HIGHLIGHTS OF PRESCRIBING INFORMATION

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

BYDUREON™ (exenatide extended-release for injectable suspension).
Initial U.S. Approval: 2012

WARNING: RISK OF THYROID C-CELL TUMORS
See full prescribing information for complete boxed warning.

- **Exenatide extended-release causes thyroid C-cell tumors at clinically relevant exposures in rats. It is unknown whether BYDUREON causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies (5.1).**
- **BYDUREON is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) (5.1).**

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

BYDUREON 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 in multiple clinical settings (1.1, 14).

BYDUREON is an extended-release formulation of exenatide. Do not co-administer with BYETTA.

Important Limitations of Use

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (5.1).
- Should not be used to treat type 1 diabetes or diabetic ketoacidosis (1.2).
- Use with insulin has not been studied and is not 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, 5.2).

----------DOSAGE AND ADMINISTRATION----------

- Administer 2 mg by subcutaneous injection once every seven days (weekly), at any time of day and with or without meals (2.1).
- Administer immediately after the powder is suspended (2.1).

----------DOSAGE FORMS AND STRENGTHS----------

BYDUREON is 2 mg exenatide for extended-release injectable suspension.

----------CONTRAINDICATIONS----------

- Do not use if personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4.1).
- Do not use if history of serious hypersensitivity to exenatide or any product components (4.2).

----------WARNINGS AND PRECAUTIONS----------

- Thyroid C-cell tumors in animals: Human relevance unknown. Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors (5.1).
- Pancreatitis: Postmarketing reports with exenatide, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies if history of pancreatitis (5.2).
- Hypoglycemia: Increased risk when BYDUREON is used in combination with a sulfonylurea. Consider reducing the sulfonylurea dose (5.3).
- Renal Impairment: Postmarketing reports with exenatide, sometimes requiring hemodialysis and kidney transplantation. Not recommended if severe renal impairment or end-stage renal disease. Use with caution in patients with renal transplantationor moderate renal impairment (5.4, 8.6, 12.3).
- Severe Gastrointestinal Disease: Not recommended if severe gastrointestinal disease (e.g., gastroparesis) (5.5).
- Hypersensitivity: Postmarketing reports with exenatide of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema). In such cases, patients are to discontinue BYDUREON 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 BYDUREON or any other antidiabetic drug (5.8).

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

- Most common (≥5%) and occurring more frequently than comparator in clinical trials: nausea, diarrhea, headache, vomiting, constipation, injection site pruritus, injection site nodule, and dyspepsia (5.3, 6.1).

To report SUSPECTED ADVERSE REACTIONS contact Amylin Pharmaceuticals, Inc at 1-877-700-7365 and www.bydureon.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 with exenatide of increased INR sometimes associated with bleeding. Monitor INR frequently until stable upon initiation of BYDUREON therapy (7.2, 6.2).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. Use 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: Use caution when administering to a nursing woman (8.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 01/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether BYDUREON causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with BYDUREON. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see *Contraindications (4.1), Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)*].

1 INDICATIONS AND USAGE

BYDUREON is an extended-release formulation of exenatide, administered as an injection once every seven days (weekly).

1.1 Type 2 Diabetes Mellitus

BYDUREON is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings [see *Clinical Studies (14)*].

1.2 Important Limitations of Use

Because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans, prescribe BYDUREON only to patients for whom the potential benefits are considered to outweigh the potential risk.

BYDUREON is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

BYDUREON is not a substitute for insulin. BYDUREON 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 BYDUREON with insulin has not been studied and cannot be recommended.

BYDUREON and BYETTA® (exenatide) injection both contain the same active ingredient, exenatide, and therefore should not be used together.

Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. BYDUREON 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 BYDUREON. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

BYDUREON (2 mg per dose) should be administered once every seven days (weekly). The dose can be administered at any time of day, with or without meals.

Missed Dose

If a dose is missed, it should be administered as soon as noticed, provided the next regularly scheduled dose is due at least three days later. Thereafter, patients can resume their usual dosing schedule of once every seven days (weekly).

If a dose is missed and the next regularly scheduled dose is due one or two days later, the patient should not administer the missed dose and instead resume BYDUREON with the next regularly scheduled dose.

Changing Weekly Dosing Schedule

The day of weekly administration can be changed if necessary as long as the last dose was administered 3 or more days before.

2.2 Administration

BYDUREON is intended for patient self-administration. BYDUREON is provided in a single-dose tray containing: one vial of 2 mg exenatide, one vial connector, one prefilled diluent syringe and two needles (one provided as a spare) [see *How Supplied/Storage and Handling (16.1)*]. **Do not substitute needles or any other components in the tray**.

BYDUREON must be injected immediately after the powder is suspended in the diluent and transferred to the syringe. BYDUREON is administered as a subcutaneous (SC) injection in the abdomen, thigh or upper arm region. Advise patients to use a different injection site each week when injecting in the same region. BYDUREON must not be administered intravenously or intramuscularly.

See the BYDUREON Instructions for Use for complete administration instructions with illustrations. The instructions can also be found at www.bydureon.com.

2.3 Changing from BYETTA to BYDUREON

Prior treatment with BYETTA is not required when initiating BYDUREON therapy. If the decision is made to start BYDUREON in an appropriate patient already taking BYETTA,

BYETTA should be discontinued. Patients changing from BYETTA to BYDUREON may experience transient (approximately two weeks) elevations in blood glucose concentrations.

3 DOSAGE FORMS AND STRENGTHS

BYDUREON is 2 mg exenatide extended-release for injectable suspension for subcutaneous administration once every seven days (weekly).

4 CONTRAINDICATIONS

4.1 Medullary Thyroid Carcinoma

BYDUREON is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

4.2 Hypersensitivity

BYDUREON is contraindicated in patients with a prior serious hypersensitivity reaction to exenatide or to any of the product components.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-cell Tumors

In both genders of rats, exenatide extended-release caused a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures compared to controls [see *Nonclinical Toxicology (13.1)*]. A statistically significant increase in malignant thyroid C-cell carcinomas was observed in female rats receiving exenatide extended-release at 25-times clinical exposure compared to controls and higher incidences were noted in males above controls in all treated groups at ≥2-times clinical exposure. The potential of exenatide extended-release to induce C-cell tumors in mice has not been evaluated. Other GLP-1 receptor agonists have also induced thyroid C-cell adenomas and carcinomas in male and female mice and rats at clinically relevant exposures. It is unknown whether BYDUREON will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies. Serum calcitonin was not assessed in the clinical trials supporting the approval of BYDUREON [see *Boxed Warning, Contraindications (4.1)*].

Serum calcitonin is a biological marker of MTC. Patients with MTC usually have calcitonin values >50 ng/L. Patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation. Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with BYDUREON. Such monitoring may increase the risk of unnecessary

procedures, due to the low specificity of serum calcitonin testing for MTC and a high background incidence of thyroid disease. If serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation [see *Patient Counseling Information (17)*].

5.2 Acute Pancreatitis

Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYDUREON, 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, BYDUREON should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYDUREON should not be restarted. Consider antidiabetic therapies other than BYDUREON in patients with a history of pancreatitis.

5.3 Hypoglycemia

The risk of hypoglycemia is increased when exenatide is used in combination with a sulfonylurea. Therefore, patients receiving BYDUREON and a sulfonylurea may require a lower dose of the sulfonylurea to minimize the risk of hypoglycemia. It is also possible that the use of BYDUREON 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

BYDUREON 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 BYDUREON may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Use BYDUREON with caution in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) [see *Use in Specific Populations (8.6) Clinical Pharmacology (12.3)*]. BYDUREON has not been studied in patients with end-stage renal disease or severe renal impairment.

There have been postmarketing reports of altered renal function with exenatide, 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

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