For the use of a Registered Medical Practitioner or a Hospital only.

MEGAPTH-G

Teriparatide solution for injection

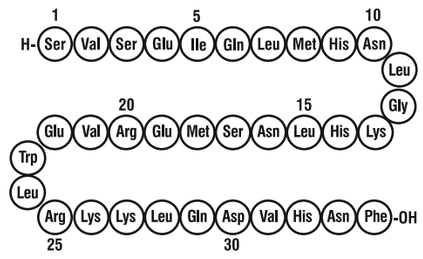
20 µg / 80 µl

Composition:
Each ml of Teriparatide (r- Human Parathyroid Hormone) (1-34)
Injection contains:
Teriparatide ..... 250 mcg
Glacial acetic acid Ph. Eur. ..... 0.410 mg
Sodium acetate (trihydrate) Ph. Eur. ..... 0.166 mg
Mannitol Ph. Eur. ..... 45.400 mg
Metacresol Ph. Eur. (preservative) ..... 3.000 mg
Water for injections Ph. Eur. ..... q.s
Hydrochloric acid solution Ph. Eur. (for pH adjustment) ..... q.s
Sodium hydroxide solution Ph. Eur. (for pH adjustment) ..... q.s

Description:
MEGAPTH-G, Teriparatide injection is a recombinant human parathyroid hormone analog (PTH 1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.
MEGAPTH-G is a biosimilar medicinal product to reference product, Forteo 250 UG Solution For Injection.
Teriparatide, rh PTH (1-34), is derived from Escherichia coli, using recombinant DNA technology.

The product is iso-osmotic with pH 3.8 to 4.5.

Molecular formula, weight:
Teriparatide: $C_{181}H_{291}N_{55}O_{51}S_2$.
Teriparatide has a molecular weight of 4117.8 daltons and its amino acid sequence is shown below:



PHARMACEUTICAL FORM:
Solution for injection

Clear, colourless solution.

Clinical Pharmacology:
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 high-affinity cell-surface receptors. Teriparatide and the 34 N-terminal amino acids of PTH bind to these receptors with the same affinity and have the same physiological actions on bone and kidney. Teriparatide is not expected to accumulate in bone or other tissues.
The skeletal effects of Teriparatide depend upon the pattern of systemic exposure. Once-daily administration of Teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. 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, the anabolic effects of Teriparatide manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. By 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.

Pharmacodynamic properties:
Effects on mineral metabolism
Teriparatide affects calcium and phosphorus metabolism in a pattern consistent with the known actions of endogenous PTH (eg: increases serum calcium and decreases serum phosphorus).
Serum calcium concentration
When Teriparatide 20 mcg is administered once daily, the serum calcium concentration increases transiently, beginning approximately 2 hours after dosing and reaching a maximum concentration between 4 and 6 hours (median increase, 0.4 mg/dL). The serum calcium concentration begins to decline approximately 6 hours after dosing and returns to baseline by 16 to 24 hours after each dose.
In a clinical study of postmenopausal women with osteoporosis, the median peak serum calcium concentration measured 4 to 6 hours after dosing with Teriparatide 20 mcg was 2.42 mmol/L (9.68 mg/dL) at 12 months. The peak serum calcium remained below 2.76 mmol/L (11.0 mg/dL) in > 99% of women at each visit. Sustained hypercalcemia was not observed.
In the study, 11.1% of women treated with Teriparatide had at least 1 serum calcium value above the upper limit of normal [2.64 mmol/L (10.6 mg/dL)] compared with 1.5% of women treated with placebo. The percentage of women treated with Teriparatide whose serum calcium was above the upper limit of normal on consecutive 4- to 6-hour post-dose measurements was 3.0% compared with 0.2% of women treated with placebo. In these women, calcium supplements and/or Teriparatide doses were reduced. The timing of these dose reductions was at the discretion of the investigator. Teriparatide dose adjustments were made at varying intervals after the first observation of increased serum calcium (median 21 weeks). During these intervals, there was no evidence of progressive increases in serum calcium.
In a clinical study of men with either primary or hypogonadal osteoporosis, the effects on serum calcium were similar to those observed in postmenopausal women. The median peak serum calcium concentration measured 4 to 6 hours after dosing with Teriparatide was 2.35 mmol/L (9.44 mg/dL) at 12 months. The peak serum calcium remained below 2.76 mmol/L (11.0 mg/dL) in 98% of men at each visit. Sustained hypercalcemia was not observed.
In this study, 6.0% of men treated with Teriparatide daily had at least 1 serum calcium value above the upper limit of normal [2.64 mmol/L (10.6 mg/dL)] compared with none of the men treated with placebo. The percentage of men treated with Teriparatide whose serum calcium was above the upper limit of normal on consecutive measurements was 1.3% (2 men) compared with none of the men treated with placebo. Although calcium supplements and/or Teriparatide doses could have been reduced in these men, only calcium supplementation was reduced
In a clinical study of women previously treated for 18 to 39 months with raloxifene (n=26) or alendronate (n=33), mean serum calcium >12 hours after Teriparatide injection was increased by 0.09 to 0.14 mmol/L (0.36 to 0.56 mg/dL), after 1 to 6 months of Teriparatide treatment compared with baseline. Of the women pretreated with raloxifene, 3 (11.5%) had a serum calcium >2.76 mmol/L (11.0 mg/dL), and of those pretreated with alendronate, 3 (9.1%) had a serum calcium >2.76 mmol/L (11.0 mg/dL). The highest serum calcium reported was 3.12 mmol/L (12.5 mg/dL). None of the women had symptoms of hypercalcemia. There were no placebo controls in this study.
In the study of patients with glucocorticoid-induced osteoporosis, the effects of Teriparatide on serum calcium were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.
Urinary calcium excretion
In a clinical study of postmenopausal women with osteoporosis who received 1000 mg of supplemental calcium and at least 400 IU of vitamin D, daily Teriparatide increased urinary calcium excretion. The median urinary excretion of calcium was 4.8 mmol/day (190 mg/day) at 6 months and 4.2 mmol/day (170 mg/day) at 12 months. These levels were 0.76 mmol/day (30 mg/day) and 0.3 mmol/day (12 mg/day) higher, respectively, than in women treated with placebo. The incidence of hypercalciuria (>7.5 mmol Ca/day or 300 mg/day) was similar in the women treated with Teriparatide or placebo.
In a clinical study of men with either primary or hypogonadal osteoporosis who received 1000 mg of supplemental calcium and at least 400 IU of vitamin D, daily Teriparatide had inconsistent effects on urinary calcium excretion. The median urinary excretion of calcium was 5.6 mmol/day (220 mg/day) at 1 month and 5.3 mmol/day (210 mg/day) at 6 months. These levels were 0.5 mmol/day (20 mg/day) higher and 0.2 mmol/day (8.0 mg/day) lower, respectively, than in men treated with placebo. The incidence of hypercalciuria (> 7.5 mmol Ca/day or 300 mg/day) was similar in the men treated with Teriparatide or placebo.
Phosphorus and vitamin D
In single-dose studies, Teriparatide produced transient phosphaturia and mild transient reductions in serum phosphorus concentration. However, hypophosphatemia (< 0.74 mmol/L or 2.4 mg/dL) was not observed in clinical trials with MEGAPTH-G.
In clinical trials of daily Teriparatide the median serum concentration of 1, 25-dihydroxyvitamin D was increased at 12 months by 19% in women and 14% in men, compared with baseline. In the placebo group, this concentration decreased by 2% in women and increased by 5% in men. The median serum 25-hydroxyvitamin D concentration at 12 months was decreased by 19% in women and 10% in men compared with baseline. In the placebo group, this concentration was unchanged in women and increased by 1% in men.
In the study of patients with glucocorticoid-induced osteoporosis, the effects of Teriparatide on serum phosphorus were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.
Effects on markers of bone turnover
Daily administration of Teriparatide to men and postmenopausal women with osteoporosis in clinical studies stimulated bone formation, as shown by increases in the formation markers serum bone-specific alkaline phosphatase (BSAP) and procollagen I carboxy-terminal propeptide (PICP). Data on biochemical markers of bone turnover were available for the first 12 months of treatment. Peak concentrations of PICP at 1 month of treatment were approximately 41% above baseline, followed by a decline to near-baseline values by 12 months. BSAP concentrations increased by 1 month of treatment and continued to rise more slowly from 6 through 12 months. The maximum increases of BSAP were 45% above baseline in women and 23% in men. After discontinuation of therapy, BSAP concentrations returned toward baseline. The increases in formation markers were accompanied by secondary increases in the markers of bone resorption: urinary N-telopeptide (NTX) and urinary deoxypyridinoline (DPD), consistent with the physiological coupling of bone formation and resorption in skeletal remodeling. Changes in BSAP, NTX, and DPD were lower in men than in women, possibly because of lower systemic exposure to Teriparatide in men.
In the study of patients with glucocorticoid-induced osteoporosis, the effects of Teriparatide on serum markers of bone turnover were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

Pharmacokinetics:
Absorption
Teriparatide is extensively absorbed after subcutaneous injection; the absolute bioavailability is approximately 95% based on pooled data from 20-, 40-, and 80-mcg doses. The rates of absorption and elimination are rapid. The peptide reaches peak serum concentrations about 30 minutes after subcutaneous injection of a 20-mcg dose and declines to non-quantifiable concentrations within 3 hours.
Distribution
Systemic clearance of Teriparatide(approximately 62 L/hr in women and 94 L/hr in men) exceeds the rate of normal liver plasma flow, consistent with both hepatic and extra-hepatic clearance. Volume of distribution, following intravenous injection, is approximately 0.12 L/kg. Intersubject variability in systemic clearance and volume of distribution is 25% to 50%. 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.
Metabolism and Excretion
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 in published literature. Peripheral metabolism of PTH is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys.
Pediatric
Pharmacokinetic data in pediatric patients are not available
Geriatric
No age-related differences in Teriparatide pharmacokinetics were detected (range 31 to 85 years).
Gender
Although systemic exposure to Teriparatide was approximately 20% to 30% lower in men than women, the recommended dose for both genders is 20 mcg/day.
Race
The populations included in the pharmacokinetic analyses were 98.5% Caucasian. The influence of race has not been determined.
Renal Impairment
No pharmacokinetic differences were identified in 11 patients with mild or moderate renal impairment [creatinine clearance (CrCl) 30 to 72 mL/min] administered a single dose of Teriparatide. In 5 patients with severe renal impairment (CrCl< 30 mL/min), the AUC and $T_{1/2}$ of Teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of Teriparatide was not increased. No studies have been performed in patients undergoing dialysis for chronic renal failure
Hepatic Impairment
No studies have been performed in patients with hepatic impairment. Non-specific proteolytic enzymes in the liver (possibly Kupffer cells) cleave PTH (1-34) and PTH(1-84) into fragments that are cleared from the circulation mainly by the kidney

CLINICAL STUDIES:
Treatment of Osteoporosis in Postmenopausal Women:
The safety and efficacy of once-daily Teriparatide, median exposure of 19 months, were examined in a double-blind, multi-center, placebo-controlled clinical study of 1637 postmenopausal women with osteoporosis. In this study 541 postmenopausal women were treated with 20 mcg Teriparatide subcutaneously once daily.
All women received 1000 mg of calcium and at least 400 IU of vitamin D per day. Baseline and endpoint spinal radiographs were evaluated using the semiquantitative scoring method. Ninety percent of the women in the study had 1 or more radiographically diagnosed vertebral fractures at baseline. The primary efficacy endpoint was the occurrence of new radiographically diagnosed vertebral fractures defined as changes in the height of previously undeformed vertebrae. Such fractures are not necessarily symptomatic.

Effect on fracture incidence:
New vertebral fractures
Teriparatide, when taken with calcium and vitamin D and compared with calcium and vitamin D alone, reduced the risk of 1 or more new vertebral fractures from 14.3% of women in the placebo group to 5.0% in the Teriparatide group (444 of the 541 patients treated with 20 mcg once daily of Teriparatide were included in this analysis). This difference was statistically significant (p< 0.001); the absolute reduction in risk was 9.3% and the relative reduction was 65%. Teriparatide was effective in reducing the risk for vertebral fractures regardless of age, baseline rate of bone turnover, or baseline BMD (see Table 1).

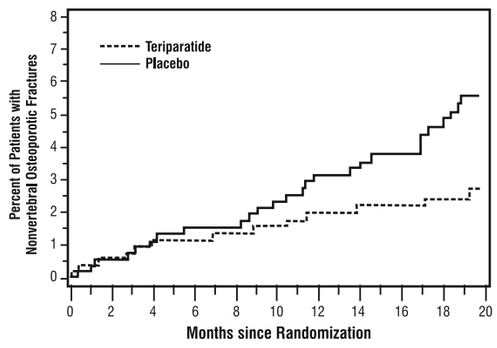
Table 1. Effect of Teriparatide on Risk of Vertebral Fractures in Postmenopausal Women with Osteoporosis

	Percent of Women With Fracture			
	Teriparatide (N=444)	**Placebo (N=448)**	**Absolute Risk Reduction (%, 95% CI)**	**Relative Risk Reduction (%, 95% CI)**
New fracture (≥1)	5.0[a]	14.3	9.3 (5.5-13.1)	65 (45-78)
1 fracture	3.8	9.4		
2 fractures	0.9	2.9		
≥ 3 fractures	0.2	2.0		

[a] P ≤ 0.001 compared with placebo

New nonvertebral osteoporotic fractures
Teriparatide significantly reduced the risk of any nonvertebral fracture from 5.5% in the placebo group to 2.6% in the Teriparatide group (p< 0.05). The absolute reduction in risk was 2.9% and the relative reduction was 53%. The incidence of new nonvertebral fractures in the Teriparatide group compared with the placebo group was ankle/foot (0.2%, 0.7%), hip (0.2%, 0.7%), humerus (0.4%, 0.4%), pelvis (0%, 0.6%), ribs (0.6%, 0.9%), wrist (0.4%, 1.3%), and other sites (1.1%, 1.5%), respectively.
The cumulative percentage of postmenopausal women with osteoporosis who sustained new nonvertebral fractures was lower in women treated with Teriparatide than in women treated with placebo (see Figure 1).

Figure 1. Cumulative percentage of postmenopausal women with osteoporosis sustaining new nonvertebral osteoporotic fractures.



Effect on bone mineral density (BMD):
Teriparatide increased lumbar spine BMD in postmenopausal women with osteoporosis. Statistically significant increases were seen at 3 months and continued throughout the treatment period. Postmenopausal women with osteoporosis who were treated with Teriparatide had statistically significant increases in BMD from baseline to endpoint at the lumbar spine, femoral neck, total hip, and total body (see Table 2).

Table 2. Mean Percent Change in BMD from Baseline to Endpoint* in Postmenopausal Women with Osteoporosis, Treated with Teriparatide or Placebo for a median of 19 months.

	Teriparatide (N=541)	**Placebo (N=544)**
Lumbar spine BMD	9.7[a]	1.1
Femoral neck BMD	2.8[b]	-0.7
Total hip BMD	2.6[b]	-1.0
Trochanter BMD	3.5[b]	-0.2
Intertrochanter BMD	2.6[b]	-1.3
Ward's triangle BMD	4.2[b]	-0.8
Total body BMD	0.6[b]	-0.5
Distal 1/3 radius BMD	-2.1	-1.3
Ultradistal radius BMD	-0.1	-1.6

* Intent-to-treat analysis, last observation carried forward; + p<0.001 compared with placebo; b p<0.05 compared with placebo.

Teriparatide treatment increased lumbar spine BMD from baseline in 96% of postmenopausal women treated. Seventy-two percent of patients treated with Teriparatide achieved at least a 5% increase in spine BMD, and 44% gained 10% or more.
Both treatment groups lost height during the trial. The mean decreases were 3.61 and 2.81 mm in the placebo and Teriparatide groups, respectively.

Bone Histology:
The effects of Teriparatide on bone histology were evaluated in iliac crest biopsies of 35 postmenopausal women treated for 12 to 24 months with calcium and vitamin D and Teriparatide. Normal mineralization was observed with no evidence of cellular toxicity. The new bone formed with Teriparatide was of normal quality (as evidenced by the absence of woven bone and marrow fibrosis).

Treatment to Increase Bone Mass in Men with Primary or Hypogonadal Osteoporosis:
The safety and efficacy of once-daily Teriparatide, median exposure of 10 months, were examined in a double-blind, multicenter placebo-controlled, clinical study of 437 men with either primary (idiopathic) or hypogonadal osteoporosis. In this study, 151 men received 20 mcg of Teriparatide given subcutaneously once daily. All men received 1000 mg of calcium and at least 400 IU of vitamin D per day. The primary efficacy endpoint was change in lumbar spine BMD.
Teriparatide increased lumbar spine BMD in men with primary or hypogonadal osteoporosis. Statistically significant increases were seen at 3 months and continued throughout the treatment period. Teriparatide was effective in increasing lumbar spine BMD regardless of age, baseline rate of bone turnover, and baseline BMD. The effects of Teriparatide at additional skeletal sites are shown in Table 3. Teriparatide treatment for a median of 10 months increased lumbar spine BMD from baseline in 94% of men treated. Fifty three percent of patients treated with Teriparatide achieved at least a 5% increase in spine BMD, and 14% gained 10% or more.

Table 3. Mean Percent Change in BMD from Baseline to Endpoint* in Men with Primary or Hypogonadal Osteoporosis, Treated with Teriparatide or Placebo for a Median of 10 Months.

	Teriparatide (n=151)	**Placebo (n=147)**
Lumbar spine BMD	5.9[a]	0.5
Femoral neck BMD	1.5[b]	0.3
Total hip BMD	1.2	0.5
Trochanter BMD	1.3	1.1
Intertrochanter BMD	1.2	0.6
Ward's triangle BMD	2.8	1.1
Total body BMD	0.4	-0.4
Distal 1/3 radius BMD	-0.5	-0.2
Ultradistal radius BMD	-0.5	-0.3

*Intent-to-treat analysis, last observation carried forward; a p<0.001 compared with placebo; b p<0.05 compared with placebo.

Treatment of Men and Women with Glucocorticoid-induced Osteoporosis:
The efficacy of Teriparatide 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 an 18-month, 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 receive 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 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.
Sixty-nine percent of patients completed the 18-month study. At endpoint, Teriparatide significantly increased lumbar spine BMD (7.2%) compared with alendronate (3.4%) (p< 0.001). Teriparatide increased BMD at the total hip (3.6%) compared with alendronate (2.2%) (p< 0.01), as well as at the femoral neck (3.7%) compared with alendronate (2.1%) (p< 0.05).
A preliminary analysis of 336 spinal X-rays showed that 10 patients in the alendronate group (6.1%) had experienced a new vertebral fracture compared with 1 patient in the Teriparatide group (0.6%). In addition, 9 patients in the alendronate group (4.2%) had experienced a nonvertebral fracture compared with 12 patients in the Teriparatide group (5.6%).
In premenopausal women, the increase in BMD from baseline to endpoint was significantly greater in the Teriparatide group compared with the alendronate group at the lumbar spine (4.2% versus −1.9%; p< 0.001) and total hip (3.8% versus 0.9%; p=0.005). However, no significant effect on fracture rates was demonstrated.

Comparability of MEGAPTH-G with FORTEO:
Study RGB1023031:
Therapeutic equivalence of MEGAPTH-G and FORTEO was demonstrated in a Japanese, multicentre, randomised, non-inferiority, active drug controlled, rater-blinded, parallel-group comparative phase III study in men and postmenopausal women with osteoporosis at high risk of fracture (a total of 250 subjects). Subjects were administered MEGAPTH-G or FORTEO (teriparatide 20 μg/80 μg solution for injection) daily via s.c. injection for 52 weeks. The percent change (mean ± standard deviation [SD]) in lumbar spine (L2-L4) BMD at Week 52, which served as the primary endpoint of the study, was 8.94% ± 6.19% in the MEGAPTH-G group and 9.65% ± 6.22% in the FORTEO group. The (adjusted) difference in the mean between the MEGAPTH-G and FORTEO groups was -0.65% (2-sided 95% CI: -2.17% to 0.87%). The 2-sided 95% CI was within the range of the pre-specified equivalence margin(± 2.8). There were no substantial differences between the MEGAPTH-G and the FORTEO groups in terms of the secondary endpoints of the absolute change in lumbar spine (L2-L4) BMD, the percent and absolute changes in lumbar spine (L I - L4) BMD, femoral neck BMD and proximal femoral BMD, the percent and absolute changes in bone metabolic marker of PI NP and the incidence of vertebral or non-vertebral fractures.
Comparative bioavailability:
The pharmacokinetic equivalence of MEGAPTH-G and FORTEO was demonstrated in a double-blind, randomised, 2-way crossover Phase I study RGB10-001 in 54 healthy female volunteers. The pharmacokinetic parameters are summarised below: Summary of statistical comparisons of plasma teriparatide pharmacokinetic parameters of MEGAPTH-G and FORTEO.

Parameters	**MEGAPTH-G**	**FORTEO**	**Geometric Mean Ratio (%)**	**94.12% confidence interval**
C^{max} (pg/mL)	83.192	90.179	92.25	85.51 to 99.52
AUC0-tlast (pg*hr/mL)	92.443	100.857	91.66	85.20 to 98.60
AUC0-inf (pg*hr/mL)	103.886	115.657	89.82	83.75 to 96.33

Immunogenicity:
Comparative immunogenicity data was generated in the Phase III comparative clinical study (Study RGB1023031) of MEGAPTH-G and FORTEO. Anti-teriparatide antibody levels were investigated at baseline and Week 52 or at the time of discontinuation to provide comparative data on the immunogenic potential of MEGAPTH-G. No subjects in the MEGAPTH-G group and 2 subjects (1.6%) in the FORTEO group were positive for anti-teriparatide antibody; both were negative for neutralising activity.

Preclinical Data:
Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenesis
Two carcinogenicity bioassays were conducted in Fischer 344 rats. In the first study, male and female rats were given daily subcutaneous teriparatide injections of 5, 30, or 75 mcg/kg/day for 24 months from 2 months of age. These doses resulted in rat systemic exposures that were 3, 20, and 60 times higher than the systemic exposure observed in humans, respectively, following a subcutaneous dose of 20 mcg (based on AUC comparison). Teriparatide treatment resulted in a marked dose-related increase in the incidence of osteosarcoma, a rare malignant bone tumor, in both male and female rats. Osteosarcomas were observed at all doses and the incidence reached 40% to 50% in the high-dose groups. Teriparatide also caused a dose-related increase in osteoblastoma and osteoma in both sexes. No osteosarcomas, osteoblastomas or osteomas were observed in untreated control rats. The bone tumors 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 tumors. Female rats were treated for different periods between 2 and 26 months of age with subcutaneous teriparatide doses of 5 and 30 mcg/kg (equivalent to 3 and 20 times the human exposure at the 20-mcg dose, respectively, based on AUC comparison). The study showed that the occurrence of osteosarcoma, osteoblastoma and osteoma was dependent upon dose and duration of teriparatide exposure. Bone tumors were observed when immature 2-month old rats were treated with 30 mcg/kg/day of teriparatide for 24 months or with 5 or 30 mcg/kg/day of teriparatide for 6 months. Bone tumors were also observed when mature 6-month old rats were treated with 30 mcg/kg/day of teriparatide for 6 or 20 months. Tumors were not detected when mature 6-month old rats were treated with 5 mcg/kg/day of teriparatide for 6 or 20 months. The results did not demonstrate a difference in susceptibility to bone tumor formation, associated with teriparatide treatment, between mature and immature rats. No bone tumors were detected in a long-term monkey study.
Mutagenesis
Teriparatide was not genotoxic in any of the following test systems: the Ames test for bacterial mutagenesis; the mouse lymphoma assay for mammalian cell mutation; the chromosomal aberration assay in Chinese hamster ovary cells, with and without metabolic activation; and the in vivo micronucleus test in mice.
Impairment of fertility
No effects on fertility were observed in male and female rats given subcutaneous teriparatide doses of 30, 100, or 300 mcg/kg/day prior to mating and in females continuing through gestation Day 6 (16 to 160 times the human dose of 20 mcg based on surface area, mcg/m^2).
Animal Toxicology
In single dose rodent studies using subcutaneous injection of teriparatide, no mortality was seen in rats given doses of 1000 mcg/kg (540 times the human dose based on surface area, mcg/m^2) or in mice given 10,000 mcg/kg (2700 times the human dose based on surface area, mcg/m^2).
In a long-term study, skeletally mature ovariectomized female monkeys (N=30 per treatment group) were given either daily subcutaneous teriparatide injections of 5 mcg/kg or vehicle. Following the 18-month treatment period, the monkeys were removed from teriparatide treatment and were observed for an additional 3 years. The 5 mcg/kg dose resulted in systemic exposures that were approximately 6 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 mcg (based on AUC comparison). Bone tumors were not detected by radiographic or histologic evaluation in any monkey in the study.

size
259 x 480 (±0,5)/40 x 70 (±1) mm

Black

INDICATIONS AND USAGE:
Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture:
Teriparatide is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture. These include women with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant of previous osteoporosis therapy, based upon physician assessment . In postmenopausal women with osteoporosis, Teriparatide increases BMD and reduces the risk of vertebral and nonvertebral fractures.

Increase of Bone Mass in Men with Primary or Hypogonadal Osteoporosis at High Risk for Fracture:
Teriparatide is indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. These include men with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant to previous osteoporosis therapy, based upon physician assessment. In men with primary or hypogonadal osteoporosis, Teriparatide increases BMD. The effects of Teriparatide on risk for fracture in men have not been studied.

Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis at High Risk for Fracture.

DOSAGE AND ADMINISTRATION:
Dosage:
The recommended dosage is 20 mcg given subcutaneously once a day.

Administration:
MEGAPTH-G should be administered as a subcutaneous injection into the thigh or abdominal wall. No data are available on the safety or efficacy of intravenous or intramuscular injection of MEGAPTH-G.
MEGAPTH-G should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur
Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. MEGAPTH-G is a clear and colorless liquid. Do not use if solid particles appear or if the solution is cloudy or colored.
Patients and caregivers who administer MEGAPTH-G should receive appropriate training and instruction on the proper use of the MEGAPTH-G delivery device from a qualified health professional.

Treatment Duration:
The safety and efficacy of Teriparatide have not been evaluated beyond 2 years of treatment.
Consequently, use of the drug for more than 2 years during a patients' lifetime is not recommended.

CONTRAINDICATIONS:
MEGAPTH-G should not be given to patients with hypersensitivity to Teriparatide or to any of its excipients.

WARNINGS & PRECAUTIONS:
Osteosarcoma:
In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. Osteosarcoma has been reported in patients treated with teriparatide in the post marketing setting; however, an increased risk of osteosarcoma has not been observed in observational studies in humans. There are limited data assessing the risk of osteosarcoma beyond 2 years of teriparatide use. Teriparatide should not be
prescribed for patients at increased baseline risk of osteosarcoma. These include:
- Paget's disease of the bone. Unexplained elevations of alkaline phosphatase may indicate Paget's disease of bone.
- Pediatric and young adult patients with open epiphyses.
- Prior external beam or implant radiation therapy involving the skeleton
- Hereditary disorders predisposing to osteosarcoma.

Bone Metastases and Skeletal Malignancies:
Patients with bone metastases or a history of skeletal malignancies should be excluded from treatment with Teriparatide.

Metabolic Bone Diseases:
Patients with metabolic bone diseases other than osteoporosis should be excluded from treatment with Teriparatide.

Hypercalcemia and Cutaneous Calcification:
Teriparatide has not been studied in patients with pre-existing hypercalcemia. These patients should be excluded from treatment with Teriparatide because of the possibility of exacerbating hypercalcemia. Patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, should not be treated with Teriparatide.
Risk of Cutaneous Calcification Including Calciphylaxis: Serious reports of calciphylaxis and worsening of previously stable cutaneous calcification have been reported in the post-marketing setting in patients taking teriparatide. Risk factors for development of calciphylaxis include underlying autoimmune disease, kidney failure, and concomitant warfarin or systemic corticosteroid use. Discontinue teriparatide in patients who develop calciphylaxis or worsening of previously stable cutaneous calcification.

Urolithiasis or Pre-existing Hypercalciuria:
In clinical trials, the frequency of urolithiasis was similar in patients treated with Teriparatide and placebo. However, Teriparatide has not been studied in patients with active urolithiasis. If active urolithiasis or pre-existing hypercalciuria are suspected, measurement of urinary calcium excretion should be considered. Teriparatide should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

Orthostatic Hypotension:
Teriparatide should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur. In short-term clinical pharmacology studies with teriparatide, transient episodes of symptomatic orthostatic hypotension were observed in 5% of patients. 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, it was relieved by placing the person in a reclining position, and it did not preclude continued treatment.

Risk of Digoxin Toxicity:
Hypercalcemia may predispose patients to digitalis toxicity because teriparatide transiently increases serum calcium. Consider the potential onset of signs and symptoms of digitalis toxicity when teriparatide is used in patients receiving digoxin [see DRUG INTERACTIONS].

DRUG INTERACTIONS:
Digoxin:
A single Teriparatide 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, because Teriparatide may transiently increase serum calcium, Teriparatide should be used with caution in patients taking digoxin.

Hydrochlorothiazide:
The coadministration of hydrochlorothiazide 25 mg with Teriparatide did not affect the serum calcium response to Teriparatide 40 mcg. The effect of coadministration of a higher dose of hydrochlorothiazide with Teriparatide on serum calcium levels has not been studied

Frusemide:
Coadministration of intravenous frusemide (20 to 100 mg) with Teriparatide 40 mcg in healthy people and patients with mild, moderate, or severe renal impairment (CrCl 13 to 72 mL/min) resulted in small increases in the serum calcium (2%) and 24-hour urine calcium (37%) responses to Teriparatide that did not appear to be clinically important.

USE IN SPECIFIC POPULATIONS:
Pregnancy:
Risk Summary:
There are no available data on Teriparatide use in pregnant women to evaluate for drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Teriparatide should not be administered to women who are pregnant.
In animal reproduction studies, Teriparatide increased skeletal deviations and variations in mouse offspring at subcutaneous doses equivalent to more than 60 times the recommended 20mcg human daily dose (based on body surface area, mcg/m^2), and produced mild growth retardation and reduced motor activity in rat offspring at subcutaneous doses equivalent to more than 120 times the human dose (see DATA).
The background risk of major birth defects and miscarriage for the indicated population is unknown. The background risk in the US general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognised pregnancies.

Data:
Animal data:
In animal reproduction studies, pregnant mice received Teriparatide during organogenesis at subcutaneous doses equivalent to 8 to 267 times the human dose (based on body surface area, mcg/m^2). At subcutaneous doses ≥ 60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received Teriparatide during organogenesis at subcutaneous doses 16 to 540 times the human dose, the fetuses showed no abnormal findings.
In a perinatal/postnatal study in pregnant rats dosed subcutaneously from organogenesis through lactation, mild growth retardation was observed in female offspring at doses ≥120 times the human dose. Mild growth retardation in male offspring and reduced motor activity in both male and female offspring were observed at maternal doses of 540 times the human dose. There were no developmental or reproductive effects in mice or rats at doses 8 or 16 times the human dose, respectively.

Nursing Mothers:
It is not known whether Teriparatide is excreted in human milk. Because of the potential for tumorigenicity shown for Teriparatide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
The safety and efficacy of Teriparatide have not been established in pediatric populations. Teriparatide should not be prescribed in patients at an increased baseline risk of osteosarcoma which include pediatric and young adult patients with open epiphyses. Therefore, Teriparatide is not indicated for use in pediatric or young adult patients with open epiphyses

Geriatric Use:
Of the patients receiving Teriparatide in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients receiving Teriparatide in the osteoporosis trial of 437 men, 39% were 65 years of age and over and 13% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment:
No studies have been performed in patients with hepatic impairment. [see CLINICAL PHARMACOLOGY].

Renal Impairment:
In 5 patients with severe renal impairment (CrCl< 30 mL/minute), the AUC and T1/2 of Teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of Teriparatide was not increased. It is unknown whether Teriparatide alters the underlying metabolic bone disease seen in chronic renal impairment [see CLINICAL PHARMACOLOGY].

ADVERSE REACTIONS:
Clinical Trials Experience:
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Men with Primary or Hypogonadal Osteoporosis and Postmenopausal Women with Osteoporosis:
The safety of Teriparatide in the treatment of osteoporosis in men and postmenopausal women was assessed in two randomized, double-blind, placebo-controlled trials of 1382 patients (21% men, 79% women) aged 28 to 86 years (mean 67 years). The median durations of the trials were 11 months for men and 19 months for women, with 691 patients exposed to Teriparatide and 691 patients to placebo. All patients received 1000 mg of calcium plus at least 400 IU of vitamin D supplementation per day.
The incidence of all cause mortality was 1% in the Teriparatide group and 1% in the placebo group. The incidence of serious adverse events was 16% in the Teriparatide group and 19% in the placebo group. Early discontinuation due to adverse events occurred in 7% in the Teriparatide group and 6% in the placebo group.
Table 4 lists adverse events from these two trials that occurred in ≥ 2% of Teriparatide-treated and more frequently than placebo-treated patients.
Table 4. Percentage of Patients with Adverse Events Reported by at Least 2% of Teriparatide-Treated Patients and in More Teriparatide-Treated Patients than Placebo-Treated Patients from the Two Principal Osteoporosis Trials in Women and Men Adverse Events are Shown Without Attribution of Causality.

	Teriparatide (N=691)	Placebo (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
Diarrhea	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
Dyspnea	3.6	2.6
Pneumonia	3.9	3.3
Skin and Appendages		
Rash	4.9	4.5
Sweating	2.2	1.7

Laboratory Findings:
Serum calcium:
Teriparatide transiently increased serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. Serum calcium measured at least 16 hours postdose was not different from pretreatment levels. In clinical trials, the frequency of at least 1 episode of transient hypercalcemia in the 4 to 6 hours after Teriparatide administration was 11% of women and 6% of men treated with Teriparatide compared to 2% of women and 0% of the men treated with placebo. The percentage of patients treated with Teriparatide whose transient hypercalcemia was verified on consecutive measurements was 3% of women and 1% of men.

Urinary calcium:
Teriparatide increased urinary calcium excretion, but the frequency of hypercalciuria in clinical trials was similar for patients treated with Teriparatide and placebo [see CLINICAL PHARMACOLOGY]

Serum uric acid:
Teriparatide increased serum uric acid concentrations. In clinical trials, 3% of Teriparatide-treated patients had serum uric acid concentrations above the upper limit of normal compared with 1% of placebo-treated patients. However, the hyperuricemia did not result in an increase in gout, arthralgia, or urolithiasis.

Renal function:
No clinically important adverse renal effects were observed in 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 functioning renal transplants has not been performed.

Men and Women with Glucocorticoid-Induced Osteoporosis:
The safety of Teriparatide in the treatment of men and women with glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥ 5mg per day prednisone or equivalent for a minimum of 3 months [see CLINICAL STUDIES]. The duration of the trial was 18 months with 214 patients exposed to Teriparatide and 214 patients exposed to an oral daily bisphosphonate (active control). All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day.
There was no increase in mortality in the Teriparatide group compared to the active control group. The incidence of serious adverse events was 21% in Teriparatide patients and 18% in active control patients, and included pneumonia (3% Teriparatide, 1% active control). Early discontinuation because of adverse events occurred in 15% of Teriparatide patients and 12% of active control patients, and included dizziness (2% Teriparatide, 0% active control).
Adverse events reported at a higher incidence in the Teriparatide group and with at least a 2% difference in Teriparatide-treated patients compared with active control-treated patients were: nausea (14%, 7%), gastritis (7%, 3%), pneumonia (6%, 3%), dyspnea (6%, 3%), insomnia (5%, 1%), anxiety (4%, 1%), and herpes zoster (3%, 1%), respectively.

Immunogenicity:
As with all peptides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other teriparatide products may be misleading.
In the clinical trial of postmenopausal women with osteoporosis, antibodies that cross reacted with teriparatide were detected in 3% of women (15/541) who received Teriparatide. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions among these patients. Antibody formation did not appear to have effects on serum calcium, or on bone mineral density (BMD) response.

Postmarketing Experience:
Adverse Reactions from Postmarketing Spontaneous Reports:
The following adverse reactions have been identified during postapproval use of Teriparatide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
- Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. [see WARNINGS and PRECAUTIONS]
- Hypercalcemia greater than 13 mg/dL has been reported with Teriparatide use.

Adverse events reported since market introduction that were temporally (but not necessarily causally) related to Teriparatide therapy include the following:
- Allergic Reactions: Anaphylactic reactions, drug hypersensitivity, angioedema, urticarial
- Investigations: Hyperuricemia
- Respiratory System: Acute dyspnea, chest pain
- Musculoskeletal: Muscle spasms of the leg or back
- Other: Injection site reactions including injection site pain, swelling and bruising; oro-facial edema

Adverse Reactions from Observational Studies to Assess Incidence of Osteosarcoma:
Two osteosarcoma surveillance safety studies (U.S. claims-based database studies) were designed to obtain data on the incidence rate of osteosarcoma among Teriparatide-treated patients. In these two studies, three and zero osteosarcoma cases were identified among 379,283 and 153,316 Teriparatide users, respectively. The study results suggest a similar risk for osteosarcoma between Teriparatide users and their comparators. However, the interpretation of the study results calls for caution owing to the limitations of the data sources which do not allow for complete measurement and control for confounders.

OVERDOSE:
Incidents of overdose in humans have not been reported in clinical trials. Teriparatide has been administered in single doses of up to 100 mcg and in repeated doses of up to 60 mcg/day for 6 weeks. The effects of overdose that might be expected include a delayed hypercalcemic effect 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 mcg) of the Terrosa delivery device (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.

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

Incompatibilities:
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

PRESENTATION:
MEGAPTH-G is available as 3 mL cartridge (siliconised Type I glass), with a plunger stopper and disc seal (aluminium and rubber liner seals), packed in a plastic tray sealed with lid foil and packed in a carton.
Each cartridge contains 2.4 mL of solution corresponding to 28 doses of 20 micrograms (per 80 microliters).

PACK SIZES:
MEGAPTH-G 1 cartridge or 3 cartridges.
MEGAPTH-G cartridge and pen pack:
1 inner carton of MEGAPTH-G cartridge (containing 1 cartridge) and 1 inner carton of Terrosa Pen (containing 1 pen).

STORAGE:
Store the cartridge in a refrigerator (2-8°C).
Do not freeze. Keep the cartridge in the outer carton in order to protect from light.
After insertion of the cartridge into the pen, the combined pen and cartridge (pre-filled pen) should be stored in a refrigerator (2-8°C). Do not freeze.
You should minimize the time of the pre-filled pen out of the refrigerator and deliver the dose shortly following removal from the refrigerator. Put back the pre-filled pen immediately in the refrigerator after use.
Do not use the pen if the cartridge is cloudy, discoloured or contains particles.
Do not store the pre-filled pen with the needle attached. Do not remove the cartridge from the pen after first use.
Keep out of reach of children.

SHELF LIFE:
"Cartridges: 2 years
After insertion of the cartridge into the pen, the pre-filled pen is to be used within 28 days of the first injection.
Chemical in-use stability supports the storage of pre-filled pen at temperatures up to 25°C for a maximum of 3 days, during the 28 days in-use period.
From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days within its shelf life at 2°C to 8°C.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING:
MEGAPTH-G solution for injection is supplied in a cartridge. MEGAPTH-G cartridges are to be used in Terrosa Pen reusable, multidose pen exclusively.
MEGAPTH-G cartridges must not be used with any other pen. The pen and injection needles are not included with this medicinal product. However, for the treatment initiation a cartridge and pen pack should be used containing one carton of MEGAPTH-G cartridge and one carton of Terrosa Pen.
Each cartridge and pen should be used by only one patient. The pen can be used with injection needles developed according to the pen needle ISO standard of a gauge between 29 G and 31 G (diameter 0.25 - 0.33 mm) and a length between 5 mm to 12.7 mm for subcutaneous injection only.
A new sterile pen needle must be used for every injection.
The expiry date on the cartridge label must always be checked before inserting the cartridge into Terrosa Pen. To avoid medication errors, make sure that the date when starting to use a new cartridge is at least 28 days before its expiry date.
Before using the pen device for the first time, the patient should read and understand the instructions on how to use the pen which are provided with the pen.
After each injection, the pen should be returned to the refrigerator. After the first use, the cartridge should not be removed from the pen during the 28 days of usage.
Each cartridge should be properly disposed of after 28 days of first use, even if it is not completely empty.
MEGAPTH-G solution for injection must not be transferred to a syringe.
Empty cartridges must not be refilled.
MEGAPTH-G should not be used if the solution is cloudy, coloured or contains visible particles.Any unused product or waste material should be disposed of in accordance with local requirements.

INTERCHANGABILITY AND AUTOMATIC SUBSTITUTION:
MEGAPTH-G has been developed as a similar biological medicinal product to FORTEO and has been shown to have a comparable quality, safety and efficacy profile to FORTEO. Therefore, interchangeability with the reference product is possible, as long as this is in agreement with the treating physician in consultation with the patient. However, automatic substitution (i.e the practice by which a different product to that specified on the prescription is dispensed to the patient without the prior informed consent of the treating physician) and active substance-based prescription cannot apply to biologicals, including biosimilars.

MEGA We care

Manufactured for:
MEGA LIFESCIENCES (AUSTRALIA) PTY LTD
Victoria 3810, Australia.

Manufactured by :
GEDEON RICHTER PLC.
Gyömrői út 19-21, 1103 Budapest, Hungary.

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