

Novel Drug Aids Type 2 Diabetics on Metformin

BY MIRIAM E. TUCKER

FROM THE ANNUAL MEETING OF THE
AMERICAN DIABETES ASSOCIATION

Dapagliflozin significantly reduced hemoglobin A_{1c} levels compared with placebo in a phase III, multicenter, randomized, double-blind, placebo-controlled trial involving 534 patients with type 2 diabetes inadequately controlled with metformin alone.

The study was funded by dapagliflozin codevelopers Bristol-Myers Squibb (BMS) and AstraZeneca (AZ). The drug is a selective inhibitor of the sodium-glucose cotransporter 2 (SGLT2), which is located in the proximal tubule of the kidney nephron and functions to reabsorb most of the glucose filtered by the glomerulus. By binding to SGLT2 and inhibiting renal glucose reabsorption, dapagliflozin promotes urinary glucose ex-

cretion and reduces blood glucose levels independently of beta-cell function or insulin sensitivity, Dr. Clifford J. Bailey reported at the meeting. The findings were published simultaneously (*Lancet* 2010;375:2223-33).

In all, 546 patients were randomized to 2.5-mg, 5.0-mg, or 10.0-mg once-daily doses of dapagliflozin or placebo for 24 weeks, in addition to their usual metformin doses. Among the 534 who com-

pleted the trial, reductions in HbA_{1c} were significantly greater in the dapagliflozin groups, with mean reductions from baseline of 0.67, 0.70, and 0.84 percentage points with the 2.5-, 5.0-, and 10.0-mg doses, respectively, compared with 0.30 for placebo.

More patients in the dapagliflozin groups achieved an HbA_{1c} value of less than 7.0% at week 24 than did those in the placebo group, with the difference reaching statistical significance for the 5.0- and 10.0-mg doses (37.5% and 40.6%, respectively, vs. 25.9% for placebo). Differences in plasma fasting glucose concentrations were notable by week 1 in the dapagliflozin groups, and by week 24 were significant for all three doses (reductions of 18-23 mg/dL compared with 6 mg/dL with placebo).

Weight loss was also greater with dapagliflozin, compared with those assigned to placebo. At week 24, the 2.5-, 5.0-, and 10.0-mg groups had lost 2.2, 3.0, and 2.9 kg, respectively, compared with 0.9 kg for placebo patients. This reduction is potentially attributable to the loss of excess energy through glucose excretion in the urine, said Dr. Bailey, of Aston University, Birmingham, England.

Urinary glucose excretion increased in all of the dapagliflozin groups, whereas creatinine remained constant, Dr. Bailey noted.

There were no deaths during the study, and overall adverse events leading to discontinuation were less frequent with dapagliflozin than placebo. There were no major hypoglycemic events.

Signs, symptoms, and other reports suggestive of urinary tract infections were not increased with dapagliflozin, but reports of those suggesting genital infections were: These were reported by 8%-13% in the dapagliflozin groups, compared with 5% in the placebo group. The increased rate occurred in both men and women. All were of mild or moderate intensity and resolved with treatment, and none led to study discontinuation.

Genital infections are not uncommon in patients with diabetes and can be appropriately managed with better appreciation of those at higher risk, Dr. Bailey pointed out.

Serious adverse events were not associated with any particular group. No clinically meaningful changes in serum electrolytes occurred in any of the groups, and abnormalities in serum sodium and serum potassium were rare and transient. No alterations were seen in measures of renal function, including serum creatinine. No apparent changes occurred in fasting lipid profiles with dapagliflozin other than greater mean HDL cholesterol and lower triglycerides compared with placebo, he noted.

Aside from BMS and AZ, Dr. Bailey also has consulted for Merck Sharp & Dohme, Novo Nordisk, GlaxoSmith-Kline, and Takeda and has received research grants from Sanofi-Aventis. Three other study authors are employees of BMS, while BMS was the only disclosure for the fifth investigator. ■

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 \geq 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 \geq 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 T_{1/2} 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.

FORTEO® (teriparatide [rDNA origin] injection)

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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.

**PLEASE SEE FULL PRESCRIBING INFORMATION
FOR ADDITIONAL INFORMATION.**

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