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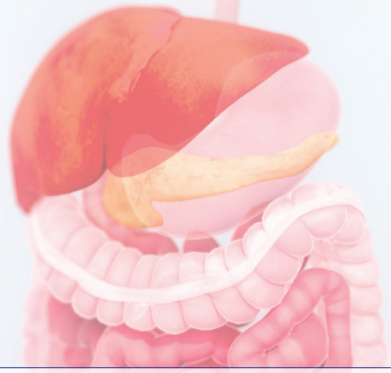
U.S. Pharmacist®
PRODUCT INFORMATION GUIDE

Treating Type 2 Diabetes With Once-Weekly BYDUREON™

(exenatide extended-release for injectable suspension)



Indications and Usage
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.

- Because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans, prescribe only to patients for whom potential benefits are considered to outweigh potential risk.
- Not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.
- Not a substitute for insulin, should not be used in patients with type 1 diabetes or diabetic ketoacidosis, and cannot be recommended for use with insulin.
- BYDUREON and BYETTA® (exenatide) injection both contain the same active ingredient, exenatide, and should not be used together.
- Exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, based on postmarketing data. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYDUREON; consider other antidiabetic therapies for these patients.

BOXED 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. Please see additional Important Safety Information on pages 6 and 7 and the accompanying Prescribing Information and Medication Guide.

This Product Information Guide is funded by Amylin Pharmaceuticals, Inc.

Treating Type 2 Diabetes With Once-Weekly BYDUREON™

(exenatide extended-release for injectable suspension)

Background

The discovery of a group of gut hormones called incretins has spurred the development of a class of incretin-based medications for the treatment of type 2 diabetes mellitus (T2DM). The pathogenesis of T2DM is complex and classically associated with progressive beta-cell failure (relative insulin deficiency) and insulin resistance in fat and muscle cells.[1] Glucose homeostasis is known, however, to be maintained by complex interactions involving insulin, glucagon, and the incretin hormones. The latter are released by enteroendocrine cells in the gut in response to meal ingestion. Incretin dysfunction, along with a number of other important physiological defects, have been implicated in the pathogenesis of T2DM. Incretin-based therapies, aimed at restoring incretin activity in people with T2DM, have been shown to be effective therapies in this population.

Despite an increasing recognition of the importance of reaching glycemic goals and a greater emphasis on diabetes care, only 55% of adults with T2DM achieved a glycosylated hemoglobin (A1C) below 7.0%, according to the National Health and Nutrition Examination Survey (NHANES).[2] Furthermore, even in patients that are compliant with their medications, the benefits of lifestyle interventions and oral hypoglycemic therapy may not be durable, which is likely due to the progressive nature of the disease.[3] As noted above, traditional models of T2DM disease progression have emphasized the core defects of peripheral insulin resistance, increased hepatic gluconeogenesis, and progressive loss of pancreatic beta-cell function (resulting in insulin deficiency).[4] These changes make the pathophysiology of T2DM quite complex.[4]

Incretin-Based Medications

First identified in the 1960s, the "incretin effect" showed that insulin secretion is greater in response to the oral intake of a meal when compared to intravenous glucose administration.[5,6] Subsequently, the incretin effect was shown to be due primarily to the secretion of two incretin hormones: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[7] Combined, these 2 hormones account for ~70% of insulin secretion following glucose ingestion.[8] The effects of GLP-1 are mediated by binding of the hormone to GLP-1 receptors.[9] GLP-1 has been shown to stimulate glucose-dependent insulin secretion, suppress glucagon secretion, slow gastric emptying, and decrease caloric intake.[10] Insulin release in response to GLP-1 is glucose-dependent, meaning that insulin release is stimulated only when blood glucose levels are elevated, and insulin secretion decreases as blood glucose levels approach normal. Circulating GLP-1 is short-lived, with a half-life of less than 2 minutes due to its rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4).[11]

The incretin response is disrupted in people with T2DM. Studies have shown, however, that the administration of exogenous GLP-1 is capable of correcting this defect.[12] In early clinical studies involving patients with T2DM, continuous exposure to GLP-1 demonstrated improved glycemic control mimicking that of healthy subjects.[13,14] The clinical utility of natural GLP-1 is

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limited, however, by its rapid degradation by the DPP-4 enzyme. Two treatment approaches have thus far been developed to overcome these limitations: GLP-1 receptor agonists, which provide a pharmacologic dose of GLP-1 analog designed to resist DPP-4 degradation, and DPP-4 inhibitors, which slow the inactivation of endogenous incretin hormones by inhibiting the DPP-4 enzyme. Clinically, DPP-4 inhibitors are oral therapies that can improve post-prandial insulin secretion and are generally weight neutral.[15] The injectable GLP-1 receptor agonists have demonstrated efficacy in terms of stimulating glucose-dependent insulin secretion and are also capable of inducing weight loss in people with T2DM.[15] BYDUREON (exenatide extended-release for injectable suspension) is a GLP-1 receptor agonist that is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM in multiple clinical settings. BYDUREON carries a boxed warning for potential risk of thyroid C-cell tumors, including medullary thyroid carcinoma. Because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans, BYDUREON is not recommended as first-line therapy for patients uncontrolled on diet and exercise alone.[16]

BYDUREON: A New Approach To T2DM Treatment

Microsphere technology. BYDUREON is the first once-weekly GLP-1 receptor agonist approved in the United States for the treatment of T2DM. BYDUREON utilizes patented biodegradable microspheres to deliver a controlled release of exenatide (FIGURE 1). The microspheres are composed of polylactide co-glycolide acid polymer, which has been used in other therapeutic applications to encapsulate small molecules, peptides, and proteins.[17] Immediately following subcutaneous injection, the BYDUREON microspheres aggregate, and exenatide at or near the surface of the microspheres diffuses. Over time, as the microspheres degrade, exenatide is continuously released into the circulation. The microsphere polymer is completely metabolized and eliminated as carbon dioxide and water.[17] This process results in a controlled release of exenatide for a continuous presence of GLP-1 receptor activation. Once steady state is achieved, therapeutic levels of exenatide are maintained with once-weekly dosing.

Pharmacokinetic profile of BYDUREON. Following initiation of once-weekly BYDUREON, plasma levels gradually increase over 6 to 7 weeks. Steady-state levels of exenatide are maintained thereafter with once-weekly dosing. After 2 weeks of therapy, decreases in fasting plasma glucose (FPG) are observed in patients with T2DM, and by week 14 (the earliest time point at which it was examined), post-prandial glucose (PPG) levels also improve.[18,19]

Clinical efficacy. Efficacy data from a 24-week, randomized, open-label clinical trial compared the addition of BYDUREON 2 mg QW (n = 129) to BYETTA® (exenatide) injection 10 mcg BID (n = 123) in adults with T2DM inadequately controlled on lifestyle intervention and/or oral antidiabetic therapy (metformin, SFU, thiazolidinedione, or a combination of any 2 of these agents).[20] Study participants in the BYDUREON and BYETTA arms had an average baseline (BL) A1C of 8.5% and 8.4%, respectively, and weighed an average of 213.8 lb and 207.9 lb, respectively. The average duration of T2DM was 7 years for both treatment groups. Participants treated with BYDUREON experienced a mean A1C reduction of 1.6% compared to a mean reduction of 0.9% for those receiving BYETTA ($P < .001$). Additionally, the proportion of patients reaching an A1C of <7% was 58% in the BYDUREON arm vs 30% in the BYETTA arm ($P < .001$). BYDUREON treatment was also associated with a reduction in mean FPG of -25 mg/dL at 24 weeks compared to a mean reduction of -5 mg/dL in the BYETTA group. And although BYDUREON is not indicated for weight loss,

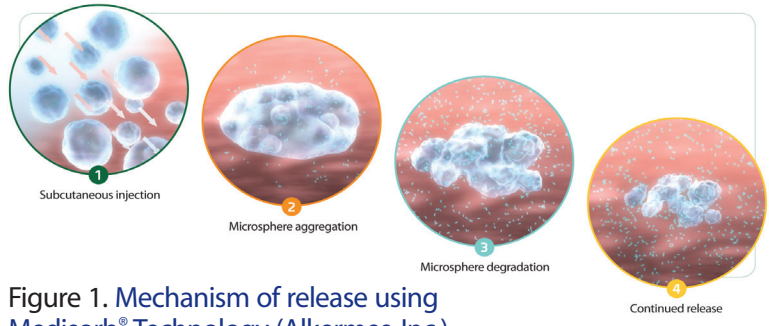

Figure 1. Mechanism of release using Medisorb® Technology (Alkermes, Inc.).

Please see Important Safety Information on pages 6 and 7, and the accompanying Prescribing Information and Medication Guide.

BYDUREON patients lost an average of 5.1 lb, which was similar to BYETTA® (exenatide) injection (3.1 lb).

BYDUREON has also been studied in 2 separate 26-week clinical trials vs Januvia (sitagliptin), a DPP-4 inhibitor that is administered as a once-daily oral agent. In the first trial, T2DM patients with inadequate glycemic control on metformin alone were randomized to receive BYDUREON 2 mg QW (n = 160) or the maximum approved dose of Januvia (100 mg QD; n = 166).[21] Patients in the BYDUREON arm experienced a mean A1C reduction of 1.5% from a BL of 8.6% vs 0.9% for Januvia patients (BL = 8.5%; $P < .0001$). Patients in the BYDUREON arm lost a mean 5.1 lb while the Januvia group lost a mean 1.8 lb ($P = .0002$). As a secondary endpoint, 62% of BYDUREON patients achieved an A1C goal of ≤7% vs 35% for Januvia. In the second trial, patients with T2DM who were drug-naïve were randomized to receive BYDUREON or Januvia.[22] A mean A1C reduction of 1.5% was achieved in the BYDUREON arm, with participants in the Januvia arm achieving a mean A1C reduction of 1.2% ($P < .001$).[22] Additionally, as secondary endpoints, patients in the BYDUREON arm lost 4.4 lb while those receiving Januvia lost 1.8 lb ($P < .001$), and 64% of patients achieved an A1C goal of ≤7% vs 46% for Januvia.

Collectively, clinical trial data with BYDUREON demonstrated improvements in glycemic control, and although not indicated for weight loss, participants receiving BYDUREON treatment realized a decrease in their weight on average.

Safety

Boxed Warning. Exenatide extended-release causes thyroid C-cell tumors at clinically relevant exposures in rats. Because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans, BYDUREON is not recommended as first-line therapy for patients inadequately controlled on diet and exercise.

Contraindications. BYDUREON is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Additionally, BYDUREON is contraindicated for use in patients with known hypersensitivity to exenatide or any components of the formulation.

Warnings.

- Cases of pancreatitis in people using exenatide have been reported, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis. BYDUREON should be discontinued promptly if pancreatitis is suspected and should not be restarted if a diagnosis of pancreatitis is made. Likewise, other antidiabetic therapies should be considered in individuals with a history of pancreatitis.
- There is an increased risk of hypoglycemia when BYDUREON is used in combination with a sulfonylurea. If initiating BYDUREON in an individual on sulfonylurea therapy, consider reducing the sulfonylurea dose.
- Postmarketing reports of renal impairment have been reported with exenatide. BYDUREON is not recommended in patients with severe renal impairment or end-stage renal disease and should be used with caution in those with renal transplantation or moderate renal impairment.
- BYDUREON is not recommended in individuals with severe gastrointestinal disease, such as gastroparesis.
- Postmarketing reports of serious hypersensitivity reactions with exenatide have been reported. In such cases, BYDUREON should be discontinued in addition to any other suspected medications and medical advice should be sought promptly.
- Clinical studies establishing conclusive evidence of macrovascular risk reduction have not been performed with BYDUREON or any other antidiabetic drug.

Adverse Reactions

Some of the most frequently reported adverse events associated with BYDUREON in clinical trials were nausea, diarrhea, headache, and vomiting. Nausea was generally mild and tended to decrease over time. While nausea was the most common side effect with BYDUREON therapy, the incidence was less than was seen with twice-daily BYETTA. In the 24-week clinical trial of BYDUREON vs BYETTA, the rates of nausea were 14% and 35%, respectively.[16] In a separate 30-week clinical trial vs BYETTA, rates of nausea were 27% vs 34%.[16] Injection-site reactions (itching, redness) are more common in BYDUREON-treated patients vs patients receiving comparator injections. In addition, small, asymptomatic, subcutaneous injection-site

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nodules are seen with the use of BYDUREON. These are consistent with the known properties of the microspheres used in BYDUREON and typically resolve within 3 to 6 weeks. In clinical trials, there were no reports of major hypoglycemia, although the risk of minor hypoglycemia was increased with concomitant SFU use.

Administration & Dosing

BYDUREON is administered once every 7 days (weekly) at any time of day, independent of meals. BYDUREON is administered as a subcutaneous injection in the abdomen, thigh, or upper arm regions. Patients should be counseled to use a different injection site each week when injecting in the same regions. The steps for administration are straightforward (connect, shake, and inject; see FIGURE 2), and BYDUREON is intended for patient self-administration. BYDUREON is provided in cartons containing 4 single-dose trays; the trays should be stored under refrigeration.

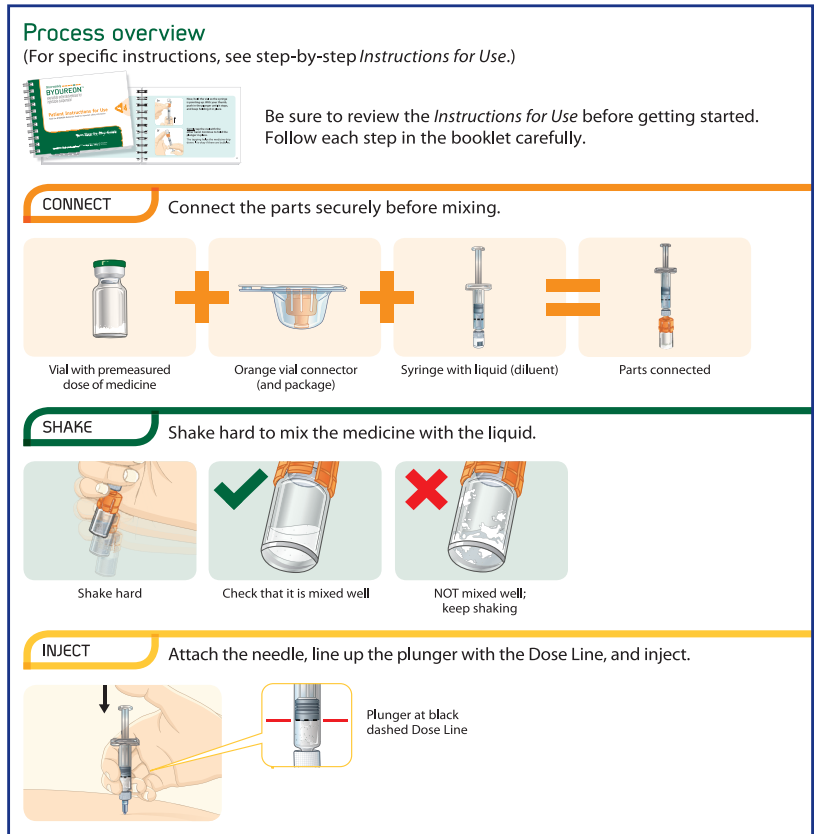

Figure 2. BYDUREON administration steps.

BYDUREON in T2DM Treatment

A cornerstone of the ADA guidelines for pharmacologic treatment of T2DM is the timely augmentation of therapy with additional agents in order to achieve and maintain individualized A1C goals.[23] The 2012 Position Statement from the ADA and the European Association for the Study of Diabetes (EASD) advocates for a "patient-centered" approach to treatment and emphasizes not only glucose-lowering efficacy, but also potential side effects, weight reduction, and cost as important considerations when choosing therapeutic agents.[24] Treatment with metformin is recommended for most patients at or soon after diagnosis, followed by dual-therapy if glyceimic goals are not being met after ~ 3 months. When progressing to dual-therapy, the ADA/EASD recommends adding 1 of 5 second-line agents: SFU, TZD, a GLP-1 receptor agonist like BYDUREON, DPP-4 inhibitor, or basal insulin. Choice is based on patient and drug characteristics, with the overriding goal of improving glycemic control while minimizing side effects. GLP-1 receptor agonists are recommended as an option for add-on therapy to metformin due to their efficacy in terms of A1C reduction, potential for weight loss, and low risk of hypoglycemia.[24] The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommends a GLP-1 receptor agonist, like BYDUREON, as a preferred agent for combination therapy (ie, add-on to metformin, or metformin plus an SFU or a thiazolidinedione) in patients not meeting glycemic goals with monotherapy due to its low risk of hypoglycemia when not used with an SFU and the potential to provide weight loss.[25] The continuous glycemic control provided with BYDUREON, along with the potential for weight loss and low risk of hypoglycemia, are meaningful considerations for achieving treatment goals in patients with T2DM.◆

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BOXED 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 (exenatide extended-release for injectable suspension) 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.

Contraindications

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

Warnings and Precautions

- **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 pancreatitis (persistent severe abdominal pain, sometimes radiating to the back, with or without vomiting). If pancreatitis is suspected, BYDUREON should be discontinued promptly and should not be restarted if pancreatitis is confirmed.**
- Increased risk of hypoglycemia when used in combination with glucose-independent insulin secretagogues (eg, sulfonylureas). Clinicians may consider reducing the sulfonylurea (SFU) dose.
- Should not be used in patients with severe renal impairment or end-stage renal disease. Use with caution in patients with renal transplantation or moderate renal failure. 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 and kidney transplantation.
- Not recommended in patients with severe gastrointestinal disease (eg, gastroparesis).
- Patients may develop antibodies to exenatide. In 5 registration trials, attenuated glycemic response was associated in 6% of BYDUREON-treated patients with antibody formation. If worsening of or failure to achieve adequate glycemic control occurs, consider alternative antidiabetic therapy.
- Postmarketing reports of serious hypersensitivity reactions (eg, anaphylaxis and angioedema). If this occurs, patients should discontinue BYDUREON and other suspect medications and promptly seek medical advice.
- No clinical studies establishing conclusive evidence of macrovascular risk reduction with BYDUREON or any other antidiabetic drug.

Withdrawals

- In 5 comparator-controlled, 24- to 30-week BYDUREON trials, the incidence of withdrawal due to adverse events was 4.9% for BYDUREON, 4.9% for BYETTA® (exenatide) injection, and 2.0% for other comparators. The most common adverse reactions leading to withdrawal for BYDUREON, BYETTA, and comparators respectively were: nausea (0.5%,1.5%, 0.3%); injection-site nodule (0.5%, 0.0%, 0.0%); diarrhea (0.3%, 0.4%, 0.3%); injection-site reaction (0.2%, 0.0%, 0.0%); and headache (0.2%, 0.0%, 0.0%). One percent of BYDUREON patients withdrew due to injection-site adverse reactions.

Adverse Reactions (≥5%)

- BYDUREON vs BYETTA: 24-week trial, nausea (14% vs 35%), diarrhea (9.3% vs 4.1%), injection-site erythema (5.4% vs 2.4%); 30-week trial, nausea (27% vs 33.8%), diarrhea (16.2% vs 12.4%), vomiting (10.8% vs 18.6%), injection-site pruritus (18.2% vs 1.4%), constipation (10.1% vs 6.2%), gastroenteritis viral (8.8% vs 5.5%), gastroesophageal reflux disease (7.4% vs 4.1%), dyspepsia (7.4% vs 2.1%), injection-site erythema (7.4% vs 0.0%), fatigue (6.1% vs 3.4%), headache (6.1% vs 4.8%), injection-site hematoma (5.4% vs 11.0%).
- BYDUREON vs titrated insulin glargine: nausea (12.9% vs 1.3%), headache (9.9% vs 7.6%), diarrhea (9.4% vs 4.0%), injection-site nodule (6.0% vs 0.0%).

- Combination trial vs sitagliptin and pioglitazone: nausea (24.4% vs 9.6% and 4.8%), diarrhea (20.0% vs 9.6% and 7.3%), vomiting (11.3% vs 2.4% and 3.0%), headache (9.4% vs 9.0% and 5.5%), constipation (6.3% vs 3.6% and 1.2%), fatigue (5.6% vs 0.6% and 3.0%), dyspepsia (5.0% vs 3.6% and 2.4%), decreased appetite (5.0% vs 1.2% and 0.0%), injection-site pruritus (5.0% vs 4.8% and 1.2%).
- Monotherapy trial vs sitagliptin, pioglitazone, and metformin: nausea (11.3% vs 3.7%, 4.3%, and 6.9%), diarrhea (10.9% vs 5.5%, 3.7%, and 12.6%), injection-site nodule (10.5% vs 6.7%, 3.7%, and 10.2%), constipation (8.5% vs 2.5%, 1.8%, and 3.3%), headache (8.1% vs 9.2%, 8.0%, and 12.2%), dyspepsia (7.3% vs 1.8%, 4.9%, and 3.3%).
- Injection-site reactions were observed more frequently in BYDUREON-treated patients (17.1%) vs patients treated with BYETTA (12.7%), titrated insulin glargine (1.8%), or placebo injection (6.4%-13.0%). Injection-site reactions were observed in 14.2% of antibody-positive patients vs 3.1% of antibody-negative patients, with higher incidence in those with higher-titer antibodies. BYETTA-treated patients had similar incidence between antibody-positive and antibody-negative patients (5.8% vs 7.0%). Small, asymptomatic, subcutaneous injection-site nodules are seen with the use of BYDUREON.

Hypoglycemia

- No major hypoglycemia was reported for BYDUREON- or comparator-treated patients in five 24- to 30-week trials. Minor hypoglycemia incidences for BYDUREON vs comparator-treated patients were as follows: 24-week trial vs BYETTA: with SFU, 12.5% vs 11.8%; without SFU, 0.0% for both; 30-week trial vs BYETTA: with SFU, 14.5% vs 15.4%; without SFU, 0.0% vs 1.1%; monotherapy trial vs sitagliptin, pioglitazone, and metformin: 2.0% vs 0.0% (all comparators); combination trial vs sitagliptin and pioglitazone: 1.3% vs 3.0% and 1.2%; vs titrated insulin glargine, with SFU, 20.0% vs 43.9%; without SFU, 3.7% vs 19.1%.

Drug Interactions

- BYDUREON slows gastric emptying and can reduce the rate of absorption of orally administered drugs. Use with caution with oral medications.
- Postmarketing reports of increased international normalized ratio (INR) sometimes associated with bleeding with concomitant use of warfarin. Monitor INR frequently until stable upon initiation or alteration of BYDUREON.

Use in Specific Populations

- Based on animal data, BYDUREON may cause fetal harm and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Caution should be exercised when administered to a nursing woman.
- Use in pediatric patients is not recommended as safety and effectiveness have not been established.

For complete safety profile and other important prescribing considerations, see the accompanying Prescribing Information and Medication Guide.◆

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COUNSELING CORNER

The following series of questions and answers serves as a patient education aid to assist healthcare professionals in counseling patients with type 2 diabetes who have been prescribed BYDUREON (exenatide extended-release for injectable suspension).

Q. How does BYDUREON work all week?

- Medicine is contained in microspheres
- Microspheres release medicine continuously over time
- Medicine works only when blood sugar levels are high

Q. When do I take BYDUREON?

- Once every 7 days on the same day each week
- Any time of the day, with or without food

Q. If I have to change my Dosing Day, how do I do that?

- New Dosing Day must be at least 3 days after your last dose
- Do not take 2 doses of BYDUREON less than 3 days apart

Q. What are the most common side effects?

- Nausea is most common; usually occurs at the start of treatment and should decrease over time for most patients
- Diarrhea, vomiting, and constipation
- Itching or redness at injection site
- Small, raised bump within 2 to 4 weeks of injecting BYDUREON, which may not be visible to the naked eye and should go away on its own within 3 to 6 weeks

Q. What are some of the serious side effects?

- Potential increased risk of thyroid tumors
- Inflammation of the pancreas (pancreatitis)
- Low blood sugar (hypoglycemia)
- Kidney problems (renal impairment)
- Stomach problems (gastrointestinal disease)
- Allergic reaction (hypersensitivity)

Q. What changes might I notice?

- Better blood sugar levels before eating (after 2 weeks)
- Patients switching from BYETTA (exenatide) injection: blood sugar levels may be higher than usual as the medicine is gradually released; this is expected and should improve within about 2 weeks
- Reduced A1C within a few months ◆

Please see Important Safety Information on pages 6 and 7, and the accompanying Prescribing Information and Medication Guide.

Introducing BYDUREON: **ORDER NOW!**

The first and only once-weekly treatment for type 2 diabetes is now available to order

- In multiple clinical trials, BYDUREON delivered powerful A1C reductions and helped patients achieve recommended A1C goals

Package information: BYDUREON

NDC	66780-219-04
UPC	3 66780-21904-0
Dispensing Quantity	1 trade pack (carton) containing 4 single-dose trays

The trade pack (carton) should not be opened nor should a single-dose tray be sold individually.

- BYDUREON will be dispensed in a trade pack (carton) containing 4 single-dose trays. Remind patients to read the enclosed Medication Guide contained in the trade pack. For more information, please visit www.BYDUREONHCP.com.

Special storage requirements

- BYDUREON should be stored in the refrigerator at 36°F to 46°F (2°C to 8°C) and protected from light until preparing for use. Do not freeze the BYDUREON trade pack (carton). After BYDUREON is dispensed, advise patients to keep it in the refrigerator, but if needed, when traveling for example, patients can keep a single-dose tray out of the refrigerator for a total of 4 weeks at a temperature no higher than 77°F (25°C).

Information

- For order information contact your wholesaler. For product or storage and handling questions, or product returns, call Amylin Customer Service at 1-866-208-1657.

Indication and Usage

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.

- Because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans, prescribe only to patients for whom potential benefits are considered to outweigh potential risk.
- Not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.
- Not a substitute for insulin, should not be used in patients with type 1 diabetes or diabetic ketoacidosis, and cannot be recommended for use with insulin.
- BYDUREON and BYETTA® (exenatide) injection both contain the same active ingredient, exenatide, and should not be used together.
- Exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, based on postmarketing data. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYDUREON; consider other antidiabetic therapies for these patients.

BOXED 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.

$ When eligible patients present the BYDUREON Steady Savings Card, they can save up to $50 each month on their prescription. For information on ***BYDUREON Steady Support***℠ and the Steady Savings Card, visit www.BYDUREONHCP.com.

To learn more, visit www.BYDUREONHCP.com/pharmacist

For additional Important Safety Information, see pages 6 to 7 and the accompanying Prescribing Information and Medication Guide.

Once-weekly
BYDUREON™
exenatide extended-release for injectable suspension

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 transplantation or 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 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 exenatide. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

5.5 Gastrointestinal Disease

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

5.6 Immunogenicity

Patients may develop antibodies to exenatide following treatment with BYDUREON. Anti-exenatide antibodies were measured in all BYDUREON-treated patients in the five comparator-controlled 24-30 week studies of BYDUREON. In 6% of BYDUREON-treated patients, 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 exenatide. If a hypersensitivity reaction occurs, the patient should discontinue BYDUREON 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 BYDUREON 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.

The safety of BYDUREON was assessed in five comparator-controlled trials, in patients who entered the studies not achieving adequate glycemic control on their current therapy. In a double-blind 26 week trial, patients on diet and exercise were treated with BYDUREON 2 mg once every seven days (weekly), sitagliptin 100 mg daily, pioglitazone 45 mg daily, or metformin 2000 mg daily. In a double-blind 26 week trial, patients on metformin were treated with BYDUREON 2 mg once every seven days (weekly), sitagliptin 100 mg daily, or pioglitazone 45 mg daily. In an open-label 26 week trial, patients on metformin or metformin plus sulfonylurea were treated with BYDUREON 2 mg once every seven days (weekly) or optimized insulin glargine. In two open-label 24 to 30 week studies, patients on diet and exercise or metformin, a sulfonylurea, a thiazolidinedione or combination of oral agents were treated with BYDUREON 2 mg once every seven days (weekly) or BYETTA 10 mcg twice daily.

Withdrawals

The incidence of withdrawal due to adverse events was 4.9% (N=45) for BYDUREON-treated patients, 4.9% (N=13) for BYETTA-treated patients and 2.0% (N=23) for other comparator-treated patients in the five comparator-controlled 24-30 week trials. The most common adverse reactions leading to withdrawal for BYDUREON-treated patients were nausea 0.5% (N=5) versus 1.5% (N=4) for BYETTA and 0.3 % (N=3) for other comparators, injection site nodule 0.5% (N=5) versus 0.0% for BYETTA and 0.0% for other comparators, diarrhea 0.3% (N=3) versus 0.4% (N=1) for BYETTA and 0.3% (N=3) for other comparators, injection site reaction 0.2% (N=2) versus 0.0% for BYETTA and 0.0% for other comparators and headache 0.2% (N=2) versus 0.0% for BYETTA and 0.0% for other comparators.

Hypoglycemia

Table 1 summarizes the incidence and rate of minor hypoglycemia in the five comparator-controlled 24-30 week trials of BYDUREON used as monotherapy or as add-on to metformin, a sulfonylurea, a thiazolidinedione or combination of these oral antidiabetic agents. In these trials, an event was classified as minor hypoglycemia if there were symptoms of hypoglycemia with a concomitant glucose <54 mg/dL and the patient was able to self-treat.

Table 1: Incidence (% of subjects) and Rate (episodes/subject year) of Minor† Hypoglycemia in the Monotherapy Trial and in the Combination Therapy Trials

26-Week Monotherapy Trial	
BYDUREON 2 mg (N = 248)	2.0% (0.05)
Sitagliptin 100 mg (N = 163)	0.0% (0.00)
Pioglitazone 45 mg (N = 163)	0.0% (0.00)
Metformin 2000 mg QD (N = 246)	0.0% (0.00)
26-Week Add-on to Metformin Trial	
BYDUREON 2 mg (N = 160)	1.3% (0.03)
Sitagliptin 100 mg (N = 166)	3.0% (0.12)
Pioglitazone 45 mg (N = 165)	1.2% (0.03)
26-Week Add-on to Metformin or Metformin + Sulfonylurea Trial	
With Concomitant Sulfonylurea Use (N = 136)	
BYDUREON 2 mg (N = 70)	20.0% (1.11)
Titrated Insulin Glargine (N = 66)	43.9% (2.87)
Without Concomitant Sulfonylurea Use (N = 320)	
BYDUREON 2 mg (N =163)	3.7% (0.11)
Titrated Insulin Glargine‡ (N = 157)	19.1% (0.64)
24-Week Monotherapy or add-on to Metformin, a Sulfonylurea, a Thiazolidinedione or Combination of Oral Agents Trial	
With Concomitant Sulfonylurea Use (N = 74)	
BYDUREON 2 mg (N = 40)	12.5% (0.72)
BYETTA 10 mcg (N = 34)	11.8% (0.31)
Without Concomitant Sulfonylurea Use (N = 178)	
BYDUREON 2 mg (N = 89)	0.0% (0.00)
BYETTA 10 mcg (N = 89)	0.0% (0.00)
30-Week Monotherapy or add-on to Metformin, a Sulfonylurea, a Thiazolidinedione or Combination of Oral Agents Trial	
With Concomitant Sulfonylurea Use (N = 107)	
BYDUREON 2 mg (N =55)	14.5% (0.55)
BYETTA 10 mcg (N = 52)	15.4% (0.37)
Without Concomitant Sulfonylurea Use (N = 186)	
BYDUREON 2 mg (N = 93)	0.0% (0.00)
BYETTA 10 mcg (N = 93)	1.1% (0.02)

Abbreviations: N = The number of intent-to-treat patients
Note: Percentages are based on the number of intent-to-treat patients in each treatment group.
†Reported event that has symptoms consistent with hypoglycemia with a concomitant glucose <54 mg/dL and the patient was able to self-treat.
‡Insulin glargine was dosed to a target fasting glucose concentration of 72 to 100 mg/dL. The mean dose of insulin glargine was 10 Units/day at baseline and 31 Units/day at endpoint.

There were no reported events of major hypoglycemia in these five comparator-controlled 24-30 week trials. Major hypoglycemia was defined as loss of consciousness, seizure or coma (or other mental status change consistent with neuroglycopenia in the judgment of the investigator or physician) which resolved after administration of glucagon or glucose or required third party assistance to resolve because of severe impairment in consciousness or behavior. Patients were to have a concomitant glucose <54 mg/dL.

Immunogenicity

Anti-exenatide antibodies were measured at prespecified intervals (4-14 weeks) in all BYDUREON-treated patients (N=918) in the five comparator-controlled studies of BYDUREON. In these five trials, 452 BYDUREON-treated patients (49%) had low titer antibodies (≤125) to exenatide at any time during the trials and 405 BYDUREON-treated patients (45%) had low titer antibodies to exenatide at study endpoint (24-30 weeks). The level of glycemic control in these patients was generally comparable to that observed in the 379 BYDUREON-treated patients (43%) without antibody titers. An additional 107 BYDUREON-treated patients (12%) had higher titer antibodies at endpoint. Of these patients, 50 (6% overall) had an attenuated glycemic response to BYDUREON (<0.7% reduction in HbA_{1c}); the remaining 57 (6% overall) had a glycemic response comparable to that of patients without antibodies [see *Warnings and Precautions (5.6)*]. In the 30-week trial in which anti-exenatide antibody assessments were performed at baseline and at 4-week intervals from week 6 to week 30, the mean anti-exenatide antibody titer in the BYDUREON-treated patients peaked at week 6 then declined by 56% from this peak by week 30.

A total of 246 patients with antibodies to exenatide in the BYETTA and BYDUREON clinical trials were tested for the presence of cross-reactive antibodies to GLP-1 and/or glucagon. No treatment-emergent cross reactive antibodies were observed across the range of titers.

Other Adverse Reactions

BYDUREON

Tables 2 and 3 summarize adverse reactions with an incidence ≥5% reported in the five comparator controlled 24-30 week trials of BYDUREON used as monotherapy or as add-on to metformin, a sulfonylurea, a thiazolidinedione or combination of these oral antidiabetic agents.

Table 2: Treatment-Emergent Adverse Reactions Reported in ≥5% of BYDUREON-Treated Patients in Monotherapy Trial

	26-Week Monotherapy Trial			
	BYDUREON 2 mg N = 248 %	**Sitagliptin 100 mg N = 163 %**	**Pioglitazone 45 mg N = 163 %**	**Metformin 2000 mg N = 246 %**
Nausea	11.3	3.7	4.3	6.9
Diarrhea	10.9	5.5	3.7	12.6
Injection Site Nodule†	10.5	6.7	3.7	10.2
Constipation	8.5	2.5	1.8	3.3
Headache	8.1	9.2	8.0	12.2
Dyspepsia	7.3	1.8	4.9	3.3

N = The number of intent-to-treat patients.
Note: Percentages are based on the number of intent-to-treat patients in each treatment group.
†Patients in the sitagliptin, pioglitazone and metformin treatment groups received weekly placebo injections.

Table 3: Treatment-Emergent Adverse Reactions Reported in ≥5% of BYDUREON-Treated Patients in 24-30 week Add-on Combination Therapy Trials

	26-Week Add-On to Metformin Trial		
	BYDUREON 2 mg N = 160 %	**Sitagliptin 100 mg N = 166 %**	**Pioglitazone 45 mg N = 165 %**
Nausea	24.4	9.6	4.8
Diarrhea	20.0	9.6	7.3
Vomiting	11.3	2.4	3.0
Headache	9.4	9.0	5.5
Constipation	6.3	3.6	1.2
Fatigue	5.6	0.6	3.0
Dyspepsia	5.0	3.6	2.4
Decreased appetite	5.0	1.2	0.0
Injection Site Pruritus†	5.0	4.8	1.2

	26-Week Add-on to Metformin or Metformin + Sulfonylurea Trial	
	BYDUREON 2 mg N = 233 %	**Insulin glargine Titrated N = 223 %**
Nausea	12.9	1.3
Headache	9.9	7.6
Diarrhea	9.4	4.0
Injection Site Nodule	6.0	0.0

	30-Week Monotherapy or as Add-on to Metformin, a Sulfonylurea, a Thiazolidinedione or Combination of Oral Agents Trial	
	BYDUREON 2 mg N = 148 %	**BYETTA 10 mcg N = 145 %**
Nausea	27.0	33.8
Diarrhea	16.2	12.4
Vomiting	10.8	18.6
Injection Site Pruritus	18.2	1.4
Constipation	10.1	6.2
Gastroenteritis viral	8.8	5.5
Gastroesophageal reflux disease	7.4	4.1
Dyspepsia	7.4	2.1
Injection site erythema	7.4	0.0
Fatigue	6.1	3.4
Headache	6.1	4.8
Injection site hematoma	5.4	11.0

24-Week Monotherapy or as Add-on to Metformin, a Sulfonylurea, a Thiazolidinedione or Combination of Oral Agents Trial

	BYDUREON 2 mg N = 129 %	BYETTA 10 mcg N = 123
Nausea	14.0	35.0
Diarrhea	9.3	4.1
Injection site erythema	5.4	2.4

N = The number of intent-to-treat patients.
Note: Percentages are based on the number of intent-to-treat patients in each treatment group.
†Patients in the sitagliptin, pioglitazone and metformin treatment groups received weekly placebo injections.
Nausea was the most common adverse reaction associated with initiation of treatment with BYDUREON, and usually decreased over time.

Injection Site Reactions

In the five comparator-controlled 24-30 week trials, injection site reactions were observed more frequently in patients treated with BYDUREON (17.1%) than in patients treated with BYETTA (12.7%), titrated insulin glargine (1.8%) or those patients who received placebo injections (sitagliptin (10.6%), pioglitazone (6.4%), and metformin (13.0%) treatment groups). These reactions for patients treated with BYDUREON were more commonly observed in antibody-positive patients (14.2%) compared with antibody-negative patients (3.1%), with a greater incidence in those with higher titer antibodies [see *Warnings and Precautions (5.6)*]. Incidence of injection site reactions for patients treated with BYETTA was similar for antibody positive patients (5.8%) and antibody negative patients (7.0%). One percent of patients treated with BYDUREON withdrew due to injection site adverse reactions (injection site mass, injection site nodule, injection site pruritus, and injection site reaction).

Small, asymptomatic subcutaneous injection site nodules are seen with the use of BYDUREON. In a separate 15-week study in which information on nodules were collected and analyzed, 24 out of 31 subjects (77%) experienced at least one injection site nodule during treatment; 2 subjects (6.5%) reported accompanying localized symptoms. The mean duration of events was 27 days. The formation of nodules is consistent with the known properties of the microspheres used in BYDUREON.

BYETTA

In three 30-week controlled trials of BYETTA (N=963) add-on to metformin and/or sulfonylurea, adverse reactions (excluding hypoglycemia) with an incidence of ≥1% and reported more frequently than with placebo included nausea (44% BYETTA, 18% placebo), vomiting (13% BYETTA, 4% placebo), diarrhea (13% BYETTA, 6% placebo), feeling jittery (9% BYETTA, 4% placebo), dizziness (9% BYETTA, 6% placebo), headache (9% BYETTA, 6% placebo), dyspepsia (6% BYETTA, 3% placebo), asthenia (4% BYETTA, 2% placebo), gastroesophageal reflux (3% BYETTA, 1% placebo), hyperhidrosis (3% BYETTA, 1% placebo) and decreased appetite (1% BYETTA, <1% placebo). Similar types of adverse reactions were observed in 24-week and 16-week controlled trials of BYETTA used as monotherapy or as add-on to a thiazolidinedione, with or without metformin, respectively.

6.2 Post-Marketing Experience

BYETTA

The following additional adverse reactions have been reported during post-approval use of BYETTA. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergy/Hypersensitivity: injection-site reactions, generalized pruritus and/or urticaria, macular or papular rash, angioedema; anaphylactic reaction [see *Warnings and Precautions (5.7)*].

Drug Interactions: increased international normalized ratio (INR), sometimes associated with bleeding, with concomitant warfarin use [see *Drug Interactions (7.2)*].

Gastrointestinal: nausea, vomiting, and/or diarrhea resulting in dehydration; abdominal distension, abdominal pain, eructation, constipation, flatulence, acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death [see *Limitations of Use (1.2) and Warnings and Precautions (5.2)*].

Neurologic: dysgeusia; somnolence

Renal and Urinary Disorders: altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure or acute renal failure (sometimes requiring hemodialysis), kidney transplant and kidney transplant dysfunction [see *Warnings and Precautions (5.4)*].

Skin and Subcutaneous Tissue Disorders: alopecia

7 DRUG INTERACTIONS

7.1 Orally Administered Drugs

Exenatide slows gastric emptying. Therefore, BYDUREON has the potential to reduce the rate of absorption of orally administered drugs. Use caution when administering oral medications with BYDUREON [see *Clinical Pharmacology (12.3)*].

In patients with type 2 diabetes, BYDUREON did not affect the absorption of orally administered acetaminophen to any clinically relevant degree.

7.2 Warfarin

BYDUREON has not been studied with warfarin. However, in a drug interaction study, BYETTA did not have a significant effect on INR [see *Clinical Pharmacology (12.3)*]. There have been postmarketing reports for BYETTA of increased INR with concomitant use of warfarin, sometimes associated with bleeding [see *Adverse Reactions (6.2)*]. In patients taking warfarin, the INR should be monitored more frequently after initiating BYDUREON. Once a stable INR has been documented, the INR can be monitored at the intervals usually recommended for patients on warfarin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of BYDUREON use in pregnant women. In rats, exenatide extended-release administered during the major period of organogenesis reduced fetal growth and produced skeletal ossification deficits in association with maternal effects; exenatide extended-release was not teratogenic in rats. In animal developmental studies, exenatide, the active ingredient of BYDUREON, caused cleft palate, irregular skeletal ossification and an increased number of neonatal deaths. BYDUREON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Fetuses from pregnant rats given subcutaneous doses of exenatide extended-release at 0.3, 1 or 3 mg/kg on gestation days 6, 9, 12 and 15 demonstrated reduced fetal growth at all doses and produced skeletal ossification deficits at 1 and 3 mg/kg in association with maternal effects (decreased food intake and decreased body weight gain). There was no evidence of malformations. Doses of 0.3, 1 and 3 mg/kg correspond to systemic exposures of 3, 7 and 17-times, respectively, the human exposure resulting from the recommended dose of 2 mg/week, based on area under the time-concentration curve (AUC) [see *Nonclinical Toxicology (13.3)*].

Female mice given subcutaneous doses of exenatide, the active ingredient of BYDUREON, at 6, 68, or 760 mcg/kg/day beginning 2 weeks prior to and throughout mating until gestation day 7, had no adverse fetal effects. At the maximal dose, 760 mcg/kg/day, systemic exposures were up to 148 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC [see *Nonclinical Toxicology (13.3)*].

In developmental toxicity studies, pregnant animals received exenatide, the active ingredient of BYDUREON, subcutaneously during organogenesis. Specifically, fetuses from pregnant rabbits given subcutaneous doses of exenatide at 0.2, 2, 22, 156, or 260 mcg/kg/day from gestation day 6 through 18 experienced irregular skeletal ossifications from exposures 4 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. Fetuses from pregnant mice given subcutaneous doses of exenatide at 6, 68, 460, or 760 mcg/kg/day from gestation day 6 through 15 demonstrated reduced fetal and neonatal growth, cleft palate and skeletal effects at systemic exposure that is equivalent to the human exposure resulting from the recommended dose of 2 mg/week, based on AUC [see *Nonclinical Toxicology (13.3)*].

Lactating mice given subcutaneous doses of exenatide, the active ingredient of BYDUREON, at 6, 68, or 760 mcg/kg/day from gestation day 6 through lactation day 20 (weaning), experienced an increased number of neonatal deaths. Deaths were observed on postpartum days 2-4 in dams given 6 mcg/kg/day, a systemic exposure that is equivalent to the human exposure resulting from the recommended dose of 2 mg/week, based on AUC [see *Nonclinical Toxicology (13.3)*].

Pregnancy Registry

Amylin Pharmaceuticals, Inc. maintains a Pregnancy Registry to monitor pregnancy outcomes of women exposed to exenatide during pregnancy. Physicians are encouraged to register patients by calling (800) 633-9081.

8.3 Nursing Mothers

Exenatide is present in the milk of lactating mice at concentrations less than or equal to 2.5% of the concentration in maternal plasma following subcutaneous dosing. It is not known whether exenatide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for exenatide extended-release in animal studies, a decision should be made whether to discontinue nursing or to discontinue BYDUREON, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of BYDUREON have not been established in pediatric patients. BYDUREON is not recommended for use in pediatric patients.

8.5 Geriatric Use

In the five comparator-controlled 24-30 week trials, BYDUREON was studied in 132 patients (16.6%) who were at least 65 years old and 20 patients who were at least 75 years old. No differences in safety (N = 152) and efficacy (N = 52) were observed between these patients and younger patients, but the small sample size for patients ≥75 years old limits conclusions.

In separate trials, BYETTA was studied in 282 patients at least 65 years old and in 16 patients at least 75 years old. No differences in safety and efficacy were observed between these patients and younger patients, but the small sample size for patients ≥75 years old limits conclusions.

Because elderly patients are more likely to have decreased renal function, use caution when initiating BYDUREON in the elderly.

8.6 Renal Impairment

BYDUREON is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min) and should be used with caution in patients with renal transplantation. Use BYDUREON with caution in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) [see *Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic impairment. Because exenatide is cleared primarily by the kidney, hepatic impairment is not expected to affect blood concentrations of exenatide [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

There were no reports of overdose in the five comparator-controlled 24-30 week trials of BYDUREON. Effects of overdoses with BYETTA in clinical studies included severe nausea, severe vomiting, and rapidly declining blood glucose concentrations, including severe hypoglycemia requiring parenteral glucose administration. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

11 DESCRIPTION

BYDUREON (exenatide extended-release for injectable suspension) is supplied as a sterile powder to be suspended in the diluent included in the single-dose tray and administered by subcutaneous injection. Exenatide is a 39-amino acid synthetic peptide amide with an empirical formula of $C_{184}H_{282}N_{50}O_{60}S$ and a molecular weight of 4186.6 Daltons. The amino acid sequence for exenatide is shown below.

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2

BYDUREON is a white to off-white powder that is available in a dosage strength of 2 mg exenatide per vial. Exenatide is incorporated in an extended release microsphere formulation containing the 50:50 poly(D,L-lactide-co-glycolide) polymer (37.2 mg per vial) along with sucrose (0.8 mg per vial). The powder must be suspended in the diluent prior to injection. The diluent is provided in a prefilled syringe. Each prefilled syringe delivers 0.65 mL of the diluent as a clear, colorless to pale yellow solution composed of carboxymethylcellulose sodium (23 mg), polysorbate 20 (0.77 mg), sodium phosphate monobasic monohydrate (0.74 mg), sodium phosphate dibasic heptahydrate (0.62 mg), sodium chloride (5.0 mg), and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

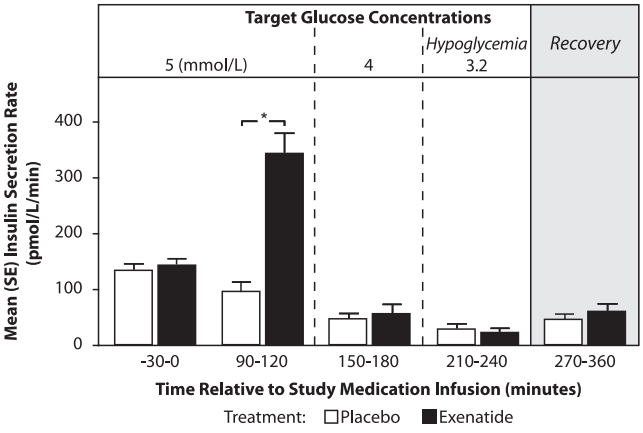
Incretins, such as glucagon-like-peptide-1 (GLP-1), enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into the circulation from the gut. BYDUREON is a GLP-1 receptor agonist that enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying.

The amino acid sequence of exenatide partially overlaps that of human GLP-1. Exenatide is a GLP-1 receptor agonist that has been shown to bind and activate the human GLP-1 receptor *in vitro*. This leads to an increase in both glucose-dependent synthesis of insulin and *in vivo* secretion of insulin from pancreatic beta cells, by mechanisms involving cyclic AMP and/or other intracellular signaling pathways. Exenatide promotes insulin release from pancreatic beta cells in the presence of elevated glucose concentrations.

12.2 Pharmacodynamics

Exenatide improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes through the actions described below.

Glucose-dependent insulin secretion: The effect of exenatide infusion on glucose-dependent insulin secretion rates (ISR) was investigated in 11 healthy subjects. In these healthy subjects, on average, the ISR response was glucose-dependent (Figure 1). Exenatide did not impair the normal glucagon response to hypoglycemia.



SE = standard error.

Notes: 5 mmol = 90mg/dL, 4 mmol/L = 72 mg/dL, 3.2 mmol/L = 58 mg/dL; Study medication infusion was started at time = 0 min.

Statistical assessments were for the last 30 min of each glycemic step, during which the target glucose concentrations were maintained.

*p <0.05, exenatide treatment relative to placebo.

Figure 1: Mean (SE) Insulin Secretion Rates During Infusion of Exenatide or Placebo by Treatment, Time, and Glycemic Condition in Healthy Subjects

Glucagon secretion: In patients with type 2 diabetes, exenatide moderates glucagon secretion and lowers serum glucagon concentrations during periods of hyperglycemia.

Gastric emptying: Exenatide slows gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation.

Food intake: Infusion of exenatide in eight healthy subjects resulted in a 19% decrease in caloric intake following an ad libitum meal.

Fasting and Postprandial Glucose

In a separate 15-week controlled study, where fasting glucose was assessed on a weekly basis, BYDUREON treatment resulted in a mean reduction in fasting glucose of 17 mg/dL following two weeks of therapy with full effect on fasting glucose not observed until approximately 9 weeks.

In a 30-week controlled study of exenatide extended-release compared to BYETTA, postprandial glucose levels were measured during a mixed meal tolerance test in a subset of patients with type 2 diabetes mellitus. Following treatment for 14 weeks, when steady-state concentrations had been achieved (approximately 280 to 310 pg/mL), the LS mean change from baseline was significantly greater with BYETTA (-126 mg/dL) than exenatide extended-release (-96 mg/dL).

Cardiac Electrophysiology

The effect of exenatide at therapeutic (253 pg/mL) and supratherapeutic (627 pg/mL) concentrations, following an intravenous infusion on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) three-period crossover thorough QT study in 74 healthy subjects. The upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on population correction method (QTcP) was below 10 ms. Therefore, exenatide was not associated with prolongation of the QTc interval at therapeutic and supratherapeutic concentrations.

12.3 Pharmacokinetics

Absorption

Following a single dose of BYDUREON, exenatide is released from the microspheres over approximately 10 weeks. There is an initial period of release of surface-bound exenatide followed by a gradual release of exenatide from the microspheres, which results in two subsequent peaks of exenatide in plasma at around week 2 and week 6-7, respectively, representing the hydration and erosion of the microspheres.

Following initiation of once every seven days (weekly) administration of 2 mg BYDUREON, gradual increase in the plasma exenatide concentration is observed over 6 to 7 weeks. After 6 to 7 weeks, mean exenatide concentrations of approximately 300 pg/mL were maintained over once every seven days (weekly) dosing intervals indicating that steady-state was achieved.

Distribution

The mean apparent volume of distribution of exenatide following subcutaneous administration of a single dose of BYETTA is 28.3 L and is expected to remain unchanged for BYDUREON.

Metabolism and Elimination

Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/h and is independent of the dose. Approximately 10 weeks after discontinuation of BYDUREON therapy, plasma exenatide concentrations generally fall below the minimal detectable concentration of 10 pg/mL.

Drug Interactions

Acetaminophen

When 1000 mg acetaminophen tablets were administered, either with or without a meal, following 14 weeks of BYDUREON therapy (2 mg weekly), no significant changes in acetaminophen AUC were observed compared to the control period. Acetaminophen C_{max} decreased by 16% (fasting) and 5% (fed) and T_{max} was increased from approximately 1 hour in the control period to 1.4 hours (fasting) and 1.3 hours (fed).

The following drug interactions have been studied using BYETTA. The potential for drug-drug interaction with BYDUREON is expected to be similar to that of BYETTA.

Digoxin

Administration of repeated doses of BYETTA 30 minutes before oral digoxin (0.25 mg once-daily) decreased the C_{max} of digoxin by 17% and delayed the T_{max} of digoxin by approximately 2.5 hours; however, the overall steady-state pharmacokinetic exposure (e.g. AUC) of digoxin was not changed.

Lovastatin

Administration of BYETTA (10 mcg twice daily) 30 minutes before a single oral dose of lovastatin (40 mg) decreased the AUC and C_{max} of lovastatin by approximately 40% and 28%, respectively, and delayed the T_{max} by about 4 hours compared with lovastatin administered alone. In the 30-week controlled clinical trials of BYETTA, the use of BYETTA in patients already receiving HMG CoA reductase inhibitors was not associated with consistent changes in lipid profiles compared to baseline.

Lisinopril

In patients with mild to moderate hypertension stabilized on lisinopril (5 to 20 mg/day), BYETTA (10 mcg twice-daily) did not alter steady-state C_{max} or AUC of lisinopril. Lisinopril steady state T_{max} was delayed by 2 hours. There were no changes in 24-h mean systolic and diastolic blood pressure.

Oral Contraceptives

The effect of BYETTA (10 mcg twice-daily) on single and on multiple doses of a combination oral contraceptive (30 mcg ethinyl estradiol plus 150 mcg levonorgestrel) was studied in healthy female subjects. Repeated daily doses of the oral contraceptive (OC) given 30 minutes after BYETTA administration decreased the C_{max} of ethinyl estradiol and levonorgestrel by 45% and 27%, respectively and delayed the T_{max} of ethinyl estradiol and levonorgestrel by 3.0 hours and 3.5 hours, respectively, as compared to the oral contraceptive administered alone. Administration of repeated daily doses of the OC one hour prior to BYETTA administration decreased the mean C_{max} of ethinyl estradiol by 15% but the mean C_{max} of levonorgestrel was not significantly changed as compared to when the OC was given alone. BYETTA did not alter the mean trough concentrations of levonorgestrel after repeated daily dosing of the oral contraceptive for both regimens. However, the mean trough concentration of ethinyl estradiol was increased by 20% when the OC was administered 30 minutes after BYETTA administration injection as compared to when the OC was given alone. The effect of BYETTA on OC pharmacokinetics is confounded by the possible food effect on OC in this study [see *Drug Interactions (7.1)*].

Warfarin

Administration of warfarin (25 mg) 35 minutes after repeated doses of BYETTA (5 mcg twice-daily on days 1-2 and 10 mcg twice-daily on days 3-9) in healthy volunteers delayed warfarin T_{max} by approximately 2 hours. No clinically relevant effects on C_{max} or AUC of S- and R-enantiomers of warfarin were observed. BYETTA did not significantly alter the pharmacodynamic properties (e.g., international normalized ratio) of warfarin [see *Drug Interactions (7.2)*].

Specific Populations

Renal Impairment

BYDUREON has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease receiving dialysis. Population pharmacokinetic analysis of renally-impaired patients receiving 2 mg BYDUREON indicate that there is a 62% and 33% increase in exposure in moderate (N=10) and mild (N=56) renally-impaired patients, respectively as compared to patients with normal renal function (N=84).

In a study of BYETTA in subjects with end-stage renal disease receiving dialysis, mean exenatide exposure increased by 3.4-fold compared to that of subjects with normal renal function [see *Use in Specific Populations (8.6)*].

Hepatic Impairment

BYDUREON has not been studied in patients with acute or chronic hepatic impairment [see *Use in Specific Populations (8.7)*].

Age

Population pharmacokinetic analysis of patients ranging from 22 to 73 years of age suggests that age does not influence the pharmacokinetic properties of exenatide [see *Use in Specific Population (8.5)*].

Gender

Population pharmacokinetic analysis suggests that gender does not influence the steady-state concentrations of exenatide following BYDUREON administration.

Race

There were no apparent differences in steady-state concentrations of exenatide among Caucasian, Hispanic, and Black patients following BYDUREON administration.

Body Mass Index

Population pharmacokinetic analysis of patients with body mass indices (BMI) ≥30 kg/m^2 and <30 kg/m^2 suggests that BMI has no significant effect on the pharmacokinetics of exenatide.

Pediatric

BYDUREON has not been studied in pediatric patients [see *Use in Specific Populations (8.4)*]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week carcinogenicity study was conducted with exenatide extended-release in male and female rats at doses of 0.3, 1.0 and 3.0 mg/kg (2, 9, and 26-times human systemic exposure based on AUC, respectively) administered by subcutaneous injection every other week. A statistically significant increase in thyroid C-cell tumor incidence was observed in both males and females. The incidence of C-cell adenomas was statistically significantly increased at all doses (27% to 31%) in females and at 1.0 and 3.0 mg/kg (46% and 47%, respectively) in males compared with the control group (13% for males and 7% for females). A statistically significantly higher incidence of C-cell carcinomas occurred in the high dose group females (6%), while numerically higher incidences of 3%, 7%, and 4% (non-statistically significant versus controls) were noted in the low, mid, and high dose group males compared with the control group (0% for both males and females). An increase in benign fibromas was seen in the skin subcutis at injection sites of males given 3 mg/kg. No treatment-related injection site fibrosarcomas were observed at any dose. The human relevance of these findings is currently unknown.

A 104-week carcinogenicity study was conducted with exenatide, the active ingredient in BYDUREON, in male and female rats at doses of 18, 70, or 250 mcg/kg/day (3, 6, and 27 times human systemic exposure based on AUC, respectively) administered by once daily bolus subcutaneous injection. Benign thyroid C-cell adenomas were observed in female rats at all exenatide doses. The incidences in female rats were 8% and 5% in the two control groups and 14%, 11%, and 23% in the low, medium, and high dose groups.

In a 104-week carcinogenicity study with exenatide, the active ingredient in BYDUREON, in male and female mice at doses of 18, 70, or 250 mcg/kg/day administered by once daily bolus subcutaneous injection, no evidence of tumors was observed at doses up to 250 mcg/kg/day, a systemic exposure up to 16 times the human exposure

resulting from the recommended dose of 2 mg/week, based on AUC. The carcinogenicity of exenatide extended-release has not been evaluated in mice.

BYDUREON and exenatide, the active ingredient in BYDUREON, were not mutagenic or clastogenic, with or without metabolic activation, in the Ames bacterial mutagenicity assay or chromosomal aberration assay in Chinese hamster ovary cells. Exenatide was negative in the *in vivo* mouse micronucleus assay.

In mouse fertility studies with exenatide, the active ingredient in BYDUREON, at twice-daily subcutaneous doses of 6, 68 or 760 mcg/kg/day, males were treated for 4 weeks prior to and throughout mating, and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 760 mcg/kg/day, a systemic exposure 148 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC.

13.3 Reproductive and Developmental Toxicology

A rat embryo-fetal developmental toxicity study was conducted with exenatide extended-release. A complete reproductive and developmental toxicity program was conducted with exenatide, the active ingredient in BYDUREON.

Fetuses from pregnant rats given subcutaneous doses of exenatide extended-release at 0.3, 1 or 3 mg/kg on gestation days 6, 9, 12 and 15 demonstrated reduced fetal growth at all doses and produced skeletal ossification deficits at 1 and 3 mg/kg in association with maternal effects (decreased food intake and decreased body weight gain). There was no evidence of malformations. Doses of 0.3, 1 and 3 mg/kg correspond to systemic exposures of 3, 7 and 17-times, respectively, the human exposure resulting from the recommended dose of 2 mg/week, based on AUC.

In female mice given twice-daily subcutaneous doses of 6, 68, or 760 mcg/kg/day exenatide, the active ingredient in BYDUREON, beginning 2 weeks prior to and throughout mating until gestation day 7, there were no adverse fetal effects at doses up to 760 mcg/kg/day, systemic exposures up to 148 times the human exposure resulting from the maximum recommended dose of 2 mg/day, based on AUC.

In pregnant mice given twice-daily subcutaneous doses of 6, 68, 460, or 760 mcg/kg/day exenatide, the active ingredient in BYDUREON, from gestation day 6 through 15 (organogenesis), cleft palate (some with holes) and irregular fetal skeletal ossification of rib and skull bones were observed at 6 mcg/kg/day, a systemic exposure equal to the human exposure resulting from the maximum recommended dose of 2 mg/day, based on AUC.

In pregnant rabbits given twice-daily subcutaneous doses of 0.2, 2, 22, 156, or 260 mcg/kg/day exenatide, the active ingredient in BYDUREON, from gestation day 6 through 18 (organogenesis), irregular fetal skeletal ossifications were observed at 2 mcg/kg/day, a systemic exposure 4 times the human exposure resulting from the maximum recommended dose of 2 mg/day, based on AUC.

In pregnant mice given twice-daily subcutaneous doses of 6, 68, or 760 mcg/kg/day exenatide, the active ingredient in BYDUREON, from gestation day 6 through lactation day 20 (weaning), an increased number of neonatal deaths was observed on postpartum days 2-4 in dams given 6 mcg/kg/day, a systemic exposure equal to the human exposure resulting from the maximum recommended dose of 2 mg/day, based on AUC.

14 CLINICAL STUDIES

BYDUREON has been studied as monotherapy and in combination with metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione.

14.1 24-Week Comparator-Controlled Study

A 24-week, randomized, open-label trial was conducted to compare the safety and efficacy of BYDUREON to BYETTA in patients with type 2 diabetes and inadequate glycemic control with diet and exercise alone or with oral antidiabetic therapy, including metformin, a sulfonylurea, a thiazolidinedione, or combination of two of those therapies.

A total of 252 patients were studied: 149 (59%) were Caucasian, 78 (31%) were Hispanic, 15 (6%) were Black and 10 (4%) were Asian. Patients were treated with diet and exercise alone (19%), a single oral antidiabetic agent (47%), or combination therapy of oral antidiabetic agents (35%). The mean baseline HbA_{1c} was 8.4%. Patients were randomly assigned to receive BYDUREON 2 mg once every seven days (weekly) or BYETTA (10 mcg twice-daily), in addition to existing oral antidiabetic agents. Patients assigned to BYETTA initiated treatment with 5 mcg twice daily then increased the dose to 10 mcg twice-daily after 4 weeks.

The primary endpoint was change in HbA_{1c} from baseline to Week 24 (or the last value at time of early discontinuation). Change in body weight was a secondary endpoint. Twenty-four week study results are summarized in Table 4.

Table 4: Results of 24-week Trial of BYDUREON

	BYDUREON 2 mg	BYETTA 10 mcg
Intent-to-Treat Population (N)	129	123
HbA_{1c} (%)		
Mean Baseline	8.5	8.4
Mean Change at Week 24†	-1.6	-0.9
Difference from BYETTA† [95% CI]	-0.7 [-0.9, -0.4]¶	
Percentage Achieving HbA_{1c} <7% at Week 24 (%)	58¶	30
Fasting Plasma Glucose (mg/dL)		
Mean Baseline	173	168
Mean Change at Week 24	-25	-5
Difference from BYETTA† [95% CI]	-20 [-31, -10]¶	

N = The number of patients in each treatment group.
Note: Mean Change is Least Squares Mean Change
*BYETTA 5 mcg twice daily before the morning and evening meals for 4 weeks followed by 10 mcg twice daily for 20 weeks.
†Least squares means are adjusted for baseline HbA_{1c} strata, background antihyperglycemic therapy, and baseline value of the dependent variable (if applicable).
¶p <0.001, treatment vs. comparator.

Reductions from mean baseline (97/94 kg) in body weight were observed in both BYDUREON (-2.3 kg) and BYETTA (-1.4 kg) treatment groups.

BYDUREON did not have adverse effects on blood pressure. An LS mean increase from baseline (74 beats per minute) in heart rate of 4 beats per minute was observed with BYDUREON treatment and 2 beats per minute with BYETTA treatment. The long term effects of the increase in pulse rate have not been established [see *Warnings and Precautions (5.8)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BYDUREON (exenatide extended-release for injectable suspension) for once every seven days (weekly) subcutaneous administration is supplied in cartons of 4 single-dose trays for use (NDC 66780-219-04).

Each single-dose tray contains:
- One vial containing 2 mg exenatide (as a white to off-white powder)
- One prefilled syringe delivering 0.65 mL diluent
- One vial connector
- Two custom needles (23G, 5/16") specific to this delivery system (one is a spare needle)

Do **not** substitute needles or any other components in the tray.

16.2 Storage and Handling

- BYDUREON should be stored in the refrigerator at 36˚F to 46˚F (2˚C to 8˚C), up to the expiration date or until preparing for use. BYDUREON should not be used past the expiration date. The expiration date can be found on the carton and the cover of the single-dose tray.
- Do not freeze the BYDUREON tray. Do not use BYDUREON if it has been frozen. Protect from light.
- Each single-dose tray can be kept at room temperature not to exceed 77˚F (25˚C) [see USP Controlled Room Temperature] for no more than a total of 4 weeks, if needed.
- Use the diluent only if it is clear and free of particulate matter.
- After suspension, the mixture should be white to off-white and cloudy.
- BYDUREON must be administered immediately after the exenatide powder is suspended in the diluent and transferred to the syringe.
- Use a puncture-resistant container to discard the syringe with the needle still attached. Do not reuse or share needles or syringes.
- Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Inform patients about the potential risks and benefits of BYDUREON and of alternative modes of therapy. Also inform patients about the importance of diabetes self-management practices, such as regular physical activity, adhering to meal planning, periodic blood glucose monitoring and HbA_{1c} testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications.

17.1 Risk of Thyroid C-cell Tumors

Inform patients that exenatide extended-release causes benign and malignant thyroid C-cell tumors in rats and that the human relevance of this finding is unknown. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia or dyspnea) [see *Warnings and Precautions (5.1)*].

17.2 Risk of Pancreatitis

Inform patients treated with BYDUREON of the potential risk for pancreatitis. Explain that persistent severe abdominal pain that may radiate to the back and which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to promptly discontinue BYDUREON and contact their healthcare provider if persistent severe abdominal pain occurs [see *Warnings and Precautions (5.2)*].

17.3 Risk of Hypoglycemia

The risk of hypoglycemia is increased when BYDUREON is used in combination with an agent that induces hypoglycemia, such as a sulfonylurea [see *Warnings and Precautions (5.3)*]. Explain the symptoms, treatment, and conditions that predispose to the development of hypoglycemia. While the patient's usual instructions for hypoglycemia management do not need to be changed, these instructions should be reviewed and reinforced when initiating BYDUREON therapy, particularly when concomitantly administered with a sulfonylurea [see *Warnings and Precautions (5.3)*].

17.4 Risk of Renal Impairment

Inform patients treated with BYDUREON of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs [see *Warnings and Precautions (5.4)*].

17.5 Risk of Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of exenatide. If symptoms of hypersensitivity reactions occur, patients must stop taking BYDUREON and seek medical advice promptly [see *Warnings and Precautions (5.7)*].

17.6 Use in Pregnancy

Advise patients to inform their healthcare provider if they are pregnant or intend to become pregnant [see *Use in Specific Populations (8.1)*].

17.7 Instructions

Each dose of BYDUREON should be administered as a subcutaneous injection at any time on the dosing day, with or without meals. Patients should be informed that the day of once every seven days (weekly) administration can be changed if necessary as long as the last dose was administered 3 or more days before. 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 once every seven days (weekly) dosing schedule. If a dose is missed and the next regularly scheduled dose is due in one or two days, the patient should not administer the missed dose and instead resume BYDUREON with the next regularly scheduled dose. [see *Dosage and Administration (2.1)*].

Counsel patients that they should never share a BYDUREON single-dose tray with another person, even if the needle is changed. Sharing of the single-dose trays or needles between patients may pose a risk of transmission of infection.

If a patient is currently taking BYETTA, it should be discontinued upon starting BYDUREON. Patients formerly on BYETTA who start BYDUREON may experience transient elevations in blood glucose concentrations, which generally improve within the first two weeks after initiation of therapy [see *Dosage and Administration (2.3)* and *Clinical Studies (14.2)*].

Treatment with BYDUREON may also result in nausea, particularly upon initiation of therapy [see *Adverse Reactions (6)*].

Inform patients about the importance of proper storage of BYDUREON, injection technique, and dosing [see *Dosage and Administration (2)* and *How Supplied/Storage and Handling (16)*].

The patient should read the BYDUREON Medication Guide and the Instructions for Use before starting BYDUREON therapy and review them each time the prescription is refilled.

Manufactured by Amylin Pharmaceuticals, Inc., San Diego, CA 92121
1-877-700-7365
http://www.bydureon.com
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Medication Guide

BYDUREON™ (by-DUR-ee-on)
(exenatide extended-release for injectable suspension)

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

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

Serious side effects may happen in people who take BYDUREON, including:

1. **Possible thyroid tumors, including cancer.** During the drug testing process, the medicine in BYDUREON caused rats to develop tumors of the thyroid gland. Some of these tumors were cancers. It is not known if BYDUREON will cause thyroid tumors or a type of thyroid cancer called medullary thyroid cancer in people.
   - Before you start taking BYDUREON, tell your healthcare provider if you or any of your family members have had thyroid cancer, especially medullary thyroid cancer, or Multiple Endocrine Neoplasia syndrome type 2. **Do not** take BYDUREON if you or any of your family members have medullary thyroid cancer, or if you have Multiple Endocrine Neoplasia syndrome type 2. People with these conditions already have a higher chance of developing medullary thyroid cancer in general and should not take BYDUREON.
   - While taking BYDUREON, tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer.
2. **Inflammation of the pancreas (pancreatitis),** which may be severe and lead to death.

   Before taking BYDUREON, tell your healthcare provider if you have had:
   - pancreatitis
   - stones in your gallbladder (gallstones)
   - a history of alcoholism
   - high blood triglyceride levels

These medical conditions can make you more likely to get pancreatitis. It is not known if having these conditions will lead to a higher chance of getting pancreatitis while taking BYDUREON.

Stop taking BYDUREON and 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. This type of pain may be a symptom of pancreatitis.

What is BYDUREON?

- BYDUREON is an injectable prescription medicine that may improve blood sugar (glucose) in adults with type 2 diabetes mellitus, and should be used along with diet and exercise.
- BYDUREON is a long-acting form of the medication contained in BYETTA. Do not use BYDUREON and BYETTA together.
- BYDUREON is not recommended as the first choice of medication for treating diabetes.
- BYDUREON is not insulin.
- It is not known if BYDUREON is safe and effective when used with insulin.
- BYDUREON is not for use in people with type 1 diabetes or people with a condition caused by very high blood sugar (diabetic ketoacidosis).
- It is not known if BYDUREON is safe and effective in children. BYDUREON is not recommended for use in children.
- It is not known if BYDUREON is safe and effective in people who have a history of pancreatitis.
- BYDUREON has not been studied in people who have severe kidney problems.

Who should not use BYDUREON?

Do not use BYDUREON if:

- you or any of your family members have a history of medullary thyroid cancer.
- you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). This is a disease where people have tumors in more than one gland in their body.
- you are allergic to exenatide or any of the ingredients in BYDUREON. See the end of this Medication Guide for a complete list of ingredients in BYDUREON. Symptoms of a severe allergic reaction 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

Talk to your healthcare provider before taking this medicine if you have any of these conditions.

What should I tell my healthcare provider before using BYDUREON?

Before using BYDUREON, tell your healthcare provider if you:

- have any of the conditions listed in the section "What is the most important information I should know about BYDUREON?"
- have severe problems with your stomach such as slow emptying of your stomach (gastroparesis) or problems digesting food.
- have or have had kidney problems, or have had a kidney transplant.
- have any other medical conditions.
- are pregnant or are planning to become pregnant. It is not known if BYDUREON may harm your unborn baby. Tell your healthcare provider if you become pregnant while taking BYDUREON.
- **Pregnancy Registry:** Amylin Pharmaceuticals, Inc. has a registry for women who take BYDUREON during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. If you take BYDUREON at any time during pregnancy, you may enroll in this registry by calling 1-800-633-9081.
- are breastfeeding or plan to breastfeed. It is not known if BYDUREON passes into your breast milk. You and your healthcare provider should decide if you will take BYDUREON or breastfeed. You should not do both without talking with your healthcare provider first.

Tell your healthcare provider about all of the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. BYDUREON may affect the way some medicines work and some other medicines may affect the way BYDUREON works.

Especially tell your healthcare provider if you take:

- other diabetes medicines, especially insulin or a sulfonylurea
- any medicine taken by mouth
- warfarin sodium (Coumadin®, Jantoven®)

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

How should I use BYDUREON?

For detailed instructions, see the Instructions for Use that comes with your BYDUREON.

- Use BYDUREON exactly as your healthcare provider tells you to.
- BYDUREON is injected once every seven days (weekly) any time during the day.
- BYDUREON is a subcutaneous injection. Inject BYDUREON into your skin exactly the way your healthcare provider told you to. You can take the injection in your stomach area (abdomen), your thigh, or the back of your upper arm. Each week you can use the same area of your body. But be sure to choose a different injection site in that area.
- You can take BYDUREON with or without food.
- **If you miss a dose of BYDUREON, it should be taken as soon as you remember, provided the next regularly scheduled dose is due at least three days later.**

- **If you miss a dose of BYDUREON and the next regularly scheduled dose is due one or two days later, do not take the missed dose but take BYDUREON on the next regularly scheduled day.**
- **Do not** take 2 doses of BYDUREON less than 3 days apart.
- If you want to change your dosing day, you can. Your new dosing day must be at least 3 days after your last dose.
- Your healthcare provider must teach you how to inject BYDUREON before you use it for the first time. If you have any questions or do not understand the instructions, talk with your healthcare provider or pharmacist.
- BYDUREON must be injected right after you mix it.
- **If you are taking BYETTA and your healthcare provider prescribed BYDUREON, you should follow your healthcare provider's instructions about when to stop taking BYETTA and when to start taking BYDUREON.** BYETTA is a different form of the same medicine that is in BYDUREON, so do not take BYETTA when you are taking BYDUREON. When you first change from BYETTA to BYDUREON, your blood sugar levels may be higher than usual and should get better in about 2 weeks.
- Inject your dose of BYDUREON under the skin (subcutaneous injection), as you are told to by your healthcare provider. **Do not inject BYDUREON into a vein or muscle.**
- **Do not** share your BYDUREON tray with another person even if the needle is changed. Sharing your tray with another person can cause you or someone else to get an infection.
- Follow your healthcare provider's instructions for diet, exercise, how often to test your blood sugar, and when to get your HbA_{1c} checked. If you see your blood sugar increasing during treatment with BYDUREON, 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.

What are the possible side effects of BYDUREON?

BYDUREON can cause serious side effects, including:

- **See "What is the most important information I should know about BYDUREON?"**
- **Low blood sugar (hypoglycemia).** Your risk for getting low blood sugar is higher if you take BYDUREON 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 BYDUREON. Signs and symptoms of low blood sugar may include:
  - shakiness
  - sweating
  - headache
  - drowsiness
  - weakness
  - dizziness
  - confusion
  - irritability
  - hunger
  - fast heartbeat
  - feeling jittery

Talk with your healthcare provider about how to recognize and treat low blood sugar. Make sure that your family and other people around you a lot know how to recognize and treat low blood sugar.

- **Kidney problems (kidney failure).** BYDUREON may cause nausea, vomiting or diarrhea leading to loss of fluids (dehydration). Dehydration may cause kidney failure, which can lead to the need for dialysis. This can happen in people who have never had kidney problems before. Drinking plenty of fluids may reduce your chance of dehydration. Call your healthcare provider right away if you have nausea, vomiting, or diarrhea that will not go away, or if you cannot drink liquids by mouth.
- **Severe allergic reactions.** Severe allergic reactions can happen with BYDUREON. Stop taking BYDUREON, and get medical help right away if you have any symptom of a severe allergic reaction. **See "Who should not take BYDUREON?"**

The most common side effects of BYDUREON include:

- nausea
- diarrhea
- headache
- vomiting
- constipation
- itching at the injection site
- a small bump (nodule) at the injection site
- indigestion

Nausea is most common when you first start using BYDUREON, but decreases over time in most people as their body gets used to the medicine.

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

These are not all the side effects of BYDUREON. For more information, ask your healthcare provider or pharmacist.

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 BYDUREON?

- Store BYDUREON in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Do not use BYDUREON past the expiration date. The expiration date is labeled *EXP* and can be found on the paper cover of the single-dose tray.
- Do not freeze BYDUREON trays. Do not use BYDUREON if it has been frozen.
- Protect BYDUREON from light until you are ready to prepare and use your dose.
- If needed, you can keep your BYDUREON tray out of the refrigerator at 68°F to 77°F (20°C to 25°C) for up to 4 weeks.
- See the Instructions for Use for information about how to throw away your used BYDUREON parts.

Keep BYDUREON, and all medicines, out of the reach of children.

General information about safe and effective use of BYDUREON

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

This Medication Guide summarizes the most important information about BYDUREON. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about BYDUREON that is written for healthcare professionals.

For more information about BYDUREON, go to www.BYDUREON.com or call 1-877-700-7365.

What are the ingredients in BYDUREON?

Contents of vial:

Active ingredient: exenatide

Inactive ingredients: polylactide-co-glycolide and sucrose.

Contents of liquid (diluent) in syringe:

Inactive ingredients: carboxymethylcellulose sodium, polysorbate 20, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, water for injection.

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

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