

Severe Hypoglycemia Signals Mortality Risk

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Severe hypoglycemia in patients with long-standing type 2 diabetes is strongly associated with adverse outcomes, including death from cardiovascular and noncardiovascular causes, according to a large analysis.

However, there is no close temporal relation between episodes of severe hypoglycemia and such adverse events, nor is there a dose-response relation in which more frequent episodes carry increasingly higher risks.

“Although our findings cannot exclude the possibility that severe hypoglycemia has a direct causal link with these outcomes, they suggest that it is as likely to be a marker of vulnerability to a wide range of clinical outcomes. In either case, the presence of severe hypoglycemia should raise clinical suspicion of the patient’s susceptibility to adverse outcomes and prompt action to address this possibility,” said Dr. Sophia Zoungas of the George Institute for International Health, University of Sydney, and her associates in the ADVANCE trial.

The Action in Diabetes and Vascular Disease: Preter-

ax and Diamicon Modified-Release Controlled Evaluation assessed 11,140 patients aged 55 years and older who had type 2 diabetes and were followed at 215 medical centers in 20 countries for a median of 5 years.

The study subjects were randomly assigned to receive either intensive or standard glucose-lowering therapy. A total of 231 (about 2%) reported experiencing 299 severe hypoglycemic events: 150 (2.7%) receiving intensive therapy reported 195 events and 81 (1.5%) receiving standard therapy reported 104 events.

Major macrovascular or microvascular events oc-

IMPORTANT SAFETY INFORMATION

WARNING: POTENTIAL RISK OF 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. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® (teriparatide [rDNA origin] injection) only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget’s disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton).

CONTRAINDICATIONS

Hypersensitivity to teriparatide or to any of its excipients. Reactions have included angioedema and anaphylaxis.

WARNINGS AND PRECAUTIONS

The following categories of patients have increased baseline risk of osteosarcoma and therefore should not be treated with FORTEO: Paget’s disease of bone, pediatric populations and young adults with open epiphyses, or prior external beam or implant radiation therapy.

Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting www.forteoregistry.rti.org.

Osteosarcoma occurs in about 4 out of every million older adults each year. Cases of bone tumor and osteosarcoma have been reported rarely in people taking FORTEO in the post-marketing period. The causality to FORTEO use is unclear.

Use of FORTEO for more than 2 years during a patient’s lifetime is not recommended.

Patients with the following conditions also should not receive FORTEO: bone metastases or a history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or hypercalcemic disorders.

FORTEO may increase serum calcium, urinary calcium, and serum uric acid.

Use with caution in patients with active or recent urolithiasis because of risk of exacerbation. If active urolithiasis or pre-existing hypercalciuria are suspected, measurement of urinary calcium excretion should be considered.

Transient orthostatic hypotension may occur with initial doses of FORTEO. In short-term clinical pharmacology studies, transient episodes of symptomatic orthostatic hypotension were observed in 5% of patients. FORTEO should be administered initially under circumstances where the patient can sit or lie down if symptoms of orthostatic hypotension occur.

Patients receiving digoxin should use FORTEO with caution because FORTEO may transiently increase serum calcium and hypercalcemia may predispose patients to digitalis toxicity.

FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on animal studies, FORTEO may cause fetal harm.

It is not known whether teriparatide is excreted in human milk. Breastfeeding mothers should discontinue nursing or FORTEO, taking into account the importance of treatment to the mother.

ADVERSE REACTIONS

The most common adverse reactions in clinical trials include: arthralgia (10.1 FORTEO vs. 8.4 placebo), pain (21.3 FORTEO vs. 20.5 placebo), and nausea (8.5 FORTEO vs. 6.7 placebo). Other adverse reactions include: dizziness, leg cramps, joint aches, and injection site reactions.

INSTRUCTIONS FOR FORTEO USE

FORTEO is provided as a fixed-dose, prefilled delivery device that can be used for up to 28 days, including the first injection. The delivery device contains 28 daily doses of 20 mcg each. Do not transfer the contents of the delivery device into a syringe. The FORTEO Delivery Device should be stored under refrigeration at 36° to 46° F (2° to 8° C) at all times. Do not use FORTEO if it has been frozen.

Please see Brief Summary of Prescribing Information on adjacent pages.

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FORTEO™
teriparatide (rDNA origin) injection
ANABOLIC ACTION FOR NEW BONE

Lilly

occurred in 2,125 subjects, 87 of whom reported severe hypoglycemic events. And 1,031 subjects died, 45 of whom reported severe hypoglycemic events.

Nearly 17% of subjects who reported severe hypoglycemia subsequently had a major macrovascular event, 12% had a subsequent major microvascular event, and 20% died. In contrast, the corresponding proportions for subjects who did not report severe hypoglycemia were 10%, 10%, and 9%, respectively, the investigators said (N. Engl. J. Med. 2010;363:1410-8).

Also, risks for disorders of the respiratory system, digestive system, and skin were high-

er in patients who had severe hypoglycemic episodes than in those who did not.

Hypoglycemia conceivably could have contributed to both cardiovascular and non-cardiovascular disorders and death by means of sympathoadrenal activation, abnormal cardiac repolarization, increased thrombogenesis, inflammation, or vasoconstriction. However, it is also possible, and more likely, that hypoglycemia merely reflected the effects of "coexisting conditions and unmeasured or incompletely quantified confounding variables," making it a marker rather than a direct cause of adverse outcomes, the investigators noted. ■

VITALS

Major Finding: Patients with type 2 diabetes who had episodes of severe hypoglycemia were at increased risk of major macrovascular events (hazard ratio, 2.88), major microvascular events (HR, 1.81), death from cardiovascular causes (HR, 2.68), and death from any cause (HR, 2.69), compared with patients who did not have severe hypoglycemia episodes.

Data Source: ADVANCE, an international, double-blind, randomized clinical trial comparing standard vs. intensive glucose-lowering therapy in 11,140 adults with longstanding type 2 diabetes.

Disclosures: The ADVANCE study was supported by Servier and the National Health and Medical Research Council of Australia. Dr. Zoungas and her associates reported ties to Servier, Norvo Nordisk, Eli Lilly, Sanofi-Aventis, Takeda, Pfizer, Roche, Amgen, Astra Zeneca, GlaxoSmithKline, Tanabe, Merck Sharpe and Dolhman, Abbott, Johnson & Johnson, and Merck Schering Plough.

FORTEO® (teriparatide [rDNA origin] 20 mcg for injection)
Brief Summary. Consult the package insert for complete prescribing information.

WARNING: POTENTIAL RISK OF 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. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton).

INDICATIONS: FORTEO is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture; to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; for the treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy at high risk for fracture.

CONTRAINDICATIONS: Do not use FORTEO in patients with:

- Hypersensitivity to teriparatide or to any of its excipients. Reactions have included angioedema and anaphylaxis.

WARNINGS AND 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. FORTEO should not be prescribed for patients at increased baseline risk of osteosarcoma.

These include:

- Paget's disease of 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.

Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting www.forteoregistry.rti.org.

Treatment Duration—The safety and efficacy of FORTEO 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.

Bone Metastases and Skeletal Malignancies—Patients with bone metastases or a history of skeletal malignancies should not be treated with FORTEO.

Metabolic Bone Diseases—Patients with metabolic bone diseases other than osteoporosis should not be treated with FORTEO.

Hypercalcemia and Hypercalcemic Disorders—FORTEO has not been studied in patients with pre-existing hypercalcemia. These patients should not be treated with FORTEO because of the possibility of exacerbating hypercalcemia. Patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, should not be treated with FORTEO.

Urolithiasis or Pre-existing Hypercalciuria—In clinical trials, the frequency of urolithiasis was similar in patients treated with FORTEO and placebo. However, FORTEO 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. FORTEO should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

Orthostatic Hypotension—FORTEO 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.

Drug Interactions—Hypercalcemia may predispose patients to digitalis toxicity. Because FORTEO transiently increases serum calcium, patients receiving digoxin should use FORTEO with caution.

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.

FORTEO® (teriparatide [rDNA origin] injection)

PA 9401 FSAMP

Treatment of Osteoporosis in Men and Postmenopausal Women—

The safety of FORTEO 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 FORTEO 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 FORTEO group and 1% in the placebo group. The incidence of serious adverse events was 16% in FORTEO patients and 19% in placebo patients. Early discontinuation due to adverse events occurred in 7% of FORTEO patients and 6% of placebo patients.

Percentage of Patients with Adverse Events Reported by at Least 2% of FORTEO-Treated Patients and in More FORTEO-Treated Patients than Placebo-Treated Patients from the Two Principal Osteoporosis Trials in Women and Men Adverse Events are Shown Without Attribution of Causality (FORTEO, N=691, Placebo, N=691): *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%), Dyspepsia (3.6%, 2.6%), Pneumonia (3.9%, 3.3%); *Skin and Appendages:* Rash (4.9%, 4.5%), Sweating (2.2%, 1.7%).

Immunogenicity—In the clinical trial, antibodies that cross-reacted with teriparatide were detected in 3% of women (15/541) receiving FORTEO. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions or allergic reactions among these patients. Antibody formation did not appear to have effects on serum calcium, or on bone mineral density (BMD) response.

Laboratory Findings—Serum Calcium—FORTEO transiently increased serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. Serum calcium measured at least 16 hours post-dose 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 FORTEO administration was increased from 2% of women and none of the men treated with placebo to 11% of women and 6% of men treated with FORTEO. The number of patients treated with FORTEO whose transient hypercalcemia was verified on consecutive measurements was 3% of women and 1% of men.

Urinary Calcium—FORTEO increased urinary calcium excretion, but the frequency of hypercalciuria in clinical trials was similar for patients treated with FORTEO and placebo.

Serum Uric Acid—FORTEO increased serum uric acid concentrations. In clinical trials, 3% of FORTEO patients had serum uric acid concentrations above the upper limit of normal compared with 1% of placebo 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.

Studies in Men and Women with Glucocorticoid-Induced Osteoporosis—The safety of FORTEO 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 ≥ 5 mg per day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to FORTEO and 214 patients exposed to oral daily bisphosphonate (active control). All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day.

The incidence of all cause mortality was 4% in the FORTEO group and 6% in the active control group. The incidence of serious adverse events was 21% in FORTEO patients and 18% in active control patients, and included pneumonia (3% FORTEO, 1% active control). Early discontinuation because of adverse events occurred in 15% of FORTEO patients and 12% of active control patients, and included dizziness (2% FORTEO, 0% active control).

Adverse events reported at a higher incidence in the FORTEO group and with at least a 2% difference in FORTEO-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.

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