

Injected Carbon Beads May Curb Fecal Incontinence

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FORT LAUDERDALE, FLA. — Injecting the anal sphincter with microscopic carbon beads led to a promising degree of improvement in fecal incontinence, based on interim results from a phase II study.

Several injection therapies have been tested for fecal incontinence caused by abnormalities of the internal anal sphincter. Injection with Durasphere FI beads is one

of the treatments that is most advanced in clinical development. It appears that this approach may relieve symptoms for some patients, but so far no injectables have been approved for this use in the United States, Dr. Eric G. Weiss said at an international colorectal disease symposium sponsored by the Cleveland Clinic Florida.

A multicenter, phase II study enrolled 77 patients who received intersphincteric injections with microscopic, pyrolytic carbon beads in a suspension gel; each bead

is 212-500 mcm in diameter. The introduced material is designed to passively close the anal canal and distal rectum and also improve anal symmetry.

The study also enrolled about 40 patients who received injections of saline only; data have not yet been released on these control patients. The study was sponsored by Carbon Medical Technologies, which makes the Durasphere beads.

At baseline, the average Cleveland Clinic Incontinence Score (CCIS) of the 77 pa-

tients randomized to receive bead treatment was 12.7, and they had a mean of 21 incontinence episodes every 2 weeks. Their average age was 65 years (range 26-90 years), and 79% were women.

By 1 month after treatment, the average CCIS had dropped to 10.5, with follow-up on all 77 patients. Six-month follow-up data were available for 49 patients, and in this subgroup the average CCIS score was 8.3 (the average CCIS at baseline for this subgroup was 12.4).

This degree of improvement is an important finding because a CCIS of less than 8.5 indicates "significant improvement in quality of life," said Dr. Weiss, a colorectal surgeon at Cleveland Clinic Florida, Weston.

Data from 12-month follow-up were available for 28 patients. In this subgroup, the mean CCIS was 8.2 after 1 year, down from an average of 12.3 at baseline.

Self-assessments by the 49 patients followed for 6 months showed that 41% said their status was much better, compared with baseline, and 29% rated themselves as a little better. Another 22% rated themselves as about the same, 2% said they were a little worse, and 6% self-rated as much worse.

Of the 77 actively treated patients, 24 had a mild adverse event, and 7 patients had a moderate adverse event. No patients had a severe adverse event.

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The most common adverse events were rectal pain or irritation in 10 patients, an abscess in 10 patients, and bead leakage in 7 patients. Two patients had rectal bleeding, and one patient each had an allergic reaction and anal stiffness.

Patients were injected with the carbon beads during an outpatient, ambulatory procedure using local anesthesia. In the initial, phase I study, some patients received the beads in the anal submucosal space, but during the study this approach was replaced by injections into the intersphincteric space using ultrasound guidance, which appeared to have better efficacy. The beads were injected at six locations set 60 degrees apart.

Durasphere beads were approved by the Food and Drug Administration in 1999 for treatment of women with urinary incontinence. The beads are approved for the fecal incontinence indication in Europe. The manufacturer is also developing the beads for treatment of gastroesophageal reflux.

Several other injectable materials have been clinically tested for treating fecal incontinence in phase I studies. Results have been reported from studies that used polytef; autologous fat; Contigen, a collagen implant; Bioplastique, a silicone polymer; Solesta, a hyaluronic acid gel; and microballoons. Bioplastique was also tested in a phase II study with 82 patients, Dr. Weiss said.



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	5 mcg	10 mcg	Placebo	5 mcg	10 mcg	Placebo	5 mcg	10 mcg
	BID	BID	BID	BID	BID	BID	BID	BID	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_{1c} 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 distension, 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
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