

## NEW DRUG UPDATE

<b>Drug Name:</b>	<b>exenatide</b>
<b>Trade Name (Manufacturer):</b>	<b>Bydureon®</b> (Amylin Pharmaceuticals)
<b>Form:</b>	Extended-Release Injectable
<b>Strength:</b>	2 mg
<b>FDA Approval:</b>	February 14, 2012
<b>Market Availability:</b>	Currently available
<b>FDA Approval Classification:</b>	Standard review
<b>Classification:</b>	Specific Therapeutic Class (HIC3): Hypoglycemics, Incretin Mimetics/Enhancers (C4I)

**Indication:**<sup>1</sup> Exenatide extended-release (Bydureon), a glucagon-like peptide-1 (GLP-1) receptor agonist, is indicated as an adjunct to diet and exercise for adults with type 2 diabetes mellitus (DM) to improve glycemic control. Exenatide extended-release is not indicated as a first-line agent for the treatment of type 2 DM.

**Contraindications/Warnings:** Exenatide extended-release, along with other GLP-1 receptor agonists, carries a black box warning for the risk of thyroid c-cell tumors. Patients with a family or individual history of medullary thyroid carcinoma (MTC) and patients with multiple endocrine neoplasia syndrome type 2 (MEN 2) should not use exenatide extended-release.

Due to postmarketing reports of acute pancreatitis, other antidiabetic therapies should be evaluated for patients with a history of pancreatitis. Patients who have severe renal impairment and patients with end stage renal disease should not use exenatide extended-release. Caution should be exercised when using exenatide extended-release in patients with moderate renal impairment, (30-50 mL/min). Since gastrointestinal (GI) adverse events are commonly identified with exenatide extended-release its use in patients with severe GI disease is not recommended.

Patients with type 1 DM or hypersensitivity to exenatide or any of its components should not use exenatide extended-release. It should be used with caution when co-administered with sulfonylurea, and is not recommended to be used with insulin or exenatide (Byetta™).

**Drug Interactions:** Increase monitoring of the international normalized ratio (INR) if exenatide extended-release is co-administered with warfarin. Postmarketing reports have indicated an effect on INR with reports of bleeding.

Exenatide is known to slow the rate of gastric emptying and consequently exenatide extended-release has the potential to reduce the absorption of certain orally administered medications such as digoxin, lovastatin, and lisinopril therefore should be used with caution.

**Common Adverse Effects:** The most common adverse reactions reported as monotherapy in a 26-week trial were nausea (11.3 percent), diarrhea and injection site pruritis (10.9 and 10.5 percent respectively), constipation (8.5 percent), headache (8.1 percent) and dyspepsia (7.3 percent).

### **Special Populations:**

***Pediatrics:*** Safety and efficacy for exenatide extended-release have not been studied in pediatric patients.

***Pregnancy:*** Pregnancy Category C. There are no adequate or well-controlled studies of exenatide extended-release use in women who are pregnant.

***Geriatrics:*** No difference in safety and efficacy were noted between a younger population and geriatric subjects. However, as older patients have a greater likelihood of decreased or impaired renal function caution should be exercised with initiating exenatide extended-release therapy.

***Renal Impairment:*** Use exenatide extended-release with caution in patients with moderate renal impairment. It is not recommended for use in patients with end stage renal disease or severe renal impairment

***Hepatic Impairment:*** Exenatide extended-release has not been studied in patients with acute or chronic hepatic impairment.

***Dosages:*** Exenatide extended-release is self-administered via a subcutaneous (SC) injection. The standard dosage is 2 mg given once every seven days, regardless of food and time of day. Should a dose be missed, it should be administered as soon as possible as long as the next dose is due at least three days later. If the next dose is due within one or two days, the patient can administer the next dose when regularly due. If a patient is converting from exenatide (Byetta) to exenatide extended-release (Bydureon) they may experience an increase in blood glucose concentrations. This is a transient effect that may last approximately two weeks.

***Clinical Trials:*** A literature search was performed using “exenatide extended release” and “type 2 diabetes mellitus”. Placebo-controlled trials were included in the absence of comparative trials.

The safety and efficacy of extended-release exenatide compared to regular exenatide (Byetta) was studied in a randomized, open-label, 24 week trial in patients who did not achieve adequate glycemic control on their current therapy. A total of 252 patients were randomized to receive exenatide extended-release (Bydureon) (n=129) or regular exenatide (Byetta) (n=123) along with their current oral antidiabetic agent. A change in hemoglobin A1c (HbA1c) was the primary endpoint with a change in body weight being the secondary endpoint. The mean change of HbA1c at week 24 for the Bydureon group was -1.6 versus the Byetta group of -0.9. The percentage of patients achieving HbA1c less than seven percent at week 24 was 58 percent for the Bydureon group versus 30 percent for the Byetta group. The difference from Byetta was -0.7. For the secondary endpoint of change in body weight, a reduction was seen in both groups, Bydureon (-2.3 kg) and Byetta (-1.4 kg). Mean change in fasting plasma glucose was also observed in the Bydureon group (-25 mg/dL) with Byetta having a -0.5 reduction.

***Other Drugs Used for Condition:***<sup>2,3</sup> Other GLP-1 receptor agonists include exenatide (Byetta), administered subcutaneously (SC) twice a day and liraglutide (Victoza™) given by a SC injection once daily.

### ***Place in Therapy:***<sup>4</sup>

In the 2009 update to the American Diabetes Association (ADA) consensus algorithm, GLP-1 receptor agonist are not considered first-line options for the treatment of type 2 diabetes. The guideline also states that exenatide may be added if a patient has failed to meet glycemic goals

following lifestyle modifications and metformin use. Patients being considered for the addition of exenatide should also have an HbA1c of less than 8 percent. Liraglutide and extended-release exenatide were not available when the algorithm was developed.

The 2011 American Academy of Clinical Endocrinologists (AACE) recommendations for glycemic control in patients with type 2 diabetes with inadequate treatment after a trial of monotherapy include the use of GLP-1 receptor agonists when considering options as part of a dual and/or triple therapy regimen.

### ***Suggested Utilization Management:***

<b>Anticipated Therapeutic Class Review (TCR) Placement</b>	Hypoglycemics, Incretin Mimetics/Enhancers
<b>Clinical Edit</b>	1. Prior authorization will be required if it is determined that this product will be non-preferred. 2. Diagnosis of Type 2 Diabetes Mellitus 3. Deny if co-administered with exenatide (Byetta) or insulin, diagnosis of Type 1 DM, history of pancreatitis, MTC or severe GI disease or if used as first-line therapy
<b>Quantity Limit</b>	Four 2 mg doses every 28 days for established patients.
<b>Duration of Approval</b>	Yearly
<b>Drug to Disease Hard Edit</b>	Type 2 DM
<b>Retro-DUR</b>	Yes
<b>Provider Profiling</b>	No

### ***References***

<sup>1</sup> Bydureon [package insert]. San Diego, CA; Amylin Pharmaceuticals; January 2012.

<sup>2</sup> Byetta [package insert]. San Diego, CA; Amylin Pharmaceuticals; December 2011.

<sup>3</sup> Victoza [package insert]. Princeton, NJ; Novo Nordisk May 2011.

<sup>4</sup> Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. Diabetes Care. 2009; 32(1):193-203

<sup>5</sup> AACE medical guidelines for clinical practice for developing a comprehensive diabetes mellitus care plan. Endocr Pract. 2011; 17(Suppl 2):1-53.