spine, total hip, and femoral neck BMD was 10.5%, 2.6%, and 3.9%, respectively. The mean increase in BMD from 18 to 24 months was 1.4%, 1.2%, and 1.6% at the lumbar spine, total hip, and femoral neck, respectively.*
>
> *<u>Analysis of only GHCA Substudy 2:</u> In an open-label study, 234 postmenopausal women with severe osteoporosis and a fragility fracture within the previous 3 years (99.1% had received previous osteoporosis therapy) were treated with Forteo for up to 24 months. At 24 months, the mean increase from baseline in lumbar spine, total hip, and femoral neck BMD was 9.2%, 2.6%, and 4.8%, respectively. The mean increase in BMD from 18 to 24 months was 1.2%, 1.3%, and 2.1% at the lumbar spine, total hip, and femoral neck, respectively).*

- There is no suggestion from the B3D-EW-GHCA data of improvement in fracture rates with increased duration of treatment.

<u>Sponsor's comment:</u>

Eli Lilly agrees. The change over time in the incidence rate of clinical (vertebral and nonvertebral) fragility fractures was a secondary objective in Study GHCA. The trial was not powered to analyse fracture risk reduction.

Our study was neither designed nor adequately powered to assess effects on fractures. As expected, the total number of patients with clinical fragility fractures during the study was small (n=70, 8.1%), and the between-group comparisons of the second, randomized treatment year do not allow any conclusions to be drawn with respect to the relative antifracture efficacy of the three treatment sequences. The gradual decrease in fracture incidence over time observed in Substudy 1 patients (Table 22) is an interesting descriptive finding that would require further larger study populations for confirmation.

[5] Obermayer-Pietsch BM, *et al. J Bone Miner Res* 2008; 23[10]:1591–1600.

Table 22. *Clinical Fragility Fractures in the Total Randomized Cohort and in Treatment Arm 1 (Continuous Teriparatide for 2 Years) by 6-Month Periods (Eastell et al. JBMR 2009).*

Time interval	*Total number of patients*	*Number (%) of patients with fracture*	*Total number of fractures*	*Fractures per 1000 patient-years*
Total randomized cohort (substudy 1)				
0–6 mo	632	20 (3.2)	24	82.9
7–12 mo	531	14 (2.6)	17	64.5
13–18 mo	501	8 (1.6)	8*	32.4
19–24 mo	475	7 (1.5)	7*	30.6
Treatment arm 1 (continuous teriparatide for 2 yr)				
0–6 mo	304	8 (2.6)	10	65.8
7–12 mo	303	7 (2.3)	9	59.4
13–18 mo	303	7 (2.3)	7	46.6
19–24 mo	287	5 (1.7)	5	36.1

* These numbers include two fragility fractures that occurred in the raloxifene group and one fracture that occurred in the no active treatment group.

For the 503 patients who received continuous treatment with teriparatide during 24 months, the number of patients with incident fractures was small (n=40; 9.1%), although it should be noted that in Study GHCA, 99.0% of patients had ≥1 fragility fracture during the 3 years prior to screening and, therefore, were at increased risk for sustaining additional fragility fractures.

Table 23. *Number of Patients with Clinical Fragility Fractures in the Total Continuous Teriparatide Group by 6-Month Intervals Descriptive Statistics Enrolled and Treated Population.*

Type of fracture Time interval	Total Patients	Number (%) of patients with clinical fragility fracture	Number of clinical fragility fractures	
			Per given interval	Per 10000 patient years
All Fractures				
0 to 6 months	503	15 (3.0%)	20	795
7 to 12 months	501	12 (2.4%)	14	559
13 to 18 months	501	10 (2.0%)	11	442
19 to 24 months	478	14 (2.9%)	17	734
0 to 24 months	503	46 (9.1%)	62	631
Vertebral Fractures				
0 to 6 months	503	5 (1.0%)	8	318
7 to 12 months	501	2 (0.4%)	2	80
13 to 18 months	501	1 (0.2%)	1	40
19 to 24 months	478	3 (0.6%)	3	130
0 to 24 months	503	11 (2.2%)	14	143
Non-vertebral Fractures				
0 to 6 months	503	10 (2.0%)	12	477
7 to 12 months	501	10 (2.0%)	12	479
13 to 18 months	501	9 (1.8%)	10	402
19 to 24 months	478	11 (2.3%)	14	605
0 to 24 months	503	37 (7.4%)	48	489

- The protocol for study B3D-EW-GHCA supplied by the sponsor in response to the CER shows that an intent-to-treat analysis was to be used, and all randomised patients in Substudy 1 entering treatment period 2 with at least one post-randomisation observation were to be included in the primary efficacy analysis. Patients in Substudy 2 were to be analysed separately with respect to BMD. Clinical Trials descriptions in the PI should refer to the primary outcome analysis as defined in the protocol. An exploratory subgroup analysis is not appropriate for regulatory purposes.

Sponsor's comment:

The explanation for the post-hoc analysis combining GHCA Substudies 1 and 2 is presented in response to the first dot point above.

- The post-marketing clinical safety profile has not changed. However the sponsor does not propose to use the same risk minimisation strategies in Australia as in the US where the duration of treatment has always been 24 months. For example, a patient register is not considered feasible and the Australian PI does not contain the same warnings regarding treating patients with skeletal malignancies.

Sponsor's comment:

The patient registry study is part of the ongoing evaluation of the possible risk of osteosarcoma in patients who receive treatment with Forteo. The registry study is only being conducted in the US, given the need for a sufficient number of patients to have a scientifically appropriate sample size and the necessary linkage to US cancer registries. It should be noted that participation in the registry is voluntary.

With respect to the warning regarding patients with skeletal malignancies, we wish to clarify that the current Australian PI does contain precautionary information in line with the US PI statement on skeletal malignancies. The sentence reads: "Patients with skeletal malignancies or bone metastases should also be excluded from treatment with Forteo."

Furthermore, because an informed patient consent is required in Australia, patients receiving Forteo treatment will continue to be apprised of the potential risk of osteosarcoma along with the duration of treatment. This informed consent has been in place since the initial approval of Forteo in 2003.

Delegate's Questions for ACPM

There are small improvements in BMD from 18 to 24 months, as shown in the CER. Although BMD change, at the lumbar spine, at 24 months versus baseline, was the prespecified efficacy outcome, any focus on the period 18-24 months was not. Is this post-hoc analysis of sufficient import to require specific mention in the PI?

Are the current risk minimisation strategies adequate for Australia if the maximum treatment duration is increased to 24 months?

Delegate's Proposed action

On balance, the risk has not changed and there is some evidence of increased BMD from 18 to 24 months. The PI should state that the newly evaluated study supports efficacy over 24 months of continuous use.

The Delegate proposes to approve the application to extend the duration of treatment to 24 months provided risk minimisation strategies are appropriate for Australia. This overview was submitted to the ACPM for advice.

Advisory Committee Considerations

The ACPM (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents recommended rejection of the submission from Eli Lilly Australia Pty Ltd to extend the approved maximal duration of lifetime use of teriparatide (Forteo) injection (multi dose) 250 µg in 2.4 mL cartridge from 18 to 24 months.

In making this recommendation, the ACPM advised that a positive risk benefit profile was not sufficiently demonstrated for the extended duration of therapy.

In addition, the ACPM noted that the evidence for the clinical endpoints of increased BMD at 24 months of treatment have not been correlated with a reduced risk of fractures versus the increment in BMD that is obtainable at 18 months.

To address these data deficiencies, a thorough and larger nonclinical carcinogenicity study, in an appropriate primate species, should be submitted. Clinical efficacy and safety data, from long term studies of greater size, are also required to address these safety concerns and the lack of evidence of incremental clinical benefit arising from longer term treatment.

The applicant is encouraged to undertake additional nonclinical and clinical studies and to submit long term clinical safety data, when available. Further information on subsequent treatment options would be desirable.

Outcome

The sponsor withdrew the application to extend the treatment duration from 18 months to 24 months before a decision was made.

Attachment 1 – Product Information

FORTEO®

Teriparatide (rbe) Injection

WARNING

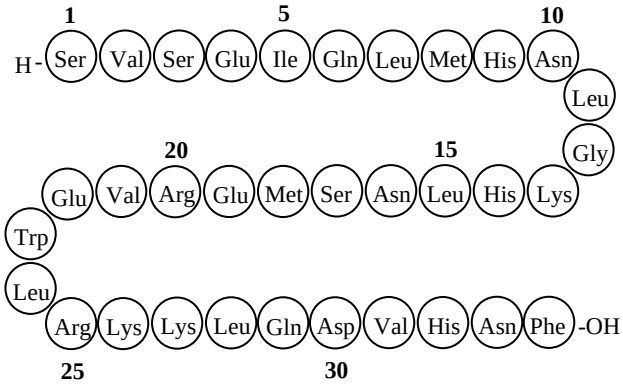
In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-µg dose and occurred after treatment durations ranging from 6 to 24 months. Effects were dependent on dose and duration of treatment, but a no-effect dose was not determined. The relevance of the rat osteosarcoma findings to humans has not yet been established (see PRECAUTIONS, Carcinogenesis and ADVERSE REACTIONS – Spontaneous data).

NAME OF THE MEDICINE

FORTEO®, teriparatide (rbe) injection [recombinant human parathyroid hormone(1-34), rhPTH(1-34)] is the first in a new class of bone formation agents. Once-daily administration of FORTEO activates osteoblasts and stimulates the formation of new bone.

Teriparatide has a molecular weight of 4117.8 daltons and is identical in sequence to the 34 N-terminal amino acids of the natural human parathyroid hormone.

The amino acid sequence of teriparatide is shown below:



FORTEO is manufactured by Eli Lilly and Company using recombinant DNA technology. The CAS number for teriparatide is 52232-67-4.

DESCRIPTION

FORTEO is supplied as a sterile, colourless, clear, isotonic solution for subcutaneous injection. Each mL of solution contains 250 µg teriparatide, 410 µg acetic acid – glacial, 100 µg sodium acetate, 45.4 mg mannitol, 3.0 mg meta-cresol and water for injections. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust product pH.

FORTEO is supplied in a 2.4 mL cartridge contained in a prefilled, disposable delivery device (pen). The pen delivers 20 µg per dose and contains dosing for 28 treatment days.

Patients must be educated to use the proper injection techniques. Please refer to the User Manual for instructions for the pen.

PHARMACOLOGY

Osteoporosis is characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and an increase in the risk of vertebral and non-vertebral fractures. The diagnosis of osteoporosis may be confirmed by the finding of low bone mass or the presence or history of osteoporotic fracture. While non-vertebral fractures are usually clinically apparent, vertebral fractures also may be manifested by back pain, height loss or kyphosis.

Mechanism of action

Endogenous 84-amino-acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. Physiological actions of PTH include regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. The biological actions of PTH and teriparatide are mediated through binding to specific PTH cell surface receptors. Teriparatide is the active fragment (1-34) of endogenous human PTH, manufactured using recombinant DNA technology. Teriparatide binds to these receptors with similar affinity as PTH, and has the same actions in bone and kidney as PTH. Like endogenous PTH, teriparatide is not expected to accumulate in bone or other tissues.

Pharmacodynamic effects

The skeletal effects of teriparatide depend upon the pattern of systemic exposure. Once-daily administration of teriparatide increases apposition of new bone on trabecular and cortical (endosteal and periosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. In contrast, continuous excess of endogenous PTH, as occurs in hyperparathyroidism, may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation. In monkey studies, teriparatide improved trabecular microarchitecture and increased bone mass and strength by stimulating new bone formation in both cancellous and cortical bone.

In humans, teriparatide affects calcium and phosphorus metabolism in a pattern consistent with the known actions of endogenous PTH.

Human Pharmacokinetics

Absorption: After subcutaneous (SC) injection, teriparatide has an absolute bioavailability of 95% (95% CI 0.824 – 1.07). Absorption and elimination are rapid. The half-life of teriparatide in serum is 5 minutes when administered by intravenous injection and approximately 1 hour when administered by subcutaneous injection. The longer half-life following subcutaneous administration reflects the time required for absorption from the injection site.

Following a subcutaneous injection of a 20-μg dose, peak molar concentrations of teriparatide briefly exceed the upper limit of normal for endogenous PTH [65 pg/mL (7.0 pM)] by 4- to 5-fold for about 30 minutes and then decline to non-quantifiable

concentrations within 3 hours. The mean systemic exposure (endogenous PTH and teriparatide) over 24 hours does not exceed the upper limit of normal and is below the levels found in patients with mild hyperparathyroidism.

Distribution: Volume of distribution is approximately 1.7 L/kg. Between-subject variability in systemic clearance and volume of distribution is 25% to 50%.

Metabolism and Excretion: Teriparatide is eliminated through hepatic and extra-hepatic clearance (approximately 62 L/hr in women and 94 L/hr in men). No metabolism or excretion studies have been performed with teriparatide. However, the mechanisms of metabolism and elimination of PTH(1-34) and intact PTH have been extensively described. Metabolism of parathyroid hormone is believed to occur predominantly in liver and kidney.

Patient characteristics

Geriatrics:
No differences in teriparatide pharmacokinetics were detected with regard to age (range 31 to 85 years). Dosage adjustment based on age is not required.

Gender:
Systemic exposure to teriparatide is approximately 20% to 30% lower in men than in women. There were, however, no gender differences with respect to safety, tolerability or pharmacodynamic responses. Dosage adjustment based on gender is not required.

Renal Impairment:
No clinically relevant pharmacokinetic or safety differences were identified in patients with mild, moderate or severe chronic renal impairment administered a single dose of teriparatide. Dosage adjustment, based on renal function, is not required.

However, patients with renal impairment had reduced calcaemic and calciuric responses to teriparatide. Long-term safety and efficacy have not been evaluated in patients with serum creatinine concentrations >177 μmol/L.

Heart Failure:
No clinically relevant pharmacokinetic, blood pressure, pulse rate or other safety differences were identified in patients with stable heart failure (New York Heart Association Class I to III and additional evidence of cardiac dysfunction) administered two 20 μg doses of teriparatide. Dosage adjustment based on the presence of mild or moderate heart failure is not required. There are no data from patients with severe heart failure.

Hepatic impairment:
Safety and efficacy have not been evaluated in patients with hepatic impairment. Preclinical data indicate that hepatic Kupffer cells are the primary site of metabolism for teriparatide. It is unlikely that disease states in which hepatocyte function is impaired will have a clinically significant effect on systemic exposure to teriparatide (see PRECAUTIONS).

CLINICAL TRIALS

The clinical program included treatment studies in women and men with osteoporosis. Postmenopausal women were treated for up to 24 months to evaluate effects on vertebral fractures. Men were treated for up to 14 months to evaluate the effect on BMD. Of the women and men who participated in the teriparatide treatment studies, 1930 have been systematically observed for 18 months in a post treatment follow-up study.

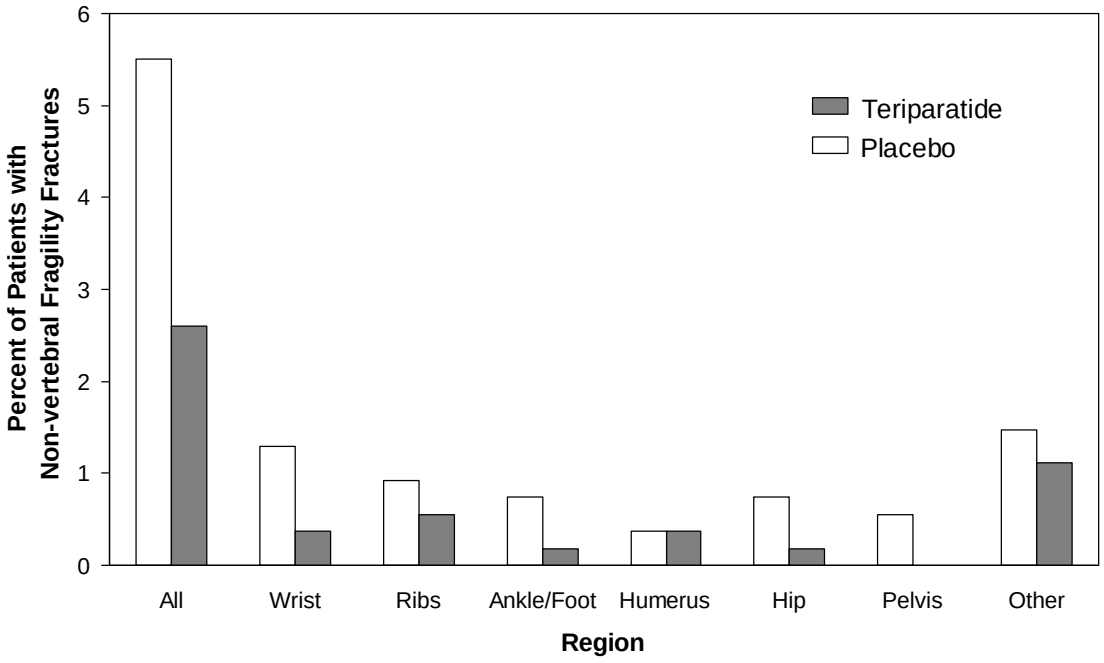
Treatment of postmenopausal women with osteoporosis

The pivotal study included 1637 postmenopausal women (mean age 69.5 years). At baseline, ninety percent of the patients had one or more vertebral fractures. All patients received 1000 mg of calcium per day and at least 400 IU of vitamin D per day. Results from a treatment period of up to 24 months (median 19 months), with teriparatide, demonstrate significant anti-fracture efficacy.

Effect on Vertebral fractures: Teriparatide, relative to placebo, given for a median of 19 months, significantly reduced the risk and severity of new vertebral fractures in postmenopausal women with osteoporosis. The relative risk for the incidence of 1 or more new vertebral fractures was reduced by 65% and multiple fractures by 77% with teriparatide treatment *(Table 1 includes data on absolute risk reduction).* Eleven women would need to be treated with teriparatide for a median of 19 months to prevent one or more new vertebral fractures.

Effect on Non-vertebral fractures: Teriparatide significantly reduced (by 53%) the overall incidence of non-vertebral fragility fractures including wrist, ribs, ankle, humerus, hip, foot, pelvis and others (see Figure 1).

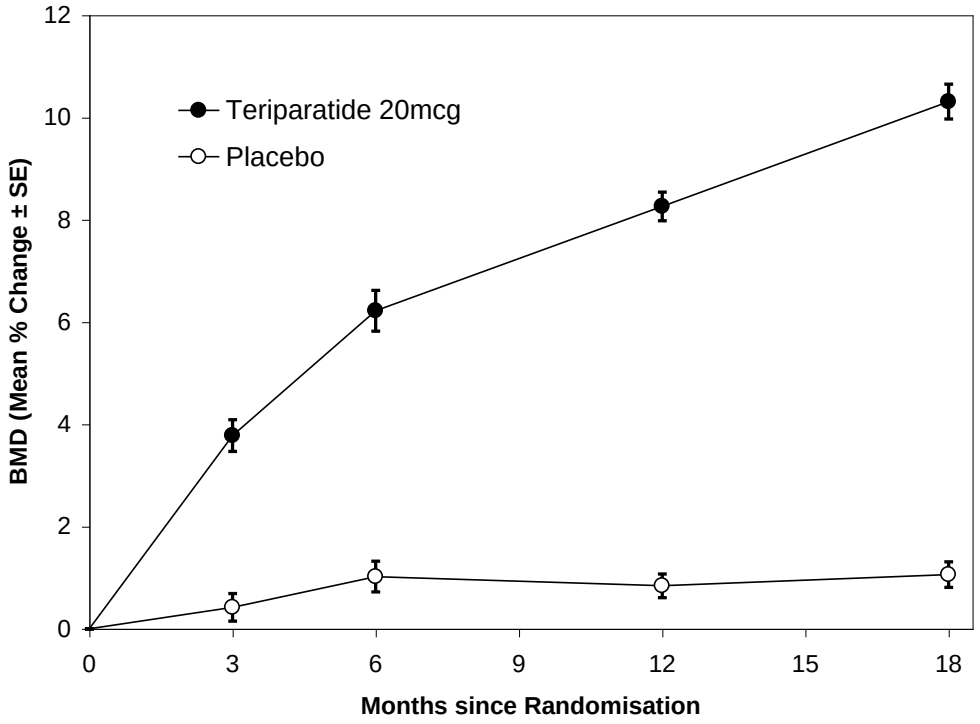
Figure 1. Effects of Teriparatide on new non-vertebral fragility fractures in postmenopausal women with osteoporosis



Effect on BMD: Teriparatide rapidly increased lumbar spine BMD. Significant increases were seen as early as 3 months and continued throughout the treatment period, as shown in Figure 2. After a median treatment period of 19 months, BMD had increased 9% and 4% in the lumbar spine and total hip, respectively, compared with placebo ($p<0.001$). Teriparatide was effective regardless of age, baseline rate of bone turnover and baseline BMD.

Figure 2. Time Course of Change in Lumbar Spine BMD in Postmenopausal Women Treated with Teriparatide 20-µg vs. Placebo

($p<0.001$ for Teriparatide compared with placebo at each post-baseline time point)



Effect on Back Pain: Teriparatide significantly reduced the incidence and severity of back pain. In women with postmenopausal osteoporosis, there was a significant ($p = 0.017$) 26% reduction in the spontaneous reports of new or worsened back pain compared to placebo.

Effects on Height Loss: For the 86 postmenopausal women who experienced vertebral fractures, those treated with teriparatide had significantly less height loss when compared to placebo ($p = 0.001$).

Bone Histology: The effects of teriparatide on bone histology were evaluated in iliac crest biopsies of 61 postmenopausal women treated for up to 24 months with placebo or teriparatide 20 µg or 40 µg per day. The increases in BMD and resistance to fracture achieved with teriparatide occurred without evidence of cellular toxicity or adverse effects on bone architecture or mineralisation. The findings in human bone samples paralleled those seen in preclinical primate studies.

Table 1

Vertebral Fracture Incidence in Postmenopausal Women:			
	Placebo (N=448) (%)	Teriparatide (N=444) (%)	Abs. Risk Reduction (%)
New fracture (≥1)	14.3	5.0 [a]	9.3
Multiple fractures (≥2)	4.9	1.1 [a]	3.8
Moderate or severe fracture (≥1)	9.4	0.9 [a]	8.5

[a] p≤0.001 compared with placebo

Post-treatment Fracture Efficacy: Following treatment with teriparatide, 1262 postmenopausal women from the pivotal trial enrolled in a post-treatment follow-up study. After 18 months, approximately 50% of the women in each former treatment group had begun an approved osteoporosis therapy (not including teriparatide) at the discretion of their physician. All women were offered 1000 mg of calcium per day and at least 400 IU of vitamin D per day.

During a median of 18 months following discontinuation of teriparatide treatment, there was a significant 40% reduction in relative risk for new vertebral fractures in women previously treated with teriparatide, compared to placebo. (The relative risk reduction was similar for women with and without osteoporosis treatment, 41% and 37%, respectively). During the same observation period, there was a 42% risk reduction for nonvertebral fragility fractures in women previously treated with teriparatide, compared with placebo.

Data from this study demonstrate that regardless of the follow-up treatment options, fracture risk was reduced for women previously treated with teriparatide.

Male Osteoporosis

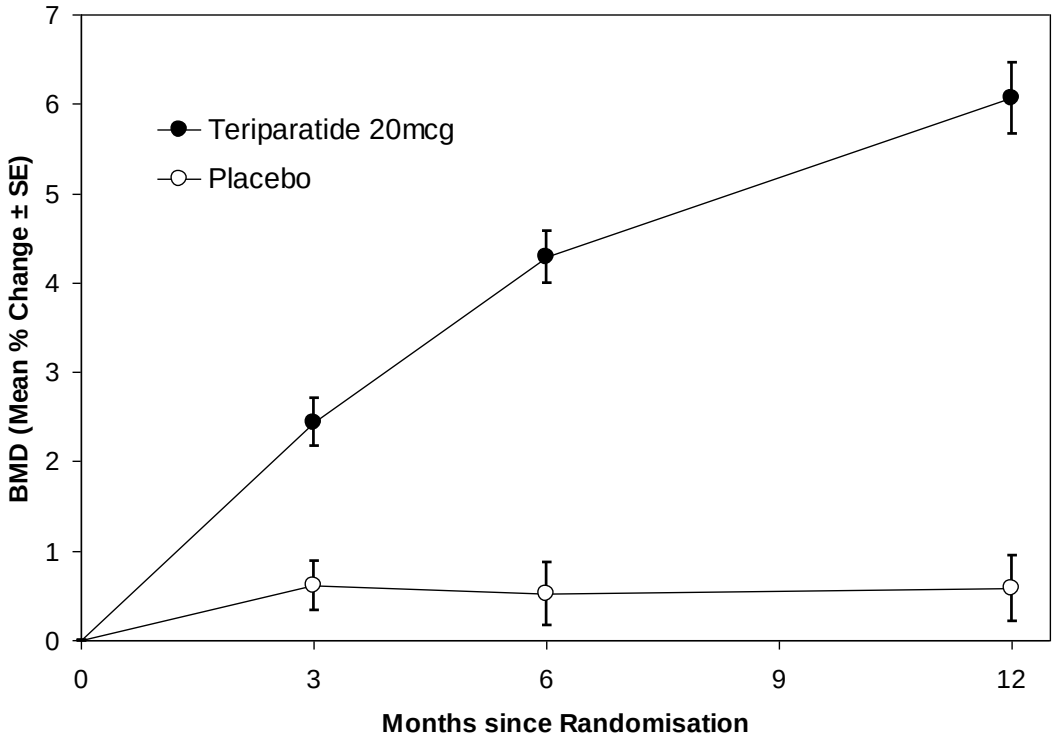
The efficacy of teriparatide was demonstrated in a double-blind, placebo-controlled clinical study in 437 men with either hypogonadal or idiopathic osteoporosis. All patients received 1000 mg of calcium per day and at least 400 IU of vitamin D per day and were treated for up to 14 months.

In this study, teriparatide rapidly increased lumbar spine BMD in men, with significant increases as early as 3 months. This increase continued throughout the treatment period, as shown in Figure 3. After a median treatment period of 11 months, BMD in the spine had (on average) increased by 5% and in the hip by 1%, compared to placebo. Increases in BMD were similar in men with hypogonadal or idiopathic osteoporosis. Teriparatide was effective regardless of age, baseline rate of bone turnover and baseline BMD.

All male patients presenting with osteoporosis should be checked for primary or secondary hypogonadism, investigated and treated appropriately as a prerequisite.

Figure 3. Time Course of Change in Lumbar Spine BMD in Osteoporotic Men Treated with Teriparatide 20-µg or Placebo

(p<0.001 for Teriparatide compared with placebo at each post-baseline time point)



Glucocorticoid-induced osteoporosis

The efficacy of FORTEO in men and women (N=428) receiving sustained systemic glucocorticoid therapy (equivalent to 5 mg or greater of prednisone for at least 3 months) was demonstrated in a 36 month (18-month primary phase plus 18-month continuation phase), randomised, double-blind, comparator-controlled study (alendronate 10 mg/day). Twenty-eight percent of patients had one or more radiographic vertebral fractures at baseline. All patients were offered 1000 mg calcium per day and 800 IU vitamin D per day. This study included postmenopausal women (N=277), premenopausal women (N=67), and men (N=83). At baseline, the postmenopausal women had a mean age of 61 years, mean lumbar spine BMD T score (number of standard deviations above or below the mean in healthy young women) of −2.7, median prednisone equivalent dose of 7.5 mg/day, and 34% had one or more radiographic vertebral fractures; premenopausal women had a mean age of 37 years, mean lumbar spine BMD T score of −2.5, median prednisone equivalent dose of 10 mg/day, and 9% had one or more radiographic vertebral fractures; and men had a mean age of 57 years, mean lumbar spine BMD T score of −2.2, median prednisone equivalent dose of 10 mg/day, and 24% had one or more radiographic vertebral fractures.

Effects on Vertebral and Non-vertebral BMD: The primary objective was the change in lumbar spine BMD from baseline to the 18-month endpoint (last observation carried forward) in men and women combined. Sixty-nine percent of patients completed the 18-month primary phase. At the 18 month endpoint (men and women combined), FORTEO increased lumbar spine BMD (7.2%) significantly more than alendronate (3.4%) (p<0.001).

Figure 4 shows the time course of mean percent change from baseline in lumbar spine BMD through 36 months for men and women combined. There was a significant difference between groups at all measured timepoints and endpoint. At 36 months (figure 4) the mean percent change from baseline in lumbar spine BMD was 11.0% in the FORTEO group versus 5.3% in the alendronate group, a difference of 5.7% (p<.001).

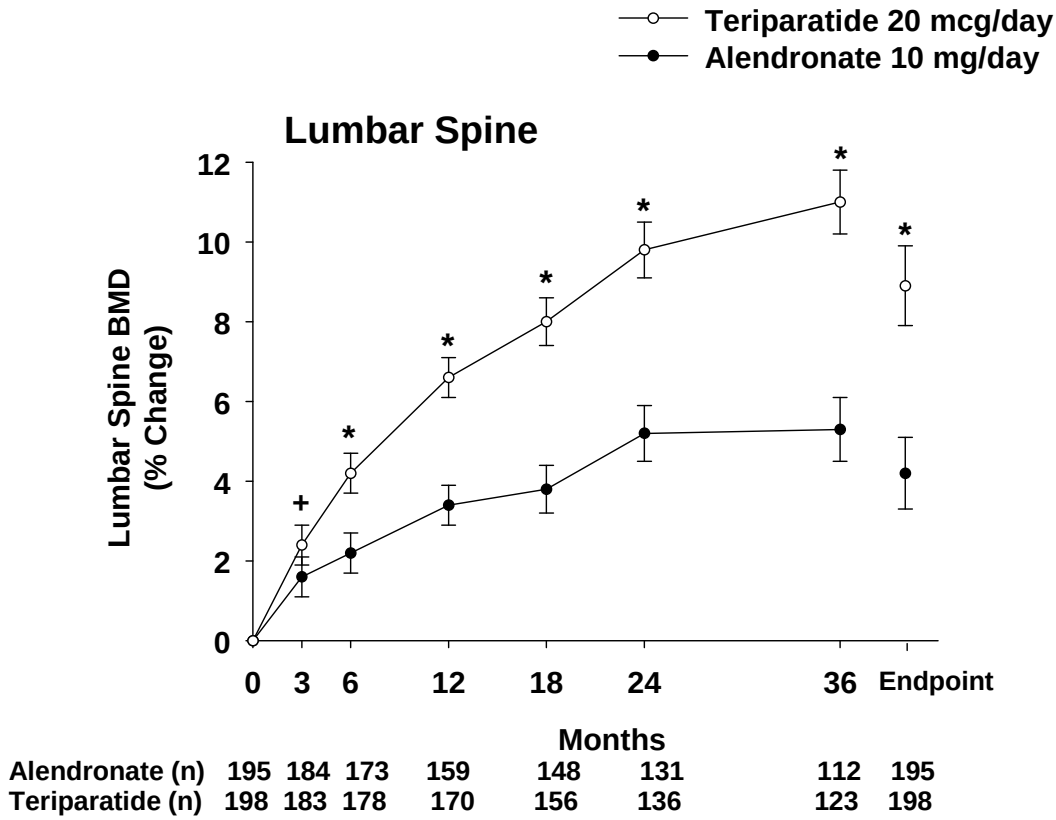


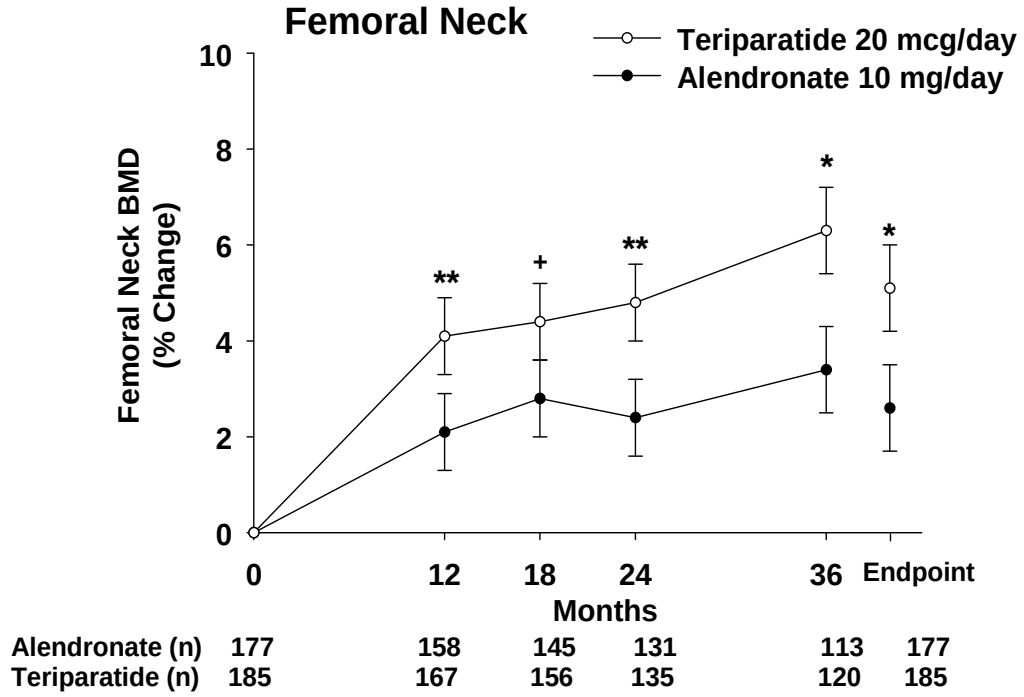
Figure 4 Percent Change in Lumbar Spine BMD (LS Mean ± SE) in Men and Women with Glucocorticoid-Induced Osteoporosis

Table 2 presents the mean percent change in lumbar spine BMD in the women only subgroup.

Table 2 Mean Percent Change from Baseline in Lumbar Spine BMD in Women with Glucocorticoid-induced Osteoporosis

Timepoint	FORTEO	alendronate	
(% change from baseline at)	LS Mean ± Std Error	LS Mean ± Std Error	p-Value
Endpoint	8.6 ± 0.9	4.0 ± 0.9	< 0.001
Month 36	10.3 ± 0.8	4.9 ± 0.8	< 0.001
Month 24	9.3 ± 0.7	5.0 ± 0.7	< 0.001
Month 18	7.8 ± 0.6	3.4 ± 0.6	< 0.001
Month 12	6.5 ± 0.5	3.0 ± 0.5	< 0.001
Month 6	4.0 ± 0.5	2.0 ± 0.5	< 0.001
Month 3	2.3 ± 0.5	1.6 ± 0.5	0.118

In men and women combined, changes from baseline in femoral neck BMD were significantly greater in the FORTEO compared with the alendronate group at all timepoints and at endpoint (figure 5). The mean percent change in femoral neck BMD from baseline to endpoint was 5.1% in the FORTEO group compared with 2.6% in the alendronate group, (p<.001).



*p<.001, **p<.01, +p<.05: teriparatide vs. alendronate

Figure 5 Mean Percent Change from Baseline in Femoral Neck BMD (LS Mean ± SE) in Men and Women with Glucocorticoid-Induced Osteoporosis

In men and women combined, changes from baseline in total hip BMD were significantly greater in the FORTEO group compared with the alendroante group at all timepoints and at endpoint (figure 6). The mean increase in total hip BMD from baseline to endpoint was 4.4% in the FORTEO group versus 2.2% in the alendronate group (p<.001).

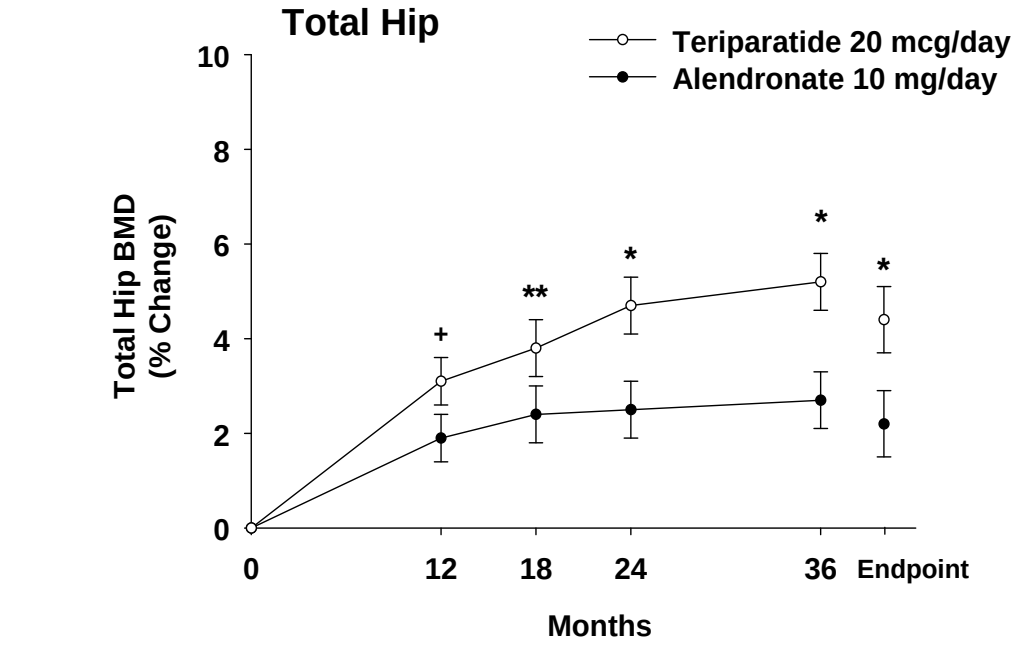


Figure 6 Mean Percent Change from Baseline in Toal Hip BMD (LS Mean ± SE) in Men and Women with Glucocorticoid-Induced Osteoporosis

In premenopausal women, the increase in BMD from baseline to endpoint at 36 months was significantly greater in the FORTEO group compared with the alendronate group at the lumbar spine (4.6% versus −0.9%; p=0.017) and total hip (4.8% versus 1.5%; p=0.026). However, no significant effect on fracture rates was demonstrated in premenopausal women.

Analysis of vertebral and non-vertebral fractures: At 18 months, analysis of spinal X-rays from 165 alendronate patients and 171 FORTEO patients showed that 10 patients in the alendronate group (6.1%) had experienced a new vertebral fracture compared with 1 patient in the FORTEO group (0.6%). In addition, 9 patients in the alendronate group (4.2%) had experienced a nonvertebral fracture compared with 12 patients in the FORTEO group (5.6%).

Table 3 below summarises the incident fractures at 36 months in men and women combined.

	PTH20 n/N (%)	ALN10 n/N (%)	P-value
≥1 Vertebral and/or nonvertebral fracture [a]	19/214 (8.9%)	27/214 (12.6%)	0.212
≥1 Vertebral fracture	3/173 (1.7%)	13/169 (7.7%)	0.007
≥1 Clinical Vertebral fracture [b]	0	4/169 (2.4%)	0.037
≥1 Nonvertebral fracture	16/214 (7.5%)	15/214 (7.0%)	0.843

Note: For vertebral fractures only those patients with baseline and postbaseline spinal radiographs were included in the analysis.

[a] One alendronate patient experienced both a vertebral fracture and a nonvertebral fracture.

[b] Clinical vertebral fracture was defined as a radiographically confirmed fracture that was associated with symptoms such as back pain.

Effects on Markers of Bone Turnover: In patients with glucocorticoid-induced osteoporosis, daily administration of FORTEO stimulated new bone formation as shown by increases from baseline in the serum concentration of biochemical markers of bone formation including bone-specific alkaline phosphatase (BSAP), procollagen I carboxy-terminal propeptide (PICP), and amino-terminal propeptide of type I collagen (PINP) (*see* Table 4). FORTEO also stimulated bone resorption as shown by increases from baseline in serum concentrations of C- terminal telopeptide of type I collagen (CTX). Alendronate 10 mg/day induced decreases from baseline in the serum concentration of BSAP, PICP, PINP and CTX (*see* Table 4). The effects of FORTEO on bone turnover markers in patients with glucocorticoid-induced osteoporosis were qualitatively similar to the effects in postmenopausal women with osteoporosis not taking glucocorticoids.

Table 4. Median Percent Changes[a, b] from Baseline in Bone Biomarkers in Patients with Glucocorticoid-Induced Osteoporosis

	PINP µcg/L		BSAP µcg/L		PICP µcg/L		CTX pmol/L	
Treatment Duration	FORTEO	ALN	FORTEO	ALN	FORTEO	ALN	FORTEO	ALN
1 month	65	-18	19	-5	36	-12	12	-46
6 month	67	-50	31	-20	0	-27	45	-56
18 month	36	-48	16	-21	-11	-28	9	-64
36 month	38	-40	22	-18	-11	-26	5	-55

[a] The median percent changes in FORTEO-treated patients were significantly different ($p<0.01$) compared with alendronate-treated (ALN) patients for each biomarker at all time points.

[b] Values represent median percent changes with n=44 to 99 among the 4 biomarkers at the different time points.

INDICATIONS

FORTEO is indicated for the treatment of osteoporosis in postmenopausal women and the treatment of primary osteoporosis in men when other agents are considered unsuitable and when there is a high risk of fractures.

FORTEO is indicated for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at high risk for fracture.

CONTRAINDICATIONS

FORTEO should not be given to patients with hypersensitivity to teriparatide or to any of its excipients.

Paget's disease of the bone.

PRECAUTIONS

To minimise the potential risk of osteosarcoma (seen in the life-time rat studies), the maximum lifetime exposure to FORTEO for an individual patient is 18 months. FORTEO should be prescribed to patients with a full explanation and their informed consent on the lifetime duration of 18 months treatment.

Information for patients – For safe and effective use of FORTEO, the physician should inform the patient on the following:
General – Patients will need to read the Consumer Medicine Information leaflet and pen User Manual before starting therapy with FORTEO and re-read them each time the prescription is renewed.
Osteosarcoma in rats – Patients should be made aware that FORTEO caused osteosarcoma in rats and that the clinical relevance of these findings is unknown.
Consent form – **Use of FORTEO is restricted to 18 months lifetime duration.** Informed consent will need to be obtained from each patient before starting therapy to ensure that the 18-month lifetime limit is understood. FORTEO should be prescribed to patients with a full explanation and their informed consent on the lifetime duration of 18 months treatment.

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumour) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-μg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, teriparatide should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risk. Teriparatide should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with unexplained elevations of alkaline phosphatase, open epiphyses or prior radiation therapy involving the skeleton) (see PRECAUTIONS, Carcinogenesis).

Children
FORTEO has not been studied in paediatric populations. FORTEO should not be used in paediatric patients or young adults with open epiphyses.

Hypercalcaemia
FORTEO has not been studied in patients with preexisting hypercalcaemia. These patients should be excluded from treatment with FORTEO because of the possibility of exacerbating hypercalcaemia. In normocalcaemic patients, slight and transient elevations of serum calcium concentrations have been observed following teriparatide injection. Serum calcium concentrations reach a maximum between 4 and 6 hours and return to baseline by 16 to 24 hours after each dose of teriparatide. Routine calcium monitoring during therapy is not required.

Bone Disorders other than Osteoporosis
Patients with metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of the bone) (see CONTRAINDICATIONS) and those with otherwise unexplained elevations of alkaline phosphatase, should generally be excluded from treatment with FORTEO. Patients with skeletal malignancies or bone metastases should also be excluded from treatment with FORTEO.

Urolithiasis
FORTEO has not been studied in patients with active urolithiasis. FORTEO should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

Hypotension
In short-term clinical studies with FORTEO, isolated episodes of transient orthostatic hypotension were observed. Typically, an event began within 4 hours of dosing and spontaneously resolved within a few minutes to a few hours. When transient orthostatic hypotension occurred, it happened within the first several doses, was relieved by placing subjects in a reclining position and did not preclude continued treatment.

Laboratory Tests
Serum Calcium – FORTEO transiently increases serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. By 16 hours post-dose, serum calcium generally has returned to, or near, baseline. These effects should be kept in mind because serum calcium concentrations observed within 16 hours after a dose may reflect the pharmacologic effect of teriparatide. Persistent hypercalcaemia was not observed in clinical trials with FORTEO. If persistent hypercalcaemia is detected, treatment with FORTEO should be discontinued pending further evaluation of the cause of hypercalcaemia. Patients known to have an underlying hypercalcaemic disorder, such as primary hyperparathyroidism, should not be treated with FORTEO (see PRECAUTIONS - Hypercalcaemia).

Teriparatide has not been studied in non-ambulant patients, thus monitoring of serum calcium may be appropriate when a previously ambulant patient is confined to bed.

Urinary Calcium - FORTEO may cause small increases in urinary calcium excretion. However, in the clinical trials, the incidence of hypercalciuria in FORTEO patients did not differ from that in the placebo-treated patients.

Renal function - No significant adverse renal effects were observed in long-term clinical studies. Assessments included creatinine clearance, measurements of blood urea nitrogen (BUN), creatinine, and electrolytes in serum, urine specific gravity and pH and

examination of urine sediment. Long-term evaluation of patients with severe renal insufficiency, patients undergoing acute or chronic dialysis, or patients who have a functioning renal transplant has not been performed.

Serum Uric Acid - FORTEO may cause small increases in serum uric acid concentrations. In clinical trials, 2.8 % of FORTEO patients had an elevated serum uric acid concentration compared to 0.7% of placebo patients. However, the hyperuricaemia did not result in an increase in gout, urolithiasis or arthralgia.

Anti-PTH antibody formation – Anti-PTH antibodies, while apparently clinically irrelevant and only occurring in a small number of treated individuals, have the potential to interfere with serum PTH estimations.

PTH receptors – As is generally known, PTH/PTH-related peptide receptors are on multiple tissues. There was no increase in non-osseous tumours in the two 24-month (lifetime) rat studies and in the two 18-month primate studies. There was no increase in incidence of any specific cancer or cancer overall in 2074 patients in long-term clinical studies or in follow-up studies conducted in a number of these patients for a median of 18 months after teriparatide treatment. Osteosarcoma is a very rare cancer that occurs in 4 out of every million people each year. None of the patients in the clinical trials or post-treatment follow-up developed osteosarcomas.

Other – New or worsened spinal stenosis was observed in 2 (0.3%) patients who received placebo, 3 (0.4%) patients who received teriparatide 20 µg, and 3 (0.4%) patients who received teriparatide 40 µg. One patient who received teriparatide 20 µg had worsening conductive hearing loss. One patient who received teriparatide 40 µg required removal of a bone spur and another patient receiving teriparatide 40 µg required surgical removal of a hyperostosis.

Carcinogenicity, mutagenicity and impairment of fertility studies

Carcinogenesis:
Two carcinogenicity bioassays were conducted in rats. In the first study, male and female rats were given daily subcutaneous teriparatide injections of 5, 30, or 75 µg/kg/day for 24 months from 2 months of age. These doses resulted in systemic exposures that were, respectively, 3, 20, and 60 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 µg (based on AUC comparison). Teriparatide treatment resulted in a marked dose-related increase in the incidence of osteosarcoma, a rare malignant bone tumour, in both male and female rats. Osteosarcomas were observed at all doses, occurred after 17 to 20 months of treatment, and reached an incidence of 38% to 52% in the high-dose groups. Teriparatide also caused increased incidences of osteoblastoma and osteoma in both sexes. No osteosarcomas, osteoblastomas or osteomas were observed in untreated control rats. The bone tumours in rats occurred in association with a large increase in bone mass and focal osteoblast hyperplasia.

The second 2-year study was carried out in order to determine the effect of treatment duration and animal age on the development of bone tumours. Female rats were treated for different periods between 2 and 26 months of age with subcutaneous doses of 5 and 30 µg/kg (equivalent to 3 and 20 times the human exposure at the 20 µg dose, based on AUC). The study showed that the occurrence of osteosarcoma, osteoblastoma and osteoma was dependent upon dose and duration of exposure. Bone tumours were observed when

immature 2-month old rats were treated with 30 µg/kg/day for 6 or 24 months. Bone tumours were also observed when mature 6-month old rats were treated with 30 µg/kg/day for 6 or 20 months. Tumours were not detected when mature 6-month old rats were treated with 5 µg/kg/day for 6 or 20 months. The results did not demonstrate a difference in susceptibility to bone tumour formation, associated with teriparatide treatment, between mature and immature rats. The relevance of these rat findings to humans is uncertain.

***Mutagenesis*:**
Teriparatide was not genotoxic in assays for gene mutations (Ames test and mouse lymphoma assay *in vitro*) and chromosomal damage (Chinese hamster ovary cells *in vitro* and the mouse micronucleus test *in vivo*).

Impairment of Fertility:
Teriparatide had no adverse effects on fertility of male or female rats at doses up to 300 µg/kg/day SC (about 120 times the human dose based on body surface area). In juvenile rats, treatment with teriparatide was associated with degeneration of the testes at doses ≥10 µg/kg/day SC (about 4 times the human dose based on body surface area). Teriparatide should not be used in paediatric patients or young adults (see also PRECAUTIONS).

Use in Pregnancy (Category B3)
In pregnant rats given subcutaneous teriparatide doses up to 1000 µg/kg/day, there were no findings. In pregnant mice given subcutaneous doses of ≥30 µg/kg/day (6 times the human dose based on body surface area) from gestation Day 6 through 15, the foetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib).

Developmental effects in a perinatal/postnatal study in pregnant rats given subcutaneous doses of teriparatide from gestation Day 6 through postpartum Day 20 included mild growth retardation in female offspring at doses of 225 µg/kg/day (approximately 95 times the human dose based on BSA) and in male offspring at 1000 µg/kg/day (420 times the human dose based on BSA). There was also reduced motor activity in both male and female offspring at 1000 µg/kg/day. There were no developmental or reproductive effects in rats at a dose of 30 µg/kg (12 times the human dose based on BSA).

The effects of teriparatide on the human foetus have not been studied. FORTEO should not be used in pregnant women. Women of childbearing potential should use effective methods of contraception during use of Forteo. If pregnancy occurs Forteo should be discontinued.

Use in lactation
It is not known whether teriparatide is excreted in human milk. Forteo should not be administered to women who are breast-feeding their children.

Interactions with other drugs
No clinically relevant drug interactions have been identified in studies administering teriparatide 40 µg (twice the recommended dose of FORTEO).

Hydrochlorothiazide: In a study of healthy subjects, the co-administration of 25-mg hydrochlorothiazide with teriparatide did not affect the serum calcium response to

teriparatide 40 μg. The 24-hour urine excretion of calcium was reduced by a clinically insignificant amount (15%).

Frusemide: In a study of healthy subjects and patients with mild, moderate and severe renal insufficiency (creatinine clearance 13 to 72 mL/min), co-administration of intravenous frusemide (20 to 100 mg) with teriparatide 40 μg resulted in small, clinically insignificant increases in serum calcium (2%) and in 24-hour urine calcium (37%).

Calcium channel antagonists: In a study of women with hypertension treated with an extended release preparation of either diltiazem, nifedipine or felodipine, the blood pressure observed after injection of teriparatide 40 μg was similar when administered alone or in combination with the long-acting calcium channel antagonists.

Atenolol: In a study of women with hypertension treated with atenolol, the blood pressure observed after injection of teriparatide 40 μg was similar when administered alone or in combination with atenolol.

Digoxin: In a study of 15 healthy people administered digoxin daily to steady state, a single FORTEO dose did not alter the effect of digoxin on the systolic time interval (from electrocardiographic Q-wave onset to aortic valve closure, a measure of digoxin's calcium-mediated cardiac effect). However, sporadic case reports have suggested that hypercalcaemia may predispose patients to digitalis toxicity. Because FORTEO transiently increases serum calcium, FORTEO should be used with caution in patients taking digoxin.

Raloxifene: In a study of healthy postmenopausal women, the co-administration of raloxifene with teriparatide 40 μg did not alter the effects of teriparatide on serum or urine calcium or on clinical adverse events.

Anti-coagulants: While this has not been studied, co-administration of anti-coagulants would not be expected to alter the effects of teriparatide. Patients co-administering anti-coagulants and teriparatide need to be advised to take appropriate precautions against the formation of haematomas at the injection sites.

ADVERSE EFFECTS

The safety of teriparatide has been evaluated in 21 clinical trials in over 2800 women and men. Four long-term, Phase 3 clinical trials included one large placebo-controlled, double-blind multinational trial with 1637 postmenopausal women, one placebo-controlled, double-blind multinational trial with 437 men and two active-controlled trials including 393 postmenopausal women. Teriparatide doses ranged from 5 to 100 μg/day in short-term trials and 20 to 40 μg/day in the long-term trials. A total of 1970 of the patients studied received teriparatide, including 738 patients at 20 μg/day and 1107 patients at 40 μg/day. In the long-term clinical trials, 1137 patients were exposed to teriparatide for greater than 1 year (500 at 20 μg/day and 637 at 40 μg/day). The maximum exposure duration to teriparatide was 2 years. Adverse events associated with FORTEO were usually mild and generally did not require discontinuation of therapy.

In the two Phase 3, placebo-controlled clinical trials in men and postmenopausal women, early discontinuation due to an adverse event occurred in 5.6% of patients on placebo and

7.1% of patients on FORTEO. Adverse events considered to be related to FORTEO therapy were nausea and leg cramps.
Table 5 lists adverse events occurring in the Phase 3, placebo-controlled clinical trials in postmenopausal women and in men at a frequency ≥2.0% in the FORTEO groups and in more FORTEO-treated patients than in placebo-treated patients. Adverse events are shown without attributing causality.

Table 5. Adverse events that occurred in placebo-controlled osteoporosis clinical trials at a frequency of at least 2% in the FORTEO-treated patients (20 µg/day) and in more FORTEO-treated patients than placebo-treated patients Adverse events are shown without attributing causality.

	FORTEO	Placebo
	N=691	N=691
Event Classification	**(%)**	**(%)**
BODY AS A WHOLE		
Pain	21.3	20.5
Headache	7.5	7.4
Asthenia	8.7	6.8
Neck Pain	3.0	2.7
CARDIOVASCULAR		
Hypertension	7.1	6.8
Angina Pectoris	2.5	1.6
Syncope	2.6	1.4
DIGESTIVE SYSTEM		
Nausea	8.5	6.7
Constipation	5.4	4.5
Diarrhoea	5.1	4.6
Dyspepsia	5.2	4.1
Vomiting	3.0	2.3
Gastrointestinal Disorder	2.3	2.0
Tooth Disorder	2.0	1.3
MUSCULOSKELETAL		
Arthralgia	10.1	8.4
Leg Cramps	2.6	1.3
NERVOUS SYSTEM		
Dizziness	8.0	5.4
Depression	4.1	2.7
Insomnia	4.3	3.6
Vertigo	3.8	2.7
RESPIRATORY SYSTEM		
Rhinitis	9.6	8.8
Cough Increased	6.4	5.5
Pharyngitis	5.5	4.8
Dyspnoea	3.6	2.6
Pneumonia	3.9	3.3
SKIN AND APPENDAGES		
Rash	4.9	4.5
Sweating	2.2	1.7
LABORATORY VALUES		
Hyperuricaemia	2.8	0.7

NOTE: The incidence of hypertension, syncope, dyspepsia, rhinitis and pharyngitis in patients treated with teriparatide 40 µg/day (twice the recommended dose) was lower than the incidence in placebo-treated patients.

Immunogenicity: In a large clinical trial, antibodies that cross-reacted with teriparatide were detected in 2.8% of female patients receiving FORTEO. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There were no hypersensitivity reactions, allergic reactions, effects on serum calcium or effects on BMD response, which indicates that the antibodies did not cause any clinically significant adverse effects.

Spontaneous data: The following table of adverse reactions is based on post-marketing spontaneous reports since market introduction. The following convention has been used for the classification of the adverse reactions: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000. <1/1000), very rare (<1/10,000).

System Organ Class	**Adverse Reactions**
General Disorders and Administration Site Conditions	Common: Mild and transient injection site events, including pain, swelling, erythema, localised bruising, pruritus and minor bleeding at injection site. Rare: Possible allergic events soon after injection: acute dyspnoea, oro/facial oedema, generalised urticaria, chest pain.
Metabolism and Nutrition Disorders	Uncommon: Hypercalcaemia greater than 2.76 mmol/L (11mg/dL). Rare: hypercalcaemia greater than 3.25 mmol/L (13 mg/dL).
Musculoskeletal and Connective Tissue and Bone Disorders	Common: Muscle spasms, such as leg or back, sometimes shortly after the first dose. Uncommon: myalgia, arthralgia. Very Rare: Serious back spasms

There has been a report of metastatic osteosarcoma with subsequent fatal outcome in a 72 year old woman with osteoporosis and low back pain who had received teriparatide for 14 months prior to presentation. Causality cannot be established on the basis of this single case and a surveillance program continues. Osteosarcoma occurs at a rate of approximately 4 in one million per year (1 in 250,000 per year) in the general population over 60 years old and at the same rate in women over the age of 70 years. At present it is not known if humans treated with FORTEO have an increased risk of osteosarcoma.

DOSAGE AND ADMINISTRATION

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

Based on clinical experience, treatment with FORTEO is recommended for a lifetime duration of 18 months treatment (for post-treatment efficacy**,** see PHARMACOLOGY, Clinical Trials). FORTEO should be prescribed to patients with a full explanation and their informed consent on the lifetime duration of 18 months treatment.

Calcium and vitamin D supplements are advised in patients with a low dietary intake of these nutrients.

Use in Males – Primary or secondary hypogonadism should first be excluded and, if relevant, be treated (see PHARMACOLOGY, Clinical Trials).

Following cessation of FORTEO therapy, patients may be continued on other osteoporosis therapies.

Patients must be educated to use the proper injection techniques. Please refer to the User Manual for instructions for the pen.

FORTEO is a clear and colourless liquid. Do not use if solid particles appear or if the solution is cloudy or coloured. The FORTEO pen should not be used after the stated expiration date.

Data are not available on the safety or efficacy of intravenous or intramuscular injection of FORTEO.

OVERDOSAGE

No cases of overdose were reported during clinical trials. Teriparatide has been safely administered in single doses of up to 100 μg. In a clinical study, doses of 60 μg/day for 6 weeks were safely tolerated. The effects of overdose that might be expected include delayed hypercalcaemia and risk of orthostatic hypotension. Nausea, vomiting, dizziness and headache might also occur.

In postmarketing spontaneous reports, there have been cases of medication error in which the entire contents (up to 800 μg) of the teriparatide pen have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. In some cases, no adverse events occurred as a result of the overdose. No fatalities associated with overdose have been reported.

In single-dose rodent studies using subcutaneous injection of teriparatide, no mortality was seen in rats given doses of 1000 μg/kg (526 times the human dose based on body surface area) or in mice given 10,000 μg/kg (2635 times the human dose).

Overdose management: There is no specific antidote for teriparatide. Treatment of suspected overdose should include discontinuation of teriparatide, monitoring of serum calcium, and implementation of appropriate supportive measures, such as hydration.

PRESENTATION AND STORAGE CONDITIONS

FORTEO is supplied as a sterile, colourless, clear, isotonic solution for subcutaneous injection. Each mL contains teriparatide 250 μg. FORTEO is supplied in a 2.4 mL cartridge contained in a prefilled delivery device (pen) that delivers 20 μg per dose and contains dosing for 28 treatment days.

FORTEO is available in packs of one 250 μg/mL pen.

Each FORTEO pen is stable for 2 years when stored under refrigeration between 2° to 8°C. The dose may be delivered immediately following removal from the refrigerator. Do not allow FORTEO to freeze. Do not use FORTEO if it has been frozen. During the use period, minimise the time the pen remains out of the refrigerator.

Each FORTEO pen can be used for up to 28 days after the first injection. After the 28-day use period, discard the FORTEO pen, even if the pen still contains some unused solution.

The FORTEO pen is for use in a single patient only.

NAME AND ADDRESS OF THE SPONSOR

Eli Lilly Australia Pty Limited
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POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

TGA Approval:

27 May 2009

Therapeutic Goods Administration

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