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Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196
www.cc.nih.gov/phar

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor
Karim Anton Calis, Pharm.D., M.P.H.
Clinical Specialist, Endocrinology & Women's Health, and Coordinator, Drug Information Service
kcalis@nih.gov

In This Issue

Teriparatide Injection (Forteo™): A Brief Review

Teriparatide is a recombinant human parathyroid hormone (1-34). It is composed of the first 34 amino acids of the 84-amino acid hormone, which are responsible for its primary biologic effects.[2] Teriparatide binds to the same receptors as the 34 N-terminal amino acids of human parathyroid hormone, with the same affinity and producing the same physiologic effects on the bone and kidney.[1] Teriparatide is produced by recombinant DNA technology utilizing a strain of *Escherichia coli*.[1]

Parathyroid hormone stimulates bone formation and resorption.[2,3] Parathyroid hormone and teriparatide bind to the PTH/PTHrP receptor, which then increases the number of osteoblasts, thus stimulating the production of new trabecular and cortical bone formation.[1]

Parathyroid hormone can increase or decrease bone mass, depending on the mode of administration. Continuous infusions and daily subcutaneous injections stimulate bone formation similarly. Continuous infusions, however, produce a persistent elevation of the serum parathyroid hormone concentration resulting in greater bone resorption over time. Daily injections produce only transient elevations in serum parathyroid hormone concentrations and are therefore associated with less bone resorption and more bone formation. Stimulation of osteoblastic activity exceeds that of osteoclastic activity with this dosage regimen.[1,2,3]

In 35 postmenopausal women treated with teriparatide 20 to 40 mcg/day for 12 to 24 months, normal bone mineralization was observed on iliac crest biopsy. There was no evidence in women of bone or marrow fibrosis.[1]

Teriparatide injection results in increased serum calcium levels, increased serum calcitriol concentrations, reduced serum magnesium concentrations, and increased serum uric acid levels. Within an average of 5 weeks, calcium, magnesium, and uric acid levels had returned to or approached pretreatment values.[2] Following administration of teriparatide 20 mcg subcutaneously, serum calcium rises approximately 2 hours after dosing, reaching a peak concentration after 4 to 6 hours and declining to baseline by 16 to 24 hours.[1] Teriparatide has also been associated with transient phosphaturia and mild transient declines in serum phosphorus concentrations.[1]

Pharmacokinetics

Teriparatide is rapidly absorbed and eliminated following subcutaneous injection. Absolute bioavailability averages 95%; however, systemic exposure to teriparatide is 20% to 30% less in men than in women. Peak levels occurred approximately 30 minutes after subcutaneous administration of a 20 mcg dose. Peak concentrations in clinical trials briefly exceeded the upper limit of normal for endogenous parathyroid hormone by 4- to 5-fold.[1,3]

The elimination half-life is 5 minutes after intravenous administration and approximately 1 hour after subcutaneous administration. Concentrations declined to non-quantifiable levels within 3 hours of subcutaneous administration.[1,3] The liver, kidney, and bone are major sites of metabolism and clearance for teriparatide and its amino- and carboxy-terminal fragments. Teriparatide is not expected to accumulate in bone or other tissues.[3]

The volume of distribution is 0.12 L/kg, however, intersubject variability was 25% to 50%.[1]

Age-related differences in pharmacokinetics were not observed in subjects ranging in age from 31 to 85 years.[1] Systemic exposure to teriparatide is higher in women than in men (20% to 30%), but no adjustments in dose are recommended.[1] The pharmacokinetics of teriparatide were not altered in subjects with mild-to-moderate renal impairment and dosage adjustments do not appear necessary in this group.[4] In patients with severe renal impairment (CrCl less than 30 mL/min), exposure was increased 73% and the half-life was increased 77%.[1] Teriparatide pharmacokinetics have not been assessed in patients with hepatic dysfunction or the pediatric population.[1]

Indications

Teriparatide injection (rDNA origin) is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture (e.g., women with a history of osteoporotic fracture, multiple risk factors for fracture, or failed or were intolerant of previous osteoporosis therapy). In postmenopausal women with osteoporosis, teriparatide can increase bone mineral density and reduce the risk of vertebral and nonvertebral fractures.[1]

Teriparatide is also indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture (e.g., men with a history of osteoporotic fracture, multiple risk factors for fracture, or failed or were intolerant of previous osteoporosis therapy). In men, teriparatide can increase bone mineral density, but the effects on fracture risk have not been assessed.[1]

Comparative Efficacy

Osteoporosis in Postmenopausal Women

Teriparatide was evaluated in a double-blind, placebo-controlled study enrolling 1,637 postmenopausal women with prior vertebral fractures. The women had to be ambulatory and at least 5 years postmenopausal, with at least one moderate or two mild atraumatic vertebral fractures of the thoracic and lumbar spine. Exclusion criteria included women with illnesses that affect bone or calcium metabolism, urolithiasis within the last 5 years, impaired hepatic function, a serum creatinine concentration greater than 2 mg/dL, alcohol or drug abuse, or having taken a drug that alters bone metabolism within the previous 2 to 24 months. All patients received daily calcium 1000 mg and vitamin D 400 to 1200 IU. Following 2 weeks of self-administered placebo injections, patients began therapy with teriparatide 20 mcg (541 women), teriparatide 40 mcg (552 women), or placebo (544 women) as a daily subcutaneous injection for 24 months. If the calcium levels were high, either the calcium supplement was discontinued or the dose of the study medication was decreased until the problem resolved. The study was terminated early after reports of osteosarcoma occurring in rats during a long-term toxicologic study of teriparatide. The mean duration of treatment was 17 to 18 months. The mean duration of observation was 21 months. The average rate of compliance ranged from 79% to 83%. New vertebral fractures occurred in 14.3% of women in the placebo group compared with 5% in the teriparatide 20 mcg group ($P<0.001$; absolute reduction in risk of 9.3%, relative risk reduction of 65%, and the number needed to treat [NNT] was 10.75), and 4% in the teriparatide 40 mcg group ($P<0.001$; absolute reduction in risk of 10.3% and the number needed to treat [NNT] was 9.7). The relative risk of one or more new vertebral fractures compared to the placebo group was 0.35 (95% CI 0.22 to 0.55) in the teriparatide 20 mcg group and 0.31 (95% CI 0.19 to 0.5) in the teriparatide 40 mcg group, representing 65% and 69% reductions in risk. Compared with placebo, teriparatide 20 mcg and 40 mcg were associated with a 77% and 86% reduced risk of two or more vertebral fractures, respectively; and a 90% and 78% reduced risk of at least one moderate or severe vertebral fracture. New or worsening back pain was reported by 23% of patients in the placebo group, compared with 17% in the teriparatide 20 mcg group and 16% in the teriparatide 40 mcg group ($P=0.007$). New non-vertebral fractures occurred in 5.5% of women in the placebo group compared to 2.6% in each teriparatide group ($P<0.05$; absolute reduction in risk was 2.9%, the relative risk reduction was 53%, and the NNT was 34.5). The relative risk of nonvertebral fracture compared to the placebo group was 0.47 (95% CI 0.25 to 0.88) in the teriparatide 20 mcg group and 0.46 (95% CI 0.25 to 0.86) in the teriparatide 40 mcg group. Compared to placebo, teriparatide 20 mcg and teriparatide 40 mcg were associated with increases in bone mineral density of 9.7% and 13.7% in the lumbar spine and by 2.8% and 5.1% in the femoral neck. A 5% or greater increase in spinal bone mineral density was achieved in 72% of teriparatide-treated patients; a 10% or greater increase was observed in 44%. Increased bone mineral density was also observed for the total hip, trochanter, intertrochanter, Ward's triangle, and total body. Increased bone mineral density in the teriparatide groups was significant compared to placebo at evaluations at 3, 6, 9, 12, 15, and 18 months. Teriparatide 40 mcg decreased bone mineral density at the shaft of the radius by 2.1% to 3.2% more than placebo.[1,2] Following completion of the study, 1,262 patients (77% of the study population) volunteered for an 18-month observational study to determine the effects of discontinuing teriparatide therapy on recurring vertebral fractures. Women were permitted to receive other approved osteoporosis therapies after discontinuing teriparatide. Vertebral fracture incidence was assessed in 1,043 patients with radiographs from the original study endpoint and the 18-month follow-up. The risk of new vertebral fracture was 19.5% in the group originally treated with placebo compared with 11.2% in the group originally treated with teriparatide ($P<0.001$; absolute reduction in risk of 8.3%, 42.6% relative risk reduction, and NNT was 17.2). The incidence of new or worsened back pain was also greater in the placebo group (19.3% vs 12.9%, $P<0.001$). The results of this follow-up study suggest that the beneficial effects of teriparatide be maintained for up to 18 months after discontinuation of therapy.[5]

The effects of therapy with alendronate following teriparatide therapy were also assessed in a follow-up study enrolling 75 women previously treated in a 1-year, Phase II trial evaluating teriparatide at doses of 50, 75, or 100 mcg or placebo injected daily. Patients originally enrolled in the teriparatide study were at least 5 years postmenopausal, 50 to 75 years of age, and had a vertebral bone mineral density of at least 2.5 SD below the mean for young women. Patients received alendronate 10 mg daily for 1 year following teriparatide therapy, in addition to calcium 500 mg and vitamin D 400 IU. Sixty-six women completed the year of alendronate therapy. During the year of treatment with teriparatide for all doses combined, bone mineral density increased 7.1% in the spine, 6.2% in the femoral neck, and decreased by 2.3% for the total body. During the year of treatment with alendronate, those previously treated with teriparatide experienced an increase in bone mineral density of 13.4% in the spine, 4.4% in the femoral neck, and 2.6% for the whole body. Among patients previously treated with teriparatide 100 mcg for 1 year, the mean increase in vertebral bone mineral density while on alendronate was 14.6% (P=0.0004).[6]

In another study, teriparatide plus hormone replacement therapy was compared to hormone replacement therapy alone in 247 postmenopausal women with osteoporosis. Bone mineral density at the spine, total hip, and femoral neck was increased to a greater extent in patients receiving teriparatide 40 mcg daily in conjunction with hormone replacement therapy than in women receiving hormone replacement therapy alone.[4]

Teriparatide 40 mcg/day was also compared with alendronate 10 mg/day in a double-blind, double-dummy study enrolling 146 postmenopausal women with osteoporosis. The study was terminated early due to the rat osteosarcoma study results. The median duration of treatment was 14 months. Compliance was 71% in the alendronate group and 67% in the teriparatide group. From baseline to endpoint, increases in bone mineral density at the lumbar spine, total hip, and femoral neck were greater in the teriparatide group than in the alendronate group. At 3 months, a 2.7% greater increase in lumbar spine bone mineral density was observed in the teriparatide group (P<0.001). At endpoint, the mean increase in bone mineral density at the lumber spine was 12.2% in the teriparatide group and 5.6% in the alendronate group (P<0.001). In contrast, at the distal radius the bone mineral density in the teriparatide group was reduced 3.34% compared to a reduction of 0.17% in the alendronate group (P≤0.05). Mean whole body bone mineral density increased to a similar extent in both groups. The incidence of nonvertebral fractures was lower in the teriparatide group (4.1% vs 13.7%; P=0.042; absolute reduction in risk of 9.6%, relative risk reduction of 70%, and NNT is 10.4).[4,7]

A number of additional studies evaluated the effects of human parathyroid hormone (1-34) on bone density and fracture incidence. A small 3-year trial enrolled 34 postmenopausal women with osteoporosis who had been on hormone replacement therapy for at least 2 years. This study evaluated human parathyroid hormone (1-34; Rhone-Poulenc-Rorer) 400 units/25 mcg subcutaneously daily in addition to hormone replacement therapy in 17 patients compared with hormone replacement alone in 17 patients. Patients treated with the combination regimen demonstrated a continuous increase in vertebral bone mineral density throughout the trial, while those treated with hormone replacement therapy alone did not demonstrate a change in vertebral bone mineral density. In the combination group vertebral bone mineral density increased 13% (P<0.001), while that at the hip was increased 2.7% (P=0.05) and total body bone mineral density increased 7.8% (P=0.002). Thirteen new vertebral fractures (using a 15% height reduction criterion) occurred overall, with 10 (77%) occurring in the hormone replacement therapy group (P<0.03).[8] Full results of this study including a total of 52 patients with 3 years of treatment plus 1 year of follow-up were also reported. Bone mineral density was increased by 13.4% at the spine, 4.4% at the hip, and 3.7% for the total body in the group receiving the combination regimen, but was unchanged in the hormone replacement therapy alone group. Bone density remained stable for 1 year after discontinuation of parathyroid hormone and continued hormone replacement therapy. With assessment using a 15% height reduction criterion, two vertebral fractures occurred in the combination group compared to 12 in the hormone replacement therapy alone group (P=0.001). Using a 20% reduction in vertebral height criterion, no vertebral fractures occurred in the combination group compared to seven in the hormone replacement therapy alone group (P=0.003).[9]

Osteoporosis in Men

Teriparatide was also evaluated in the treatment of idiopathic osteoporosis or osteoporosis associated with primary hypogonadism in a double-blind, placebo-controlled trial enrolling 437 men. Men were randomly assigned therapy with placebo or teriparatide 20 mcg or 40 mcg daily. All patients also received supplemental calcium 1000 mg and vitamin D 400 to 1200 IU daily. This trial was also terminated prematurely as a result of the animal safety trial that discovered the osteosarcomas; therefore, patients received therapy for approximately 300 days. Treatment with teriparatide resulted in placebo-subtracted increases in lumbar spine bone mineral density of 5.19% at month-12 and 5.35% at endpoint in the 20 mcg group and 8.21% at month-12 and 8.51% at endpoint in the 40 mcg group (P<0.001 for all within group comparisons vs. baseline). Over 50% of patients treated with teriparatide 20 mcg had increases in lumber spine bone mineral density of 5% or greater, 70.5% of patients treated with teriparatide 40 mcg had increases of 5% or more, and over 40% had increases of 10% or more. However, the bone mineral density did not significantly increase in trochanter, intertrochanter, Ward's triangle of the hip, distal third of the radius,

or the ultra-distal radius in the 20 mcg group, but did reach significance in the total hip, intertrochanter, and Ward's triangle of the hip with the 40 mcg dose.[1,4]

Other Potential Uses

Several other studies also demonstrated a prevention in bone loss with parathyroid hormone therapy in young women with gonadotropin-releasing hormone analog-induced estrogen deficiency.[10] In these studies, human parathyroid hormone (1-34; Bachem, Inc.) 40 mcg subcutaneously daily was administered in conjunction with nafarelin 200 mcg intranasal twice daily.[10,11,12] Increased bone mineral density was also observed in a study evaluating human parathyroid hormone (1-34; Bachem, Inc.) in postmenopausal women with corticosteroid-induced osteoporosis.[13,14] In another study enrolling 23 men, human parathyroid hormone (1-34; Bachem, Inc.) was demonstrated to increase spine and hip bone mineral density in men with idiopathic osteoporosis. Parathyroid hormone 400 units subcutaneously daily in conjunction with calcium and vitamin D was associated with a 13.5% increase in lumbar bone mineral density, compared to no change observed in men treated with calcium and vitamin D alone ($P<0.001$).[15] Human parathyroid hormone (1-34; Bachem, Inc.) was also demonstrated to be effective in the treatment of hypoparathyroidism.[16]

Contraindications

Teriparatide is contraindicated in patients with hypersensitivity to teriparatide or any of the product excipients (glacial acetic acid, sodium acetate, mannitol, and metacresol).[1] Teriparatide should not be used in patients at increased risk for osteosarcoma, including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric patients or young adults with open epiphyses, or prior radiation therapy involving the skeleton. Teriparatide also should not be administered to patients with bone metastases or a history of skeletal malignancies or patients with metabolic bone diseases other than osteoporosis.[1,4,17]

Warnings and Precautions

Boxed Warning — Osteosarcoma, a rare malignant bone cancer, occurred with teriparatide in a long-term toxicology study in both male and female rats. These rats received daily injections of parathyroid hormone throughout most of their lives. The incidence of osteosarcoma in these rats was duration- and dose-dependent and occurred after parathyroid hormone-induced osteosclerosis. These effects were observed at doses ranging from 3 to 60 times the amount of teriparatide used in the human clinical trials.[1,2]

Osteosarcomas were not observed in oophorectomized monkeys given parathyroid hormone at daily doses 4 to 10 times the maximal dose in humans for 18 months.[2] The growth of osteosarcomas in parathyroid hormone-treated animals is biologically plausible.[4] However, some of the experts feel that the increased risk of osteosarcoma in the animal model may not occur in humans because of important differences between the rat carcinogenicity model and the intended clinical use of teriparatide in the treatment of osteoporosis.[3] No cases of osteosarcoma were observed in the teriparatide study enrolling 1,637 postmenopausal women or in other studies of human parathyroid hormone enrolling approximately 1,000 patients. In addition, chronic primary hyperparathyroidism has not been associated with an increased risk of osteosarcoma.[2,4]

Until more information is available on the relationship between teriparatide and osteosarcoma in humans, this agent should only be used in patients for whom the potential benefits outweigh the potential risk. Teriparatide should not be used in patients at increased risk for osteosarcoma, including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric patients or young adults with open epiphyses, or prior radiation therapy involving the skeleton. Teriparatide also should not be administered to patients with bone metastases or a history of skeletal malignancies or patients with metabolic bone diseases other than osteoporosis.[1]

In clinical trials calcium levels were monitored before and 4 to 6 hours after injection at baseline and after 1, 3, 6, 12, 18, and 24 months of therapy. If post-injection serum calcium concentrations were high or if urinary calcium excretion exceeded 350 mg (8.8 mmol) per day, and if the increase persisted on repeated testing within a few weeks, the calcium supplement was discontinued permanently or the teriparatide dose was reduced by half until the abnormality disappeared.[2] Mild hypercalcemia (greater than 10.6 mg/dL) occurred at least once in 2% of women in the placebo group, 11% of women in the teriparatide 20 mcg group, and 28% of women in the teriparatide 40 mcg group. Calcium or teriparatide dosage adjustments were required in less than 1% of women in the placebo group, 3% of women in the teriparatide 20 mcg group, and 11% of women in the teriparatide 40 mcg group.[2] Teriparatide has not been studied in patients with pre-existing hypercalcemia and should not be administered to such patients due to the risk for exacerbating their hypercalcemia.[1]

In clinical trials urolithiasis occurred with similar frequency in teriparatide- and placebo-treated patients, however, teriparatide was not evaluated in patients with active urolithiasis. If active urolithiasis or pre-existing hypercalciuria is suspected, measurement of urinary calcium excretion should be considered. Teriparatide should be used with caution in patients with recent urolithiasis.[1]

Transient symptomatic orthostatic hypotension occurred infrequently following teriparatide injections. Episodes typically occurred within 4 hours of dosing and resolved spontaneously within a few minutes to a few hours. Such events did not preclude continued teriparatide treatment.[1]

As part of its Phase IV study commitments, Eli Lilly & Company has agreed to evaluate heart rate and electrocardiograms within 6 hours after initial and subsequent injections of teriparatide 20 mcg in a sample of osteoporosis patients. Monitoring of new cases of osteosarcoma or other types of primary bone cancer has also been recommended.[17]

The safety and efficacy of teriparatide have not been evaluated for longer than 2 years of treatment; therefore, use of this agent for more than 2 years is not currently recommended.[1]

The safety and effectiveness of teriparatide in the treatment of children have not been established. Teriparatide is not indicated for use in pediatric patients.[1,4]

Teriparatide is indicated for postmenopausal women and is not indicated for use in women who are pregnant or breast feeding, or to women of childbearing potential.[1,4] Teriparatide is in Pregnancy Category C. In animal studies an increased incidence of skeletal deviations or variations, mild growth retardation, and reduced motor activity was observed.[1]

Adverse Reactions

Adverse effects have included nausea, headache, back pain, dizziness, vertigo, syncope, and leg cramps (see Table 1).[1,2,17]

Table 1: Adverse Reactions Occurring More Frequently than Placebo in the Two Pivotal Clinical Trials[1]

Adverse Event	Teriparatide (n=691)	Placebo (n=691)
Pain	21.3%	20.5%
Arthralgia	10.1%	8.4%
Rhinitis	9.6%	8.8%
Asthenia	8.7%	6.8%
Nausea	8.5%	6.7%
Dizziness	8%	5.4%
Headache	7.5%	7.4%
Hypertension	7.1%	6.8%
Cough – increased	6.4%	5.5%
Pharyngitis	5.5%	4.8%
Constipation	5.4%	4.5%
Dyspepsia	5.2%	4.1%
Diarrhea	5.1%	4.6%
Rash	4.9%	4.5%
Insomnia	4.3%	3.6%
Depression	4.1%	2.7%
Pneumonia	3.9%	3.3%
Vertigo	3.8%	2.7%
Dyspnea	3.6%	2.6%
Neck pain	3%	2.7%
Vomiting	3%	2.3%
Syncope	2.6%	1.4%
Leg cramps	2.6%	1.3%
Angina pectoris	2.5%	1.6%
Gastrointestinal disorder	2.3%	2%
Sweating	2.2%	1.7%
Tooth disorder	2%	1.3%

Teriparatide therapy is associated with increased serum calcium, urine calcium, serum uric acid, serum total alkaline phosphatase, serum creatinine, and reduced serum magnesium.[1,17]

At doses of 40 mcg/day or higher, an increased incidence of headache, nausea, dizziness, and orthostatic hypotension was observed, as well as an increased incidence of asymptomatic hypercalcemia and hypercalcinuria.[4]

A positive test for anti-teriparatide antibodies occurred in 15 patients (2.8%) treated with teriparatide and 1 patient (0.2%) treated with placebo.[17]

Drug Interactions

Pharmacokinetic interactions are not anticipated with teriparatide. No clinically important interactions were observed with furosemide or hydrochlorothiazide. Concomitant administration with hydrochlorothiazide 25 mg resulted in a 15% increase in 24-hour urine calcium excretion. Concomitant administration with furosemide 20 to 100 mg resulted in a 2% increase in serum calcium and a 37% increase in 24-hour urine calcium excretion.[1]

In 15 patients administered digoxin to steady-state, a single teriparatide dose did not alter the effects of digoxin on systolic time intervals (time from Q wave on ECG to closure of the aortic valve, left ventricular ejection time, and pre-ejection period).[18] Hypercalcemia may predispose digoxin-treated patients to digitalis toxicity. Because teriparatide transiently increases calcium concentrations, teriparatide should be used with caution in patients receiving digoxin.[1]

Recommended Monitoring

Calcium levels should be monitored before and 4 to 6 hours after injection at baseline and then after 1, 3, 6, 12, 18, and 24 months of therapy.

Dosing

The recommended teriparatide dose is 20 mcg daily, administered as a subcutaneous injection to the thigh or abdominal wall.[1,4] The initial dose should be administered under circumstances where the patient may sit or lie down if symptoms of orthostatic hypotension occur.[1] Teriparatide can be dosed at any time of day, but should be dosed at the same time each day.[1]

The maximum tolerable dose of teriparatide is 40 mcg per day.[4] The maximum recommended duration is 2 years.[1]

Teriparatide is available only in a prefilled delivery device (pen), to be used to deliver a 20 mcg dose subcutaneously daily for 28 days. A new needle should be used for each injection. The pen should be primed before each injection.[1] Each pen may be used for up to 28 days after the first injection. After 28 days, the pen should be discarded, even if it still contains some unused solution.[1]

Product Availability

Teriparatide received FDA approval in November 2002. It is available as a sterile, colorless, clear, isotonic solution for subcutaneous administration. It is supplied in a glass cartridge which is pre-assembled into a disposable pen device for injection. The pen delivers teriparatide 20 mcg per dose. Each prefilled device contains 3.3 mL to deliver

3 mL. Each mL contains 250 mcg teriparatide, 0.41 glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg metacresol, and Water for Injection. Hydrochloric acid 10% solution and/or sodium hydroxide 10% solution are added to adjust the pH to 4.[1]

Teriparatide is supplied as a solution for subcutaneous injection containing 250 mcg teriparatide/mL. It is supplied in 3 mL cartridges, with a disposable prefilled pen-injector delivery device that delivers teriparatide 20 mcg per dose. The prefilled glass cartridge provides a 28-day supply; it should be discarded 28 days after the first injection.[1,4]

Teriparatide should be stored under refrigeration 2° to 8° C (36° to 46° F) at all times. Time out of the refrigerator should be minimized; the dose may be delivered immediately after removal from the refrigerator.[1] The solution should not be frozen and should not be used if it has been frozen.[1] The pen should be recapped when not in use to protect the cartridge from physical damage and light.[1] It should not be stored with the needle attached, as such storage may let the solution leak from the cartridge and may permit air bubbles to form within the cartridge.[1]

Conclusion

Teriparatide offers a novel therapy for osteoporosis that appears to induce a sizable increase in vertebral bone mineral density and reduction in vertebral fractures. Further experience with this agent will clarify its side effect profile and its role in therapy. Initially, teriparatide use should be reserved for patients who have not responded adequately to other therapies or who have severe osteoporosis.

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Selected FDA Safety Alerts

Aralen (chloroquine phosphate tablets)
Aralen Hydrochloride (chloroquine hydrochloride injection)

Chloroquine resistance is widespread and, at present, is particularly prominent in various parts of the world including sub-Saharan Africa, Southeast Asia, the Indian subcontinent, and over large portions of South America, including the Amazon basin.

Chloroquine should not be used for treatment of *P. falciparum* infections acquired in areas of chloroquine resistance or malaria occurring in patients where chloroquine prophylaxis has failed.

Usage in Pregnancy: There are no adequate and well-controlled studies evaluating the safety and efficacy of chloroquine in pregnant women. Usage of chloroquine during pregnancy should be avoided except in the

suppression or treatment of malaria when in the judgment of the physician the benefit outweighs the potential risk to the fetus.

Artane (trihexyphenidyl hydrochloride) Tablets and Elixir

Artane is contraindicated in patients with hypersensitivity to trihexyphenidyl HCl or to any of the tablet or elixir ingredients. Artane is also contraindicated in patients with narrow angle glaucoma. Blindness after long-term use due to narrow angle glaucoma has been reported.

Administer with caution in hot weather, especially when given concomitantly with other atropine-like drugs to the chronically ill, alcoholics, those who have central nervous system disease, or those who do manual labor in a hot environment. Anhidrosis may occur more readily when some disturbance of sweating already exists.

AtroPen (atropine) Injection

AtroPen should be administered with extreme caution to individuals with significant renal insufficiency or a recent myocardial infarction.

Cefotan (cefotetan disodium for injection) for Intravenous or Intramuscular Use
Cefotan (cefotetan injection) for Intravenous Use Only

There appears to be an increased risk of developing hemolytic anemia on cefotetan relative to other cephalo-sporins of at least threefold.

Patients who receive courses of cefotetan for the treatment or prophylaxis of infections should have periodic monitoring for signs and symptoms of hemolytic anemia including a measurement of hematological parameters where appropriate.

Cognex (Tacrine Hydrochloride Capsules)

Because of its pharmacological action, Cognex may have vagotonic effects on the sinoatrial and atrioventricular nodes possibly leading to bradycardia and/or heart block. These effects may be particularly harmful to patients with conduction abnormalities, bradyarrythmias, or a sick sinus syndrome, but may also occur in patients without known preexisting cardiac disease.

Lactated Ringer's Injection

Allergic reactions or anaphylac-toid symptoms such as localized or generalized urticaria and pruritus; periorbital, facial, and/or laryngeal edema; coughing, sneezing, and/or difficulty with breathing have been reported during administration of Lactated Ringer's Injection, USP. The reporting frequency of these signs and symptoms is higher in women during pregnancy.

Phenergan (promethazine HCl) Syrup and Fortis

Phenergan Syrup Plain and Phenergan Syrup Fortis:

- Contraindicated in comatose states, and in individuals known to be hypersensitive or to have had an idiosyncratic reaction to promethazine or to other phenothiazines.
- May impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery.
- May lead to potentially fatal respiratory depression. Use in patients with compromised respiratory function (e.g., COPD, sleep apnea) should be avoided.
- May lower seizure threshold. It should be used in caution in persons with seizure disorder or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.
- Used with caution in patients with bone-marrow depression. Leukopenia and granulocytosis have been reported, usually when Phenergan has been used in association with other known marrow-toxic agents.
- NMS has been reported in association with promethazine HCl alone or in combination with antipsychotic drugs.
- Not recommended for use in pediatric patients less than 2 years of age.
- Caution should be exercised when administering Phenergan Syrup Plain and Phenergan Syrup Fortis to pediatric patients 2 years of age and older because of the potential for fatal respiratory depression.
- Cholestatic jaundice has been reported.

Ultane (sevoflurane) Volatile Liquid for Inhalation

Rare cases of malignant hyperthermia and allergic reactions, such as rash, urticaria, pruritus, bronchospasm, anaphylactic or anaphylactoid reactions have been reported.

Venofer (iron sucrose injection)

Hypersensitivity reactions have been reported with injectable iron products.

Zemuron (rocuronium bromide) for Injection

Although rare, severe anaphylactic reactions to neuromuscular blocking agents, including Zemuron, have been reported. These reactions have, in some cases, been life threatening. Due to the potential severity of these reactions, the necessary precautions, such as the immediate availability of appropriate emergency treatment, should be taken.

Special precautions should be taken in patients who have had previous anaphylactic reactions to other neuromuscular blocking agents, since allergic cross-reactivity has been reported in this class of drugs.

Note: Detailed information on these and other FDA safety alerts is available via the FDA homepage (*www.fda.gov*).

FDA Safety Alerts

- You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.
- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov.* In the message body enter: *subscribe medwatch* and your e-mail address.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- Aprepitant (Emend), an injectable antiemetic
- Corticorelin (Acthrel), an injectable ovine corticotropin releasing hormone
- Ezetimibe (Zetia), an oral antihyperlipidemic
- Atazanavir (Reyataz), an oral antiretroviral
- Enfuvirtide (Fuzeon), an injectable antiretroviral
- Gelclair, an oral gel for treating mucositis and stomatitis
- Aripiprazole (Abilify), an oral antipsychotic
- Factor VIIa (NovoSeven), an injectable coagulation factor

Deletions

None

Drug Information Service

- Patient-specific pharmacotherapy evaluation and management
- Comprehensive information about medications, biologics, and nutrients
- Critical evaluation of drug therapy literature
- Assistance with study design and protocol development
- Clinical trial drug safety monitoring
- Investigational drug information
- Parenteral nutrition assessment and management

301-496-2407

Pager 301-285-4661

Building 10, Room 1S-259