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----------

Indications and Usage	10/2009
Monotherapy and Combination Therapy (1.1)	
Important Limitations of Use	10/2009
History of Pancreatitis (1.2)	
Warnings and Precautions	10/2009
Pancreatitis (5.1)	
Renal Impairment (5.3)	
Macrovascular Outcomes (5.7)	

----------INDICATIONS AND USAGE----------

BYETTA 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.

Important Limitations of Use

- BYETTA is not a substitute for insulin. BYETTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (1.2).
- The concurrent use of BYETTA with insulin has not been studied and cannot be recommended (1.2).
- BYETTA 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----------

- Pancreatitis: Postmarketing reports, 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 (5.1).
- Hypoglycemia: Increased risk when BYETTA is used in combination with a sulfonylurea. Consider reducing the sulfonylurea dose (5.2).
- Renal Impairment: Postmarketing reports, 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 (5.3).
- Severe Gastrointestinal Disease: Use of BYETTA is not recommended in patients with severe gastrointestinal disease (e.g., gastroparesis) (5.4).
- Hypersensitivity: Postmarketing reports of hypersensitivity reactions (e.g. anaphylaxis and angioedema). The patient should discontinue BYETTA and other suspect medications and promptly seek medical advice (5.6).
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug (5.7).

----------ADVERSE REACTIONS----------

- Most common (≥5%) and occurring more frequently than placebo in clinical trials: nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia. Nausea usually decreases over time (5.2; 6).
- Postmarketing reports of increased international normalized ratio (INR) with concomitant use of warfarin, sometimes with bleeding (6.2).

To report SUSPECTED ADVERSE REACTIONS contact Amylin Pharmaceuticals, Inc. and Eli Lilly and Company at 1-800-868-1190 and www.byetta.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Warfarin: Postmarketing reports of increased INR sometimes associated with bleeding. Monitor INR frequently until stable upon initiation or alteration of BYETTA therapy (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 FDA-approved patient labeling.

Revised: 10/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Type 2 Diabetes Mellitus

BYETTA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

1.2 Important Limitations of Use

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

The concurrent use of BYETTA with 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 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. 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 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.

5.2 Hypoglycemia

The risk of hypoglycemia is increased when BYETTA is used in combination with a sulfonylurea (hypoglycemia can also occur when other antidiabetic agents are 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. 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)*.

5.3 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 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 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.

5.4 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.

5.5 Immunogenicity

Patients may develop antibodies to exenatide following treatment with BYETTA, consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals. In a small proportion of patients, the formation of antibodies to exenatide at high titers could result in failure to achieve adequate improvement in glycemic control. If there is worsening glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered *[see Adverse Reactions (6.1)]*.

5.6 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)]*.

5.7 Macrovascular Outcomes

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

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Hypoglycemia

Table 1 summarizes the incidence and rate of hypoglycemia with BYETTA in five placebo-controlled clinical trials.

Table 1: Incidence (%) and Rate of Hypoglycemia When BYETTA was Used as Monotherapy or With Concomitant Antidiabetic Therapy in Five Placebo-Controlled Clinical Trials*

	BYETTA		
	Placebo twice daily	**5 mcg twice daily**	**10 mcg twice daily**
Monotherapy (24 Weeks)			
N	77	77	78
% Overall	1.3%	5.2%	3.8%
Rate (episodes/patient-year)	0.03	0.21	0.52
% Severe	0.0%	0.0%	0.0%
With Metformin (30 Weeks)			
N	113	110	113
% Overall	5.3%	4.5%	5.3%
Rate (episodes/patient-year)	0.12	0.13	0.12
% Severe	0.0%	0.0%	0.0%
With a Sulfonylurea (30 Weeks)			
N	123	125	129
% Overall	3.3%	14.4%	35.7%
Rate (episodes/patient-year)	0.07	0.64	1.61
% Severe	0.0%	0.0%	0.0%
With Metformin and a Sulfonylurea (30 Weeks)			
N	247	245	241
% Overall	12.6%	19.2%	27.8%
Rate (episodes/patient-year)	0.58	0.78	1.71
% Severe	0.0%	0.4%	0.0%
With a Thiazolidinedione (16 Weeks)			
N	112	Dose not studied	121
% Overall	7.1%	Dose not studied	10.7%
Rate (episodes/patient-years)	0.56	Dose not studied	0.98
% Severe	0.0%	Dose not studied	0.0%

* For the 30-week trials, a hypoglycemia episode was recorded if the patient reported symptoms consistent with hypoglycemia and was recorded as severe if the subject required the assistance of another person to treat the event. For the other trials, a hypoglycemic episode was recorded if a patient reported signs or symptoms of hypoglycemia or had a blood glucose value consistent with hypoglycemia regardless of associated symptoms or treatment and was recorded as severe if the subject required the assistance of another person to treat the event. The requirement for assistance had to be accompanied by a blood glucose measurement of <50 mg/dL or prompt recovery after administration of oral carbohydrate.

N = The number of Intent-to-Treat subjects in each treatment group.

Immunogenicity

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