

## THE REST OF YOUR LIFE

## The 50 Peaks That 'Changed My Life'

Dr. Douglas Butler and a climbing guide were trekking to the summit of Wyoming's tallest mountain, Gannett Peak (13,804 feet), when danger struck.

They had gotten off route and the morning sun began to loosen large rocks from steep snow-covered slopes on both sides of the trail. "Fortunately, they were coming down one at a time," said Dr. Butler, a fam-

ily physician who lives in Crumpler, N.C.

They dodged the falling rocks and escaped unharmed. It marked the most threatened Dr. Butler felt in his quest to reach Gannett and the highest geographical points in the other 49 United States, a pursuit—known as highpointing—he began in 1999 and completed in 2003.

The idea came from one of his high school teachers in Denver. "He had gone to

Kansas, which was a 2-3 hour drive from Denver, and spent most of the day trying to find that state's high point, because most of the hills in West Kansas are about the same height. He said it took him just about the whole day to find the correct hill. As a teenager, the quest seemed odd but intriguing to me. As my life went on, it seemed less odd and more intriguing."

Dr. Butler starting visiting mountain

peaks when he was in his mid-30s. He initially was drawn to remote destinations such as the volcanoes in Mexico and Ecuador, and Aconcagua, the highest peak in the Americas. "Then I got to thinking the state high points would be neat to do."

Now 53, Dr. Butler wrote a travel memoir about his journey, "A Walk Atop America: Fifty State Summits and a Dream to Reach Them All" ([www.awalkatopamerica.com](http://www.awalkatopamerica.com)). "People [enjoy] the way I did it, not just doing peak to peak but seeing the country and meeting the people near the peaks. ... People helped me. This is a great country, full of good people."

Dr. Butler topped most of the summits in 2000 and 2001. Most were accessible by automobile or by 2- to 5-mile hikes, but five required assistance from guides: Gannett Peak,



**Brief Summary:** For complete details, please see full Prescribing Information.

**INDICATIONS AND USAGE:** BYETTA is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione, but have not achieved adequate glycemic control.

**CONTRAINDICATIONS:** BYETTA is contraindicated in patients with known hypersensitivity to exenatide or to any of the product components.

**PRECAUTIONS: General—BYETTA is not a substitute for insulin in insulin-requiring patients. BYETTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.**

Patients may develop anti-exenatide antibodies following treatment with BYETTA, consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals. Patients receiving BYETTA should be observed for signs and symptoms of hypersensitivity reactions. In a small proportion of patients, the formation of anti-exenatide antibodies at high titers could result in failure to achieve adequate improvement in glycemic control.

The concurrent use of BYETTA with insulin, D-phenylalanine derivatives, meglitinides, or alpha-glucosidase inhibitors has not been studied.

BYETTA is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min; see Pharmacokinetics, Special Populations). In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg were not well tolerated due to gastrointestinal side effects.

BYETTA has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Its use is commonly associated with gastrointestinal adverse effects, including nausea, vomiting, and diarrhea. Therefore, the use of BYETTA is not recommended in patients with severe gastrointestinal disease. The development of severe abdominal pain in a patient treated with BYETTA should be investigated because it may be a warning sign of a serious condition.

**Hypoglycemia—**In the 30-week controlled clinical trials with BYETTA, a hypoglycemia episode was recorded as an adverse event if the patient reported symptoms associated with hypoglycemia with an accompanying blood glucose <60 mg/dL or if symptoms were reported without an accompanying blood glucose measurement. When BYETTA was used in combination with metformin, no increase in the incidence of hypoglycemia was observed. In contrast, when BYETTA was used in combination with a sulfonylurea, the incidence of hypoglycemia was increased over that of placebo in combination with a sulfonylurea. Therefore, patients receiving BYETTA in combination with a sulfonylurea may have an increased risk of hypoglycemia (Table 1).

Table 1: Incidence (%) of Hypoglycemia\* by Concomitant Antidiabetic Therapy

	BYETTA			BYETTA			BYETTA		
	Placebo BID	5 mcg BID	10 mcg BID	Placebo BID	5 mcg BID	10 mcg BID	Placebo BID	5 mcg BID	10 mcg BID
	With Metformin			With a Sulfonylurea			With MET/SFU		
N	113	110	113	123	125	129	247	245	241
Hypoglycemia	5.3%	4.5%	5.3%	3.3%	14.4%	35.7%	12.6%	19.2%	27.8%

\* In three 30-week placebo-controlled clinical trials. BYETTA and placebo were administered before the morning and evening meals. Abbreviations: BID, twice daily; MET/SFU, metformin and a sulfonylurea.

Most episodes of hypoglycemia were mild to moderate in intensity, and all resolved with oral administration of carbohydrate. To reduce the risk of hypoglycemia associated with the use of a sulfonylurea, reduction in the dose of sulfonylurea may be considered (see DOSAGE AND ADMINISTRATION). When used as add-on to a thiazolidinedione, with or without metformin, the incidence of symptomatic mild to moderate hypoglycemia with BYETTA was 11% compared to 7% with placebo.

BYETTA did not alter the counter-regulatory hormone responses to insulin-induced hypoglycemia in a randomized, double-blind, controlled study in healthy subjects.

**Information for Patients—**Patients should be informed of the potential risks of BYETTA. Patients should also be fully informed about self-management practices, including the importance of proper storage of BYETTA, injection technique, timing of dosage of BYETTA as well as concomitant oral drugs, adherence to meal planning, regular physical activity, periodic blood glucose monitoring and HbA<sub>1c</sub> testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications.

Patients should be advised to inform their physicians if they are pregnant or intend to become pregnant.

The risk of hypoglycemia is increased when BYETTA is used in combination with an agent that induces hypoglycemia, such as a sulfonylurea (see PRECAUTIONS, Hypoglycemia).

Patients should be advised that treatment with BYETTA may result in a reduction in appetite, food intake, and/or body weight, and that there is no need to modify the dosing regimen due to such effects. Treatment with BYETTA may also result in nausea (see ADVERSE REACTIONS).

**Drug Interactions—**The effect of BYETTA to slow gastric emptying may reduce the extent and rate of absorption of orally administered drugs. BYETTA should be used with caution in patients receiving oral medications that require rapid gastrointestinal absorption. For oral medications that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those drugs at least 1 h before BYETTA injection. If such drugs are to be administered with food, patients should be advised to take them with a meal or snack when BYETTA is not administered. The effect of BYETTA on the absorption and effectiveness of oral contraceptives has not been characterized.

**Warfarin:** Since market introduction there have been some spontaneously reported cases of increased INR with concomitant use of warfarin and BYETTA, sometimes associated with bleeding.

**Carcinogenesis, Mutagenesis, Impairment of Fertility—**A 104-week carcinogenicity study was conducted in male and female rats and benign thyroid C-cell adenomas were observed in female rats at all exenatide doses. The incidences in female rats were 8% and 5% in the two control groups and 14%, 11%, and 23% in the low-, medium-, and high-dose groups with systemic exposures of 5, 22, and 130 times, respectively, the human exposure resulting from the maximum recommended dose of 20 mcg/day.

In a 104-week carcinogenicity study in mice, no evidence of tumors was observed at doses up to 250 mcg/kg/day, a systemic exposure up to 95 times the human exposure resulting from the maximum recommended dose of 20 mcg/day.

Exenatide was not mutagenic or clastogenic, with or without metabolic activation, in the Ames bacterial mutagenicity assay or chromosomal aberration assay in Chinese hamster ovary cells.

**Pregnancy—Pregnancy Category C—**Exenatide has been shown to cause reduced fetal and neonatal growth, and skeletal effects in mice at systemic exposures 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day. Exenatide has been shown to cause skeletal effects in rabbits at systemic exposures 12 times the human exposure resulting from the maximum recommended dose of 20 mcg/day. There are no adequate and well-controlled studies in pregnant women. BYETTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant mice an increased number of neonatal deaths were observed on postpartum days 2-4 in dams given 6 mcg/kg/day, a systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day.

**Nursing Mothers—**It is not known whether exenatide is excreted in human milk. Caution should be exercised when BYETTA is administered to a nursing woman.

**Pediatric Use—**Safety and effectiveness of BYETTA have not been established in pediatric patients.

**Geriatric Use—**BYETTA was studied in 282 patients 65 years of age or older and in 16 patients 75 years of age or older. No differences in safety or effectiveness were observed between these patients and younger patients.

**ADVERSE REACTIONS: Use with metformin and/or a sulfonylurea—**In the three 30-week controlled trials of BYETTA add-on to metformin and/or sulfonylurea, adverse events with an incidence  $\geq$  5% (excluding hypoglycemia; see Table 1) that occurred more frequently in patients treated with BYETTA (N = 963) vs placebo (N = 483) were: nausea (44% vs 18%), vomiting (13% vs 4%), diarrhea (13% vs 6%), feeling jittery (9% vs 4%), dizziness (9% vs 6%), headache (9% vs 6%), and dyspepsia (6% vs 3%).

The adverse events associated with BYETTA generally were mild to moderate in intensity. The most frequently reported adverse event, mild to moderate nausea, occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased over time in most of the patients who initially experienced nausea. Adverse events reported in  $\geq$  1.0 to  $<$ 5.0% of patients receiving BYETTA and reported more frequently than with placebo included asthenia (mostly reported as weakness), decreased appetite, gastroesophageal reflux disease, and hyperhidrosis. Patients in the extension studies at 52 weeks experienced similar types of adverse events observed in the 30-week controlled trials.

The incidence of withdrawal due to adverse events was 7% for BYETTA-treated patients and 3% for placebo-treated patients. The most common adverse events leading to withdrawal for BYETTA-treated patients were nausea (3% of patients) and vomiting (1%). For placebo-treated patients,  $<$ 1% withdrew due to nausea and 0% due to vomiting.

**Use with a thiazolidinedione—**In the 16-week placebo-controlled study of BYETTA add-on to a thiazolidinedione, with or without metformin, the incidence and type of other adverse events observed were similar to those seen in the 30-week controlled clinical trials with metformin and/or a sulfonylurea. No serious adverse events were reported in the placebo arm. Two serious adverse events, namely chest pain (leading to withdrawal) and chronic hypersensitivity pneumonitis, were reported in the BYETTA arm.

The incidence of withdrawal due to adverse events was 16% (19/121) for BYETTA-treated patients and 2% (2/112) for placebo-treated patients. The most common adverse events leading to withdrawal for BYETTA-treated patients were nausea (9%) and vomiting (5%). For placebo-treated patients,  $<$ 1% withdrew due to nausea. Chills (n = 4) and injection-site reactions (n = 2) occurred only in BYETTA-treated patients. The two patients who reported an injection-site reaction had high titers of anti-exenatide antibody.

**Spontaneous Data—**Since market introduction of BYETTA, the following additional adverse reactions have been reported. Because these events 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. **General:** injection-site reactions; dysgeusia; somnolence, INR increased with concomitant warfarin use (some reports associated with bleeding). **Allergy/Hypersensitivity:** generalized pruritus and/or urticaria, macular or papular rash, angioedema; rare reports of anaphylactic reaction. **Gastrointestinal:** nausea, vomiting, and/or diarrhea resulting in dehydration with some reports associated with increased serum creatinine/acute renal failure that may be reversible if treated appropriately; abdominal distention, abdominal pain, eructation, constipation, flatulence, acute pancreatitis.

**Immunogenicity—**Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-exenatide antibodies following treatment with BYETTA.

**OVERDOSAGE:** Effects of an overdose include severe nausea, severe vomiting, and rapidly declining blood glucose concentrations. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

**DOSAGE AND ADMINISTRATION:** BYETTA therapy should be initiated at 5 mcg per dose administered twice daily at any time within the 60-minute period before the morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). BYETTA should not be administered after a meal. Based on clinical response, the dose of BYETTA can be increased to 10 mcg twice daily after 1 month of therapy. Each dose should be administered as a SC injection in the thigh, abdomen, or upper arm.

#### Rx ONLY

Manufactured for Amylin Pharmaceuticals, Inc., San Diego, CA 92121  
Marketed by Amylin Pharmaceuticals, Inc. and Eli Lilly and Company  
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COURTESY DR. DOUGLAS BUTLER

Dr. Douglas Butler, a family physician, is shown here scaling Mount Rainier.

Mount McKinley in Alaska (20,320 feet), Mount Rainier in Washington (14,411), Granite Peak in Montana (12,799 feet), and Mount Hood in Oregon (11,239 feet).

His effort to reach Panorama Point, the highest summit in Nebraska at 5,424 feet, would have been thwarted were it not for the kindness of perfect strangers. The 20 miles of dirt road leading to the peak were covered with 6 inches of snow, and a blizzard was approaching. "I had this little rental car. I got about one-third of the way. ... It was getting dark." He flagged down a farmer, who took him to his house and "called somebody with a four-wheel drive, who drove me to the farm where the high point was. People left their dinners; they did all of this for a stranger."

These kinds of encounters "changed my life," said Dr. Butler, who is a locum tenens physician with Project USA, which provides medical care for Native Americans. "Physicians don't get [much] kindness from anybody except their patients. To get out and see that kindness made me want to go back in a system where I can work more directly with the patients and not have to fight the reimbursement systems. That's one reason I chose [American] Indian health."

"There are some mountains I'd like to climb in South America, but the knees and the hips aren't what they used to be." ■

By Doug Brunk, San Diego Bureau