

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-919

REMS

NDA 21-773, 21-919

BYETTA (exenatide) injection
(glucagon-like peptide (GLP)-1 receptor agonist)

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS FOR RISK MITIGATION

A. Pancreatitis: To mitigate the potential risk of undiagnosed and/or complicated pancreatitis associated with BYETTA (exenatide) by:

1. Raising the level of patient and healthcare professional (HCP) awareness of:
(i) the signs and symptoms of pancreatitis, including necrotizing and hemorrhagic pancreatitis; and (ii) how to distinguish between common gastrointestinal adverse reactions of BYETTA (exenatide) (nausea, vomiting) versus the hallmark symptom of pancreatitis, which is severe and persistent abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting;
2. Informing HCPs of the importance of timely evaluation of patients for possible pancreatitis when they present with symptoms.

B. Renal Failure: To mitigate the potential risk of renal failure associated with BYETTA (exenatide) by:

1. raising the level of patient and HCP awareness of: (i) the signs and symptoms of newly developed or worsening renal impairment; and (ii) when to use caution in treating patients with renal impairment.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be enclosed with each BYETTA (exenatide) prescription in accordance with 21 CFR 208.24. The Medication Guide is enclosed within each BYETTA carton at the time of final product assembly along with the Prescribing Information and User Manual.

The Medication Guide is appended as [Appendix 1](#).

B. Communication Plan

In accordance with FDCA 505-1(e)(3), Amylin will implement the following elements of a communication plan to HCPs likely to prescribe BYETTA (exenatide):

A Dear HCP (DHCP) Letter will be distributed concurrent with implementation of the revised product labeling. The letter will also be available via a link from the BYETTA (exenatide) website and through the medical information department. The intended audience for this letter is HCPs who are likely to prescribe BYETTA (exenatide) as well as pharmacists likely to dispense BYETTA (exenatide). This audience will be HCPs who have written at least one BYETTA (exenatide) prescription within the last 12 months, which includes physicians, nurse practitioners, and physicians' assistants predominantly in the specialties of endocrinology, internal medicine, and family practice, as well as all retail pharmacists. The DHCP letter is appended as [Appendix 2](#).

C. Elements to Assure Safe Use

Elements to Assure Safe Use are not required.

D. Implementation System

An Implementation System is not required.

E. Timetable for Submission of Assessments

REMS Assessments will be submitted to FDA no later than 18 months, 3 years, and, if necessary, 7 years following the date of the REMS approval by FDA.

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Amylin Pharmaceuticals will submit each assessment so that it will be received by the FDA on or before the due date.

APPENDIX 1.

MEDICATION GUIDE

Medication Guide
BYETTA[®] (bye-A-tuh)
(exenatide)
Injection

Read this Medication Guide and the Pen User Manual that come with BYETTA before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment. If you have questions about BYETTA after reading this information, ask your healthcare provider or pharmacist.

What is the most important information I should know about BYETTA?

Serious side effects can happen in people who take BYETTA, including inflammation of the pancreas (pancreatitis) which may be severe and lead to death.

Certain medical conditions make you more likely to get pancreatitis.

Before taking BYETTA, tell your healthcare provider if you have had:

- pancreatitis.
- stones in your gallbladder (gallstones).
- a history of alcoholism.
- high blood triglyceride levels.

While taking BYETTA:

Call your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe, and will not go away. The pain may happen with or without vomiting. The pain may be felt going from your abdomen through to your back. These may be symptoms of pancreatitis.

What is BYETTA?

- BYETTA is an injectable prescription medicine that may improve blood sugar (glucose) control in adults with type 2 diabetes mellitus, when used with a diet and exercise program.
- BYETTA is not insulin.
- You should not take BYETTA instead of insulin.
- The use of BYETTA with insulin is not recommended.
- BYETTA is not for people with type 1 diabetes or people with diabetic ketoacidosis.
- It is not known if BYETTA is safe and effective in children.
- BYETTA has not been studied in people who have pancreatitis.
- BYETTA should not be used in people who have severe kidney problems.

Who should not use BYETTA?

Do not use BYETTA if:

- you have had an allergic reaction to exenatide or any of the other ingredients in BYETTA. See the end of this Medication Guide for a complete list of ingredients in BYETTA.

Symptoms of a severe allergic reaction with BYETTA may include:

- swelling of your face, lips, tongue, or throat
- problems breathing or swallowing
- severe rash or itching
- fainting or feeling dizzy
- very rapid heartbeat

What should I tell my healthcare provider before using BYETTA?

Before taking BYETTA, tell your healthcare provider if you:

- have or have had pancreatitis, stones in your gallbladder (gallstones), a history of alcoholism, or high blood triglyceride levels.
- have severe problems with your stomach, such as delayed emptying of your stomach (gastroparesis) or problems with digesting food.

- have or have had kidney problems, or have had a kidney transplant.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if BYETTA will harm your unborn baby.

Pregnancy Registry: Amylin Pharmaceuticals, Inc. has a registry for women who take BYETTA during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. If you take BYETTA at any time during pregnancy you may enroll in this registry by calling (800) 633-9081.

- are breastfeeding or plan to breast-feed. It is not known if BYETTA passes into your breast milk. You and your healthcare provider should decide if you will take BYETTA or breast-feed. You should not do both without talking with your healthcare provider first.

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements. BYETTA slows stomach emptying and can affect medicines that need to pass through the stomach quickly. BYETTA may affect the way some medicines work and some other medicines may affect the way BYETTA works.

Especially tell your healthcare provider if you take:

- insulin, or any other anti-diabetes medicines.
- birth control pills that are taken by mouth (oral contraceptives). BYETTA may lower the amount of the medicine in your blood from your birth control pills and they may not work as well to prevent pregnancy. Take your birth control pills at least one hour before your injection of BYETTA. If you must take your birth control pills with food, take it with a meal or snack where you do not also take BYETTA.
- an antibiotic. Take antibiotic medicines at least one hour before taking BYETTA. If you must take your antibiotic with food, take it with a meal or snack where you do not also take BYETTA.
- warfarin sodium (Coumadin[®], Jantoven[®]).
- a blood pressure medicine.
- a water pill (diuretic).

- a pain medicine.
- lovastatin (Altoprev[®], Mevacor[®], Advicor[®]).

Ask your healthcare provider if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist each time you get a new medicine.

How should I use BYETTA?

See the Pen User Manual that comes with BYETTA for instructions for using the BYETTA Pen and injecting BYETTA.

- Your healthcare provider may prescribe BYETTA alone or with certain other medicines to help control your blood sugar.
- BYETTA comes in a prefilled pen.
- Use BYETTA exactly as prescribed by your healthcare provider. Do not change your dose unless your healthcare provider has told you to change your dose.
- Your healthcare provider must teach you how to inject BYETTA before you use it for the first time. If you have questions or do not understand the instructions, talk to your healthcare provider or pharmacist.
- Pen needles are not included. You may need a prescription to purchase pen needles from your pharmacist. Ask your healthcare provider which needle length and gauge is best for you.
- Inject your dose of BYETTA under the skin (subcutaneous injection) of your upper leg (thigh), stomach area (abdomen), or upper arm as instructed by your healthcare provider. **Do not inject into a vein or muscle.**
- BYETTA is injected two times each day, at any time within the 60 minutes (1 hour) **before** your morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). **Do not take BYETTA after your meal.**
- If you miss a dose of BYETTA, skip that dose and take your next dose at the next prescribed time. Do not take an extra dose or

increase the amount of your next dose to make up for a missed dose.

- If you use too much BYETTA, call your healthcare provider or poison control center right away. Too much BYETTA can cause your blood sugar to drop quickly and you may have symptoms of low blood sugar. You may need medical treatment right away. Too much BYETTA can also cause severe nausea and vomiting.
- Follow your healthcare provider's instructions for diet, exercise, and how often to test your blood sugar. If you see your blood sugar increasing during treatment with BYETTA, talk to your healthcare provider because you may need to adjust your current treatment plan for your diabetes.
- Talk to your healthcare provider about how to manage high blood sugar (hyperglycemia) and low blood sugar (hypoglycemia), and how to recognize problems that can happen with your diabetes.
- Never share your BYETTA pen with another person. You may give an infection to them, or get an infection from them, and BYETTA may harm them.

What are the possible side effects of BYETTA?

BYETTA can cause serious side effects.

See "What is the most important information I should know about BYETTA?"

It is not known whether BYETTA, or other anti-diabetes medications, increase your risk of a heart attack or stroke.

- **Low blood sugar (hypoglycemia).** Your risk for getting low blood sugar is higher if you take BYETTA with another medicine that can cause low blood sugar, such as a sulfonylurea. The dose of your sulfonylurea medicine may need to be lowered while you use BYETTA. Signs and symptoms of low blood sugar may include:
 - headache
 - drowsiness
 - weakness
 - dizziness
 - confusion
 - irritability
 - hunger
 - fast heart beat
 - sweating
 - feeling jittery

Talk with your healthcare provider about how to treat low blood sugar.

- **Kidney problems.** BYETTA may cause new or worse problems with kidney function, including kidney failure. Dialysis or kidney transplant may be needed.
 - **While taking BYETTA:**
Call your healthcare provider right away if you have nausea, vomiting, or diarrhea that will not go away, or if you cannot take liquids by mouth. You may be at increased risk for kidney problems.
- **Severe allergic reactions.** Severe allergic reactions can happen with BYETTA. Stop taking BYETTA, and get medical help right away if you have any symptom of a severe allergic reaction. See “Who should not take BYETTA?”

The most common side effects with BYETTA include:

- nausea. Nausea most commonly happens when first starting BYETTA, but may become less over time.
- vomiting.
- diarrhea.
- dizziness.
- headache.
- feeling jittery.
- acid stomach.

Talk to your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with BYETTA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BYETTA?

- Store your new, unused BYETTA Pen in the original carton in a refrigerator at 36°F to 46°F (2°C to 8°C).

- After first use, keep your BYETTA Pen at a temperature cooler than 77°F (25°C).
- Do not freeze your BYETTA Pen. Do not use BYETTA if it has been frozen.
- Protect BYETTA from light.
- Use a BYETTA Pen for only 30 days. Throw away a used BYETTA Pen after 30 days, even if there is some medicine left in the pen.
- Do not use BYETTA after the expiration date printed on the label.
- Do not store the BYETTA Pen with the needle attached. If the needle is left on, medicine may leak from the BYETTA Pen or air bubbles may form in the cartridge.
- See the BYETTA Pen User Manual for instructions about the right way to throw away your BYETTA Pen.
- **Keep your BYETTA Pen, pen needles, and all medicines out of the reach of children.**

General information about BYETTA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BYETTA for a condition for which it was not prescribed. Do not give BYETTA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide includes the most important information you should know about using BYETTA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about BYETTA that is written for health professionals.

For more information about BYETTA, go to <http://www.BYETTA.com> or call BYETTA Customer Service at 1-800-868-1190.

What are the ingredients in BYETTA?

Active Ingredient: exenatide

Inactive Ingredients: metacresol, mannitol, glacial acetic acid, and sodium acetate trihydrate in water for injection.

Revised October 2009

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

BYETTA is a registered trademark of Amylin Pharmaceuticals, Inc.
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APPENDIX 2

DHCP Letter

September 2009

IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Professional:

In 2006, acute pancreatitis and acute renal failure were added to the BYETTA[®] (exenatide) injection Prescribing Information (PI) as postmarketing adverse events. The PI was updated in October 2007 to add Precautions about acute pancreatitis, renal impairment and renal failure based on postmarketing reports. A Dear Healthcare Professional Letter was distributed at that time.

At this time, Amylin Pharmaceuticals, Inc. (Amylin) and Eli Lilly and Company (Lilly) wish to inform you of further updates to the Prescribing Information for BYETTA regarding acute pancreatitis and renal impairment.

Listed below are the revised paragraphs in the *Important Limitations of Use* and *Warnings and Precautions* sections of the PI. Please refer to the enclosed complete Prescribing Information for the full text of all information contained within these sections.

1.2 Important Limitations of Use:

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.

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.

5.3 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.

To better understand any potential relationship between the use of BYETTA and reports of adverse events, Amylin and Lilly continue to carefully monitor adverse events through ongoing surveillance and analysis, in addition to ongoing epidemiologic investigations.

To report adverse events among patients taking BYETTA, please call 1-800-868-1190. Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by facsimile at 1-800-FDA-0178, or by mail using FDA Form 3500 at <http://www.fda.gov/medwatch/index.html>.

Please contact our Medical Information department at 1-800-868-1190 if you have any questions about the information in this letter or the safe and effective use of BYETTA.

Sincerely,

Lisa Porter, MD
Vice President
Research & Development, ExenatideOne
Amylin Pharmaceuticals, Inc.

Donald Therasse, MD
Vice President, Global Patient Safety
Eli Lilly and Company

Enclosure: BYETTA® (exenatide) injection Full Prescribing Information (version)

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|-----------------------------------|---|
| NDA-21773 | SUPPL-9 | AMYLIN PHARMACEUTICA LS INC | BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML |
| NDA-21773 | SUPPL-11 | AMYLIN PHARMACEUTICA LS INC | BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML |
| NDA-21773 | SUPPL-17 | AMYLIN PHARMACEUTICA LS INC | BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML |
| NDA-21773 | SUPPL-18 | AMYLIN PHARMACEUTICA LS INC | BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML |
| NDA-21773 | SUPPL-22 | AMYLIN PHARMACEUTICA LS INC | BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML |
| NDA-21773 | SUPPL-25 | AMYLIN PHARMACEUTICA LS INC | BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML |

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/s/

MARY H PARKS
10/30/2009