

# Estrogen Patches Slashed PSA in Prostate Cancer

BY PATRICE WENDLING

ORLANDO — Estrogen patches produce a similar fall in testosterone and prostate-specific antigen levels when compared with luteinizing hormone-releasing hormone analogues in locally advanced and metastatic prostate cancer, according to interim results from the phase II, multicenter PATCH trial.

Intention-to-treat data from the first

100 patients show that castration was achieved at 4 weeks in 67% of 30 men who started treatment with three patches that were changed twice weekly. This increased to 91% of 33 men who started with four patches changed twice weekly. In comparison, 64% of 33 men who were treated with LHRH analogues achieved castration by that time point.

At 12 weeks, castration rates were

72%, 87%, and 93%, respectively, coauthors Dr. Ruth Langley and Dr. Paul Abel reported in a poster at a symposium on genitourinary cancers. Castration was defined as a testosterone level of 50 ng/dL or less.

PSA responses were observed in all three groups at 6 months. Levels fell from a baseline median of 51 ng/mL in both patch groups to 1.3 ng/mL with four patches changed twice weekly and

3.2 ng/mL with three patches changed twice weekly. They went from a median of 35 ng/mL at baseline to 0.9 ng/mL at 6 months in the control group.

“Providing [that these data] continue to look promising, we are aiming to extend this to a phase III study,” Dr. Langley of the U.K. Medical Research Council Clinical Trials Unit said in an interview.

The hypothesis behind the PATCH (Prostate Adenocarcinoma: Transcutaneous Hormones) trial is that the application of estrogen to the skin will avoid first-pass hepatic metabolism (that is, the hepatic metabolism of a drug when it is absorbed from the gut and delivered to the liver via the portal vein), and therefore will not be associated with the same cardiovascular toxicity previously shown by oral estrogen.

Prolonged use of LHRH analogues has also raised concerns about long-term toxicity, particularly osteoporosis and metabolic syndrome.

Estrogen has been shown in previous studies to protect against bone mineral density loss in women, and pilot data from a study in 20 men with prostate cancer show that transdermal estrogen improved bone density at 1 year (J. Urol. 2004;172:2203-7).

“The mechanism underlying this is not clear, but it has been postulated that androgens are converted by aromatase to estradiol in bone, and thus some of the protective effects of androgens on bone are mediated through local production of estrogen,” Dr. Langley said.

As of mid-February 2009, 172 men had been randomized to three arms: three estrogen patches changed twice weekly for 4 weeks, followed by two patches changed twice weekly for an indefinite time; four patches changed twice weekly for 4 weeks, followed by three patches changed indefinitely; or a control arm of LHRH analogues, as per local practice. The primary end point is cardiovascular mortality and morbidity.

A Gleason score greater than 7 was reported in 44% of control patients and in 49% of patch patients. Their median age was 75 years and 73 years, respectively.

Four patients have stopped using patches because they were falling off, and two stopped by choice.

Noncardiovascular toxicity has been as expected, and includes gynecomastia and some erythema, the authors reported at the meeting, which was sponsored by the American Society of Clinical Oncology, the American Society for Radiation Oncology, and the Society of Urologic Oncology. One patient developed erythema nodosum, which started approximately 4 weeks after the patches were placed, and resolved when they were discontinued.

The PATCH trial is sponsored by the Imperial College London and funded by Cancer Research U.K. Dr. Abel, of Imperial College London, disclosed consultancy with Ascend Pharmaceuticals, which makes an estrogen gel. ■



**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.

Postmarketing cases of acute pancreatitis have been reported in patients treated with BYETTA. Patients should be informed that persistent severe abdominal pain, which may be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. If pancreatitis is suspected, BYETTA and other potentially suspect drugs should be discontinued, confirmatory tests performed and appropriate treatment initiated. Resuming treatment with BYETTA is not recommended if pancreatitis is confirmed and an alternative etiology for the pancreatitis has not been identified.

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.

There have been rare, spontaneously reported events of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis. Some of these events occurred in patients receiving one or more pharmacologic agents known to affect renal function/hydration status and/or in patients experiencing nausea, vomiting, and/or diarrhea, with or without dehydration. Concomitant agents included angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, and diuretics. Reversibility of altered renal function has been observed with supportive treatment and discontinuation of potentially causative agents, including exenatide. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

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.

**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). Patients should be informed that persistent severe abdominal pain, which may be accompanied by vomiting, is the hallmark symptom of acute pancreatitis and be instructed to contact their physician if this symptom occurs (see PRECAUTIONS).

**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 ≥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 (5% 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 ≥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 (5% 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; abdominal distension, abdominal pain, eructation, constipation, flatulence, acute pancreatitis (see PRECAUTIONS). **Renal and Urinary Disorders:** altered renal function, including acute renal failure, worsened chronic renal failure, renal impairment, increased serum creatinine (see PRECAUTIONS).

**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 by Amylin Pharmaceuticals, Inc., San Diego, CA 92121  
Marketed by Amylin Pharmaceuticals, Inc. and Eli Lilly and Company  
1-800-868-1190

Literature Revised October 2007

BYETTA is a registered trademark of Amylin Pharmaceuticals, Inc.

© 2007 Amylin Pharmaceuticals, Inc. All rights reserved.

www.BYETTA.com  
02-07-5784-A

822007-AA

