

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BYETTA safely and effectively. See full prescribing information for BYETTA.

BYETTA (exenatide) Injection

Initial U.S. Approval: 2005

RECENT MAJOR CHANGES

Warnings and Precautions (5.1) 2/2015

INDICATIONS AND USAGE

BYETTA (exenatide) is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1.1, 1.4).

Important Limitations of Use

- Not a substitute for insulin. BYETTA should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis (1.2).
- Concurrent use with prandial insulin has not been studied and cannot be recommended (1.2).
- Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis (1.2).

DOSAGE AND ADMINISTRATION

- Inject subcutaneously within 60 minutes prior to morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart) (2.1).
- Initiate at 5 mcg per dose twice daily; increase to 10 mcg twice daily after 1 month based on clinical response (2.1).

DOSAGE FORMS AND STRENGTHS

BYETTA is supplied as 250 mcg/mL exenatide in:

- 5 mcg per dose, 60 doses, 1.2 mL prefilled pen
- 10 mcg per dose, 60 doses, 2.4 mL prefilled pen

CONTRAINDICATIONS

- History of severe hypersensitivity to exenatide or any product components (4.1).

WARNINGS AND PRECAUTIONS

- Never share a BYETTA pen between patients, even if the needle is changed (5.1).
- Pancreatitis: Postmarketing reports with exenatide, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. *Discontinue BYETTA promptly. BYETTA should not be restarted.* Consider other antidiabetic therapies in patients with a history of pancreatitis (5.2).
- Hypoglycemia: Increased risk when BYETTA is used in combination with medications known to cause hypoglycemia (e.g., insulin or insulin secretagogue). Consider reducing the dose of insulin or insulin secretagogue (5.3).

- Renal Impairment: Postmarketing reports with exenatide, sometimes requiring hemodialysis and kidney transplantation. BYETTA should not be used in patients with severe renal impairment or end-stage renal disease and should be used with caution in patients with renal transplantation. Caution should be applied when initiating BYETTA or escalating the dose of BYETTA in patients with moderate renal failure (5.4, 8.6, 12.3).
- Severe Gastrointestinal Disease: Use of BYETTA is not recommended in patients with severe gastrointestinal disease (e.g., gastroparesis) (5.5).
- Hypersensitivity: Postmarketing reports with exenatide of hypersensitivity reactions (e.g., anaphylaxis and angioedema). The patient should discontinue BYETTA and other suspect medications and promptly seek medical advice (5.7).
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug (5.8).

ADVERSE REACTIONS

- Most common ($\geq 5\%$) and occurring more frequently than placebo in clinical trials: nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia, constipation, asthenia. Nausea usually decreases over time (5.3, 6).
- Postmarketing reports with exenatide of increased international normalized ratio (INR) with concomitant use of warfarin, sometimes with bleeding (6.2, 7.2).

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 and www.byetta.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- May impact absorption of orally administered medications (7.1, 12.3).
- Warfarin: Postmarketing reports of increased INR sometimes associated with bleeding. Monitor INR frequently until stable upon initiation or alteration of BYETTA therapy (6.2, 7.2).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, BYETTA may cause fetal harm. BYETTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To report drug exposure during pregnancy call 1-800-633-9081 (8.1).
- Nursing Mothers: Caution should be exercised when BYETTA is administered to a nursing woman (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Type 2 Diabetes Mellitus

BYETTA (exenatide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [see [Clinical Studies \(14\)](#)].

1.2 Important Limitations of Use

BYETTA is not a substitute for insulin. BYETTA should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis, as it would not be effective in these settings.

The concurrent use of BYETTA with prandial insulin has not been studied and cannot be recommended.

Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. BYETTA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYETTA. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

BYETTA should be initiated at 5 mcg administered twice daily (BID) 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. Initiation with 5 mcg reduces the incidence and severity of gastrointestinal side effects. Each dose should be administered as a subcutaneous (SC) injection in the thigh, abdomen, or upper arm. Do not mix BYETTA with insulin. Do not transfer BYETTA from the pen to a syringe or a vial. No data are available on the safety or efficacy of intravenous or intramuscular injection of BYETTA.

Use BYETTA only if it is clear, colorless and contains no particles.

3 DOSAGE FORMS AND STRENGTHS

BYETTA is supplied as a sterile solution for subcutaneous injection containing 250 mcg/mL exenatide in the following packages:

- 5 mcg per dose, 60 doses, 1.2 mL prefilled pen

- 10 mcg per dose, 60 doses, 2.4 mL prefilled pen

4 CONTRAINDICATIONS

4.1 Hypersensitivity

BYETTA is contraindicated in patients with prior severe hypersensitivity reactions to exenatide or to any of the product components.

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a BYETTA Pen Between Patients

BYETTA pens must never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.

5.2 Acute Pancreatitis

Based on postmarketing data, BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYETTA, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, BYETTA should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYETTA should not be restarted. Consider antidiabetic therapies other than BYETTA in patients with a history of pancreatitis.

5.3 Use with Medications Known to Cause Hypoglycemia

The risk of hypoglycemia is increased when BYETTA is used in combination with a sulfonylurea. Therefore, patients receiving BYETTA and a sulfonylurea may require a lower dose of the sulfonylurea to reduce the risk of hypoglycemia.

When BYETTA is used in combination with insulin, the dose of insulin should be evaluated. In patients at increased risk of hypoglycemia consider reducing the dose of insulin [see [Adverse Reactions \(6.1\)](#)]. The concurrent use of BYETTA with prandial insulin has not been studied and cannot be recommended. It is also possible that the use of BYETTA with other glucose-independent insulin secretagogues (e.g., meglitinides) could increase the risk of hypoglycemia.

For additional information on glucose-dependent effects see [Mechanism of Action \(12.1\)](#).

5.4 Renal Impairment

BYETTA should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation [see [Use in Specific Populations \(8.6\)](#)]. In patients with end-stage renal disease

receiving dialysis, single doses of BYETTA 5 mcg were not well tolerated due to gastrointestinal side effects. Because BYETTA may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Caution should be applied when initiating or escalating doses of BYETTA from 5 to 10 mcg in patients with moderate renal impairment (creatinine clearance 30-50 mL/min).

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

5.5 Gastrointestinal Disease

BYETTA has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Because BYETTA is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhea, the use of BYETTA is not recommended in patients with severe gastrointestinal disease.

5.6 Immunogenicity

Patients may develop antibodies to exenatide following treatment with BYETTA. Antibody levels were measured in 90% of subjects in the 30-week, 24-week, and 16-week placebo-controlled studies and the 30-week comparator-controlled study of BYETTA. In 3%, 4%, 1%, and 1% of these patients, respectively, antibody formation was associated with an attenuated glycemic response. If there is worsening glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered [see [Adverse Reactions \(6.1\)](#)].

5.7 Hypersensitivity

There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) in patients treated with BYETTA. If a hypersensitivity reaction occurs, the patient should discontinue BYETTA and other suspect medications and promptly seek medical advice [see [Adverse Reactions \(6.2\)](#)].

5.8 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug.

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