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comprehensive. Phase III trials for empagliflozin are underway, and we are continuing to evaluate the drug's safety profile." Currently, there are 11 ongoing, multinational, phase III clinical trials, including a large cardiovascular outcomes safety trial, she said.

At the EASD meeting in September, Dr. Michaela Diamant, scientific director of the diabetes center at Free University Medical Center in Amsterdam, commented that SGLT2 inhibitors have "an interesting mechanism that addresses, to a certain extent, a pathogenic defect that has been largely overlooked in diabetes. … I'm sure there is a huge group of patients who can profit from these novel agents."

Regarding the safety issue, she asked, "If you would have a trial of 2-5 years, would you definitely address causality of cancer? We know that cancer development takes 20 years. It's very unlikely that the drug caused cancer. We have to do what is feasible. The industry is not going to develop any more of these drugs if they are required to do a trial of 10 years. It's difficult to tease out [contributors] to the development of cancer," Dr. Diamant continued.

Dr. Diamant has been a board member, advisory panel member, consultant, research support recipient, and/or speakers bureau participant for Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Abbott, AstraZeneca/BMS, Boehringer Ingelheim, Poxel Pharma, Sanofi-Aventis, Amylin Pharmaceuticals, Novartis, and Takeda. ■

Sue Sutter of "The Pink Sheet" contributed to this story. "The Pink Sheet" and this publication are owned by Elsevier.

Once-Weekly Exenatide Approved

BY ELIZABETH MECHCATIE

The first once-weekly diabetes drug has been approved by the Food and Drug Administration. An extended-release formulation of the type 2 diabetes medication exenatide, a glucagonlike peptide–1 (GLP-1) receptor, was approved last month, the manufacturer announced.

The formulation, called Bydureon, is administered once a week in a subcutaneous injection, and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The regular formulation of exenatide (Byetta), approved in 2005, is administered twice a day.

Approval was based on the results of the DURATION-5 study, which compared treatment with the two formulations in 252 patients with type 2 diabetes and inadequate glycemic control (mean baseline hemoglobin A_{1c} was 8.4%) with diet and exercise alone or with oral therapy, including metformin, a sulfonylurea, a thiazolidinedione, or a combination of two of these treatments.

The mean reduction in HbA_{1c} was 1.6 percentage points in those treated with 2 mg of extended-release exenatide once weekly, compared with a reduction of 0.9 percentage points in those treated with the regular form of exenatide, a statistically significant difference, according to the prescribing information.

Bydureon has been approved with a Risk Evaluation and Mitigation Strategy to ensure that the benefits of the drug outweigh the risks of acute pancreatitis and the "potential" risk of medullary thyroid cancer with treatment. There have been postmarketing reports of pancreatitis associated with exenatide, including nonfatal hemorrhagic or necrotizing pancreatitis.

Bydureon is contraindicated in people with a personal or family history of medullary thyroid cancer or those with multiple endocrine neoplasia syndrome type 2. ■

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 ≥ 5mg 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. **Postmarketing Experience:** The following adverse reactions have been identified during postapproval use of FORTEO. 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. **Osteosarcoma**: Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. The causality to FORTEO use is unclear. Long term osteosarcoma surveillance studies are ongoing. **Hypercalcemia**: Hypercalcemia greater than 13.0 mg/dL has been reported with FORTEO use. Adverse events reported since market introduction that were temporally (but not necessarily causally) related to FORTEO therapy include the following: *Allergic Reactions*: Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria; *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.

USE IN SPECIFIC POPULATIONS

Pregnancy Category C. There are no adequate and well-controlled studies of FORTEO in pregnant women. In animal studies, teriparatide increased skeletal deviations and variations in mouse offspring at doses more than 60 times the equivalent human dose and produced mild growth retardation and reduced motor activity in rat offspring at doses more than 120 times the equivalent human dose. FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In animal studies, pregnant mice received teriparatide during organogenesis at subcutaneous doses 8 to 267 times the human dose. At 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 subcutaneous teriparatide during organogenesis at doses 16 to 540 times the human dose, the fetuses showed no abnormal findings. In a perinatal/postnatal study, pregnant rats received subcutaneous teriparatide from organogenesis through lactation. Mild growth retardation in female offspring at doses ≥120 times the human dose (based on surface area, mcg/m2). Mild growth retardation in male offspring and reduced motor activity in both male and female offspring occurred at maternal doses 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. Exposure multiples were normalized based on body surface area (mcg/m2). Actual animal doses: mice (30 to 1000 mcg/kg/day); rats (30 to 1000 mcg/kg/day). **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 FORTEO have not been established in any pediatric population. FORTEO should not be prescribed in patients at an increased baseline risk of osteosarcoma which include pediatric and young adult patients with open epiphyses. Therefore, FORTEO is not indicated for use in pediatric or young adult patients with open epiphyses. **Geriatric Use:** Of the patients receiving FORTEO 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 FORTEO 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. **Renal Impairment:** In 5 patients with severe renal impairment (CrCl<30 mL/min), the AUC and T1/2 of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased.

OVERDOSAGE

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 errors in which the entire contents (up to 800 mcg) of the FORTEO 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 FORTEO, monitoring of serum calcium and phosphorus, and implementation of appropriate supportive measures, such as hydration.

DOSAGE FORMS AND STRENGTHS

Multi-dose prefilled delivery device (pen) for subcutaneous injection containing 28 daily doses of 20 mcg.

PATIENT COUNSELING INFORMATION

Patients should read the FDA-approved *Medication Guide* and delivery device (pen) *User Manual* before starting therapy with FORTEO and re-read them each time the prescription is renewed. Patients need to understand and follow the instructions in the FORTEO delivery device *User Manual*. Failure to do so may result in inaccurate dosing.

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PLEASE SEE FULL PRESCRIBING INFORMATION FOR ADDITIONAL INFORMATION.

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Manufactured by Lilly France – F-67640 Fegersheim, France for Eli Lilly and Company – Indianapolis, IN 46285, USA
www.forteo.com

PA 097 FSAM00

Rx only.

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