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).**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Injection-Site Reactions (5.8) 5/2014

----------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 (1.1, 14).

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

Important Limitations of Use

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (1.2).
- 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 dose is prepared (2.1).

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

BYDUREON 2 mg exenatide for extended-release injectable suspension has two dosage forms (3):

- BYDUREON single-dose tray containing 2 mg vial
- BYDUREON Pen single-dose 2 mg pen

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

- Do not use for patients with personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4.1).
- Do not use for patients with 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 patient has 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 patient has 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 in patients with 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).
- Injection-site reactions: There have been postmarketing reports of serious injection-site reactions with or without subcutaneous nodules (5.8).
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYDUREON or any other antidiabetic drug (5.9).

----------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 AstraZeneca at 1-800-236-9933 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 (6.2, 7.2).

----------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 Medication Guide.

Revised: 5/2014

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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 7 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 [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.

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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 7 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 3 days later. Thereafter, patients can resume their usual dosing schedule of once every 7 days (weekly).

If a dose is missed and the next regularly scheduled dose is due 1 or 2 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.

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2.2 Administration

BYDUREON must be injected immediately after the dose is prepared. 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. BYDUREON is intended for patient self-administration.

Prior to initiation of BYDUREON, patients should be trained by their healthcare professional. For the BYDUREON Pen, study data demonstrated that training reduced the risk of administration errors such as inadequate mixing or incomplete dosing. Patients using the BYDUREON Pen should be trained on proper mixing and injection technique to ensure the product is adequately mixed and a full dose is delivered. **Refer to the accompanying 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 2 weeks) elevations in blood glucose concentrations.

3 DOSAGE FORMS AND STRENGTHS

BYDUREON exenatide extended-release for injectable suspension is available as:

- BYDUREON single-dose tray which contains one vial of 2 mg exenatide, one vial connector, one prefilled diluent syringe, and two needles (one provided as a spare).
- BYDUREON Pen. Each single-dose pen contains 2 mg of exenatide and diluent, and includes one needle. Each carton contains one spare needle.

Do not substitute needles or any other components provided with BYDUREON. See *How Supplied/Storage and Handling (16.1)* for additional information.

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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* and *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,

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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 *Clinical Pharmacology (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 30-50 mL/min) [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*]. BYDUREON has not been studied in patients with end-stage renal disease or severe renal impairment.

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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- to 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)*].

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5.8 Injection-Site Reactions

There have been postmarketing reports of serious injection-site reactions (e.g., abscess, cellulitis, and necrosis), with or without subcutaneous nodules, with the use of BYDUREON. Isolated cases required surgical intervention [see *Adverse Reactions (6.2)*].

5.9 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 7 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 7 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 7 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 7 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- to 30-week trials. The most common adverse reactions leading to withdrawal for BYDUREON-treated patients were nausea 0.5%

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(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- to 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)

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Table 1: Incidence (% of Subjects) and Rate (Episodes/Subject Year) of Minor† Hypoglycemia in the Monotherapy Trial and in the Combination Therapy Trials

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)

N = 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- to 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

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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- to 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 = 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.

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Table 3: Treatment-Emergent Adverse Reactions Reported in ≥5% of BYDUREON-Treated Patients in 24- to 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	

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

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 = 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- to 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).

Subcutaneous injection-site nodules may occur 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 1 injection-site nodule during treatment; 2 subjects (6.5%)

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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 Postmarketing Experience

BYDUREON

Allergy/Hypersensitivity: injection-site reactions [see *Warnings and Precautions (5.8)*].

BYETTA

The following additional adverse reactions have been reported during postapproval 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

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and necrotizing pancreatitis sometimes resulting in death [see *Indications and Usage (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.

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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)*].

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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 to 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

A Pregnancy Registry has been implemented to monitor pregnancy outcomes of women exposed to exenatide during pregnancy. Physicians are encouraged to register patients by calling 1-800-633-9081.

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- to 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.

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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 30-50 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- to 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 diluent 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 or per pen. Exenatide is incorporated in an extended-release microsphere formulation containing the 50:50 poly(D,L-lactide-co-glycolide) polymer (37.2 mg per dose)

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along with sucrose (0.8 mg per dose). The powder must be suspended in the diluent prior to injection.

The diluent for the BYDUREON vial is supplied in a prefilled syringe within each single-dose tray. The diluent for the BYDUREON Pen is contained within each single-dose pen. Each configuration contains sufficient diluent to deliver 0.65 mL. The diluent is a clear, colorless to pale-yellow solution composed of carboxymethylcellulose sodium (19 mg), polysorbate 20 (0.63 mg), sodium phosphate monobasic monohydrate (0.61 mg), sodium phosphate dibasic heptahydrate (0.51 mg), sodium chloride (4.1 mg), and water for injection. Sodium hydroxide may be added during manufacture of BYDUREON Pen for pH adjustment.

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

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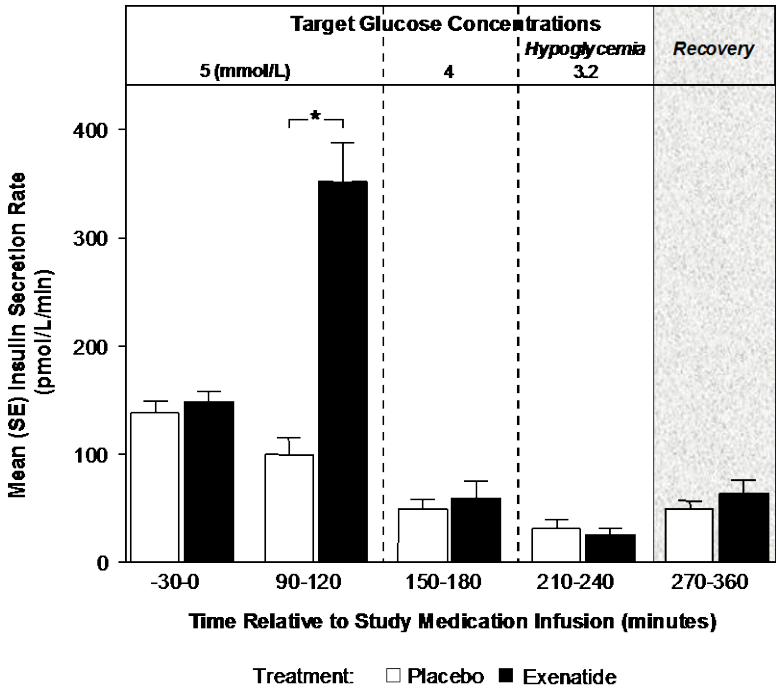
glucose-dependent (Figure 1). Exenatide did not impair the normal glucagon response to hypoglycemia.

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



SE = standard error.
Notes: 5 mmol = 90 mg/dL, 4 mmol/L = 72 mg/dL, 3.2 mmol/L = 58 mg/dL; Study medication infusion was started at time = 0 minutes.
Statistical assessments were for the last 30 minutes of each glycemic step, during which the target glucose concentrations were maintained.
* $p < 0.05$, exenatide treatment relative to placebo.

Glucagon Secretion

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

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Gastric Emptying

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

Food Intake

Infusion of exenatide in 8 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 2 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 280-310 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

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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 to 7, respectively, representing the hydration and erosion of the microspheres.

Following initiation of once every 7 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 7 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/hour 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

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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 (5-20 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-hour 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)*].

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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 Populations (8.5)*].

Gender

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

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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%-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% (nonstatistically 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

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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

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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 to 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%) Hispanic, 15 (6%) Black, and 10 (4%) 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

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baseline HbA_{1c} was 8.4%. Patients were randomly assigned to receive BYDUREON 2 mg once every 7 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 = 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 (LS) 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)*].

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BYDUREON (exenatide extended-release for injectable suspension) for once every 7 days (weekly) subcutaneous administration is supplied as:

BYDUREON single-dose tray, supplied in cartons that contain four single-dose trays (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)

BYDUREON Pen, supplied in cartons that contain four single-dose pens and one spare needle (NDC 0310-6530-04). Each single-dose pen contains:

- One pen containing 2 mg of exenatide (as a white to off-white powder) and delivering 0.65 mL diluent.
- One custom needle (23G, 9/32”) specific to this delivery system.

Do **not** substitute needles or any other components provided with BYDUREON.

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, on the cover of the single-dose tray, or on the pen label.
- Do not freeze BYDUREON. Do not use BYDUREON if it has been frozen. Protect from light.
- BYDUREON 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.

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- Use a puncture-resistant container to discard BYDUREON with the needle still attached. Do not reuse or share needles or syringes.
- Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide. **Prior to initiation of BYDUREON, patients should be trained by their healthcare professional.**

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 discontinue BYDUREON promptly 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

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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 Risk of Injection-Site Reactions

Inform patients that there have been postmarketing reports of serious injection-site reactions with or without subcutaneous nodules, with the use of BYDUREON. Isolated cases of injection-site reactions required surgical intervention. Advise patients to seek medical advice if symptomatic nodules occur, or for any signs or symptoms of abscess, cellulitis, or necrosis [see *Warnings and Precautions (5.8)*].

17.7 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)*].

17.8 Instructions

Patients should be trained on how to use BYDUREON properly prior to self-administration. Instruct patients on proper mixing and injection technique to ensure the product is adequately mixed and a full dose is delivered. Refer patients to the accompanying Instructions for Use for complete administration instructions with illustrations.

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 7 days (weekly) administration can be changed if necessary as long as the last dose was

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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 3 days later. Thereafter, patients can resume their usual once every 7 days (weekly) dosing schedule. If a dose is missed and the next regularly scheduled dose is due in 1 or 2 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 BYDUREON with another person, even if the needle is changed. Sharing of BYDUREON 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 2 weeks after initiation of therapy [see *Dosage and Administration (2.3)* and *Clinical Studies (14.1)*].

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.

BYDUREON is a registered trademark of the AstraZeneca group of companies.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

By:
Amylin Ohio LLC
West Chester, OH 45071

Reference ID: 3511713

Medication Guide

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

Read this Medication Guide 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.

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

Serious side effects may happen in people who use 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 using 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** use 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 use BYDUREON.
   - While using 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 using BYDUREON, tell your healthcare provider if you have had:

   - pancreatitis
   - stones in your gallbladder (gallstones)

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- 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 using 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.

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- 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 using 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: There is a registry for women who use BYDUREON during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. If you use 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 use 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 over-the-counter 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.

- BYDUREON comes as a single-dose tray or as a single-dose pen. Your healthcare provider will prescribe the BYDUREON that is best for you.
- **Your healthcare provider should teach you how to use 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.
- Pay special attention to mixing BYDUREON well, as shown in the Instructions for Use.
- After injecting with the BYDUREON Pen, make sure you hold the needle in your skin for 10 seconds, to get the full dose.
- 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 use 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 use BYDUREON with or without food.
- **If you miss a dose of BYDUREON, it should be used as soon as you remember, provided the next regularly scheduled dose is due at least 3 days later.**
- **If you miss a dose of BYDUREON and the next regularly scheduled dose is due 1 or 2 days later, do not use the missed dose. Use BYDUREON on the next regularly scheduled day.**
- **Do not** use 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.
- BYDUREON must be injected right after you mix it.

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- **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 with another person even if the needle is changed. Sharing your tray or pen 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 use 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:

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- shakiness
- headache
- drowsiness
- weakness
- dizziness
- confusion
- sweating
- irritability
- hunger
- fast heartbeat
- feeling jittery

- **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 using BYDUREON, and get medical help right away if you have any symptom of a severe allergic reaction. See "**Who should not use BYDUREON?**"
- **Injection-site reactions.** Serious injection-site reactions, with or without bumps (nodules), have happened in some people who use BYDUREON. Some of these injection-site reactions have required surgical intervention. Call your healthcare provider right away if you have any of the following at your injection site:
  - severe pain
  - swelling
  - blisters
  - an open wound
  - a dark scab

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

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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 printed on the BYDUREON carton, single-dose tray cover, or pen label. The expiration date is labeled *EXP* and can be found on the paper cover of the single-dose tray or single-dose pen.
- **Do not** freeze BYDUREON. **Do not** use BYDUREON if it has been frozen.
- Keep BYDUREON within its sealed tray until ready for use.
- Protect BYDUREON from light until you are ready to prepare and use your dose.
- If needed, you can keep BYDUREON single-dose 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.

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

What are the ingredients in BYDUREON?

Contents of the powder:

Active Ingredient: exenatide

Inactive Ingredients: polylactide-co-glycolide and sucrose

Contents of liquid (diluent):

Inactive Ingredients: carboxymethylcellulose sodium, polysorbate 20, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, water for injection. Sodium hydroxide may be added during manufacture of BYDUREON Pen for pH adjustment.

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

BYDUREON is a registered trademark and BYETTA is a registered trademark of the AstraZeneca group of companies. All other marks are the marks of their respective owners.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

By:
Amylin Ohio LLC
West Chester, OH 45071

Approved: May 2014

Reference ID: 3511713

Instructions for Use

BYDUREON® (by-DUR-ee-on) Single-Dose Tray

(exenatide extended-release for injectable suspension)

Before using Bydureon, your healthcare provider should show you how to use it the right way.

Read these Instructions for Use before you start using BYDUREON Single-Dose Tray and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Getting ready

Never share your BYDUREON vials or needles with anyone else. You may give an infection to them or get an infection from them.

BYDUREON Single-Dose Tray is not for self-injection by people who are blind or cannot see well.

Supplies needed to give your BYDUREON Single-Dose Tray injection (not all supplies are included):

- 1 BYDUREON Single-Dose Tray that contains:
    - 1 BYDUREON vial
    - 1 Syringe
    - 2 Needles
    - 1 Vial connector
- alcohol swab
- a clean flat surface
- sharps container for throwing away used needles, vials, and syringes. See **Step 4h "Disposing of used Needles and Syringes**."

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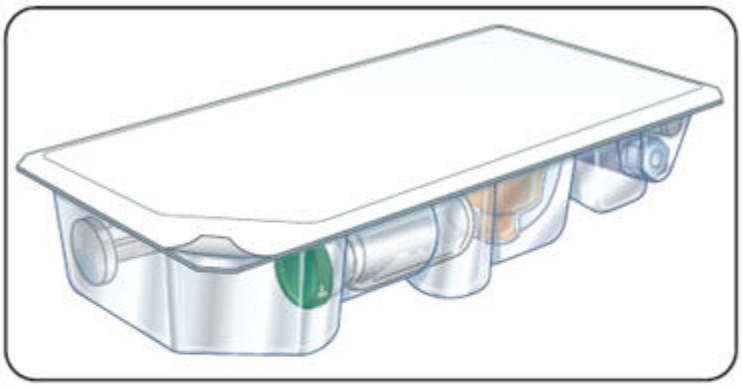
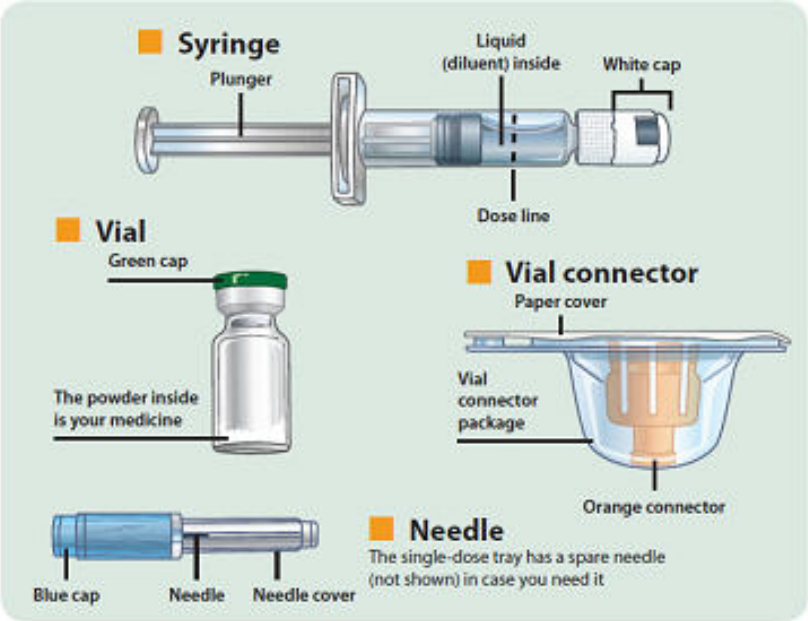
Your guide to your BYDUREON Single-Dose Tray

- Single-dose tray

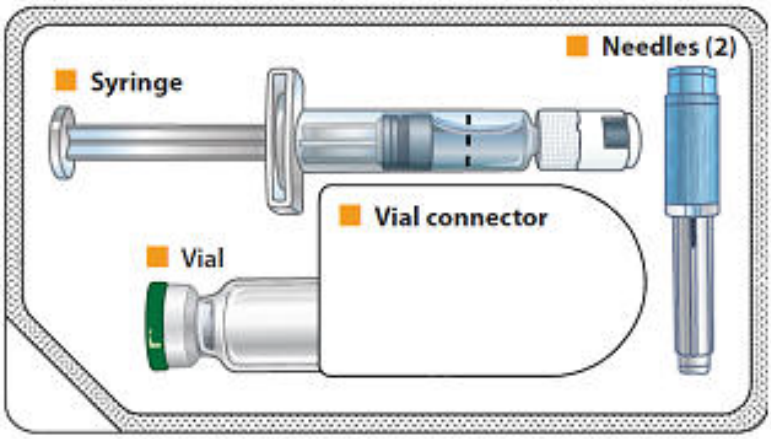


Keep this flap open so you can refer to it as you go through the steps.



Your guide to the parts

- Single-dose tray



What's Inside

To take the correct dose, read **each** page so that you do **every** step in order.

This step-by-step guide is divided into 4 sections:

- Getting Started
- Connecting the Parts
- Mixing the Medicine and Filling the Syringe
- Injecting the Medicine

For **Common Questions and Answers,** see page X.

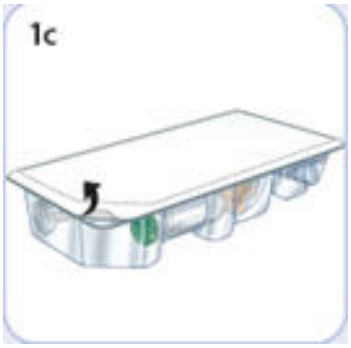
How to store your Single-Dose Trays of BYDUREON

- Store your BYDUREON trays in the refrigerator at 36°F to 46°F (2°C to 8°C).
- 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.
- Protect BYDUREON from light until you are ready to prepare and use your dose.
- Do not freeze BYDUREON trays.
- Do not use BYDUREON past the expiration date. The expiration date is labeled *EXP* and can be found on the paper cover of each tray.
- Keep BYDUREON, and all medicines, out of the reach of children.

1. Getting Started

1a) Take a Single-Dose Tray from the refrigerator.

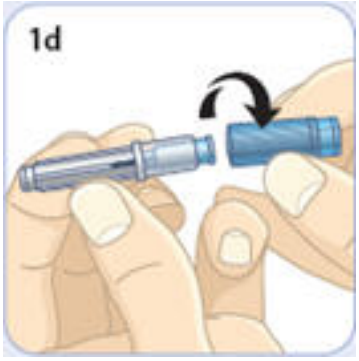
1b) **Wash your hands.** Prepare to clean your injection site with soap and water or an alcohol swab prior to injecting your medicine.



Peel back the paper cover to open.

Remove the syringe. The liquid in the syringe should be clear with no particles in it. It is okay if there are bubbles.

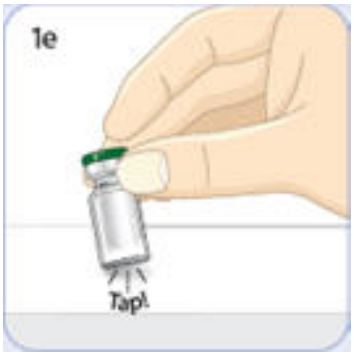
Place the needle, vial connector package, vial, and syringe on a clean, flat surface.



Pick up the needle, and twist off the blue cap.

Set the covered needle aside. You will use it later.

There is a spare needle in the tray if you need it.



Pick up the vial.

Tap the vial several times against a hard surface to loosen the powder.

Use your thumb to remove the green cap.

Put the vial aside.

2. Connecting the Parts

Pick up the vial connector package and peel off the paper cover. Do not touch the orange connector inside.

Hold the vial connector package.

In your other hand, hold the vial.

Press the top of the vial firmly into the orange connector.

Then lift the vial with the orange connector now attached out of the clear package.

This is what the vial should now look like.

Put it aside for later.

Pick up the syringe.

With your other hand, firmly grasp the 2 gray squares on the white cap.

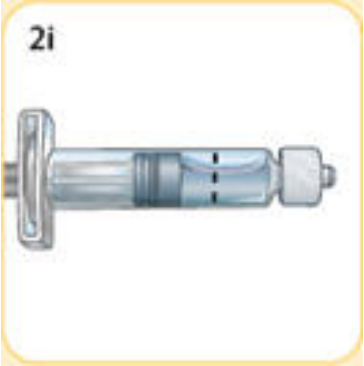
Break off the cap.

Be careful not to push in the plunger.

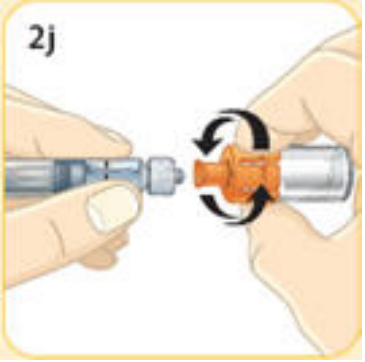
Just like you might break a stick, you are breaking off the cap.

This is what the broken-off cap looks like.

You will not be using the cap and can throw it away.



This is what the syringe should now look like.



Now, pick up the vial with the orange connector attached.

Twist the orange connector onto the syringe until snug. While twisting, be sure to grasp the orange connector. Do not over tighten.

This is how the parts should now look when they are connected.

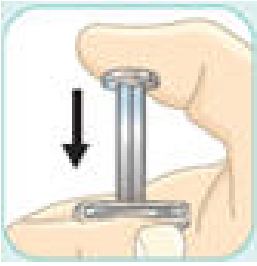
3. Mixing the Medicine and Filling the Syringe

IMPORTANT:

During these next steps, you will be mixing the medicine and filling the syringe. Once you mix the medicine, you must inject it. You cannot save the mixed medicine to inject at a later time.

With your thumb, push down the plunger until it stops.

The plunger may feel like it is springing back a little.



For steps 3a to 3f, keep pushing down on the plunger with your thumb.

Hold the plunger down and shake hard. Keep shaking until the liquid and powder are mixed well.

The vial will not come off. The orange connector will keep it attached to the syringe.

Shake hard like you would shake a bottle of oil-and-vinegar salad dressing.

When the medicine is mixed well, it should look cloudy.

If you see clumps of dry powder on the sides or bottom of the vial, the medicine is not mixed well.

Shake hard again until well mixed.

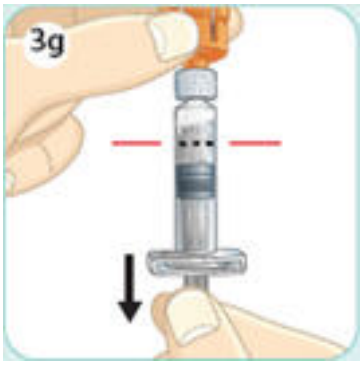
Keep pushing down on the plunger while shaking.

If you have any questions or are not sure if your BYDUREON is mixed well, call 1-877-700-7365 for help.

Now, hold the vial upside down so the syringe is pointing up. Continue to hold the plunger in place with your thumb.

Gently tap the vial with the other hand. Continue to hold the plunger in place.

The tapping helps the medicine drip down. It is okay if there are bubbles.



Pull the plunger down beyond the black dashed Dose Line.

This draws the medicine from the vial into the syringe. You may see air bubbles. This is normal.

A little bit of liquid may cling to the sides of the vial.

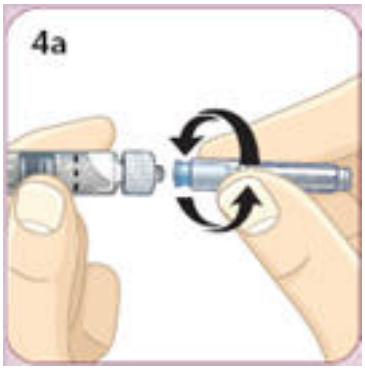
With 1 hand, hold the plunger in place so it does not move.

With the other hand, twist the orange connector to remove it from the syringe.

Be careful not to push in the plunger.

This is what the syringe should now look like.

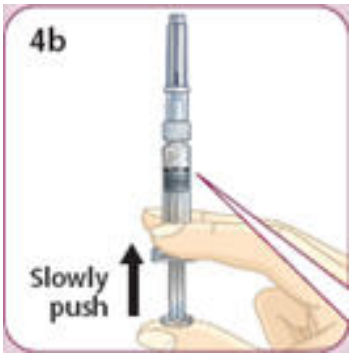
4. Injecting the Medicine



Pick up the needle. Twist the needle onto the syringe until snug. Do not remove the needle cover yet.

IMPORTANT:

Read the next steps carefully and look closely at the pictures. This helps you get the correct dose of medicine.



Slowly push in the plunger so the top of the plunger lines up with the black dashed Dose Line.

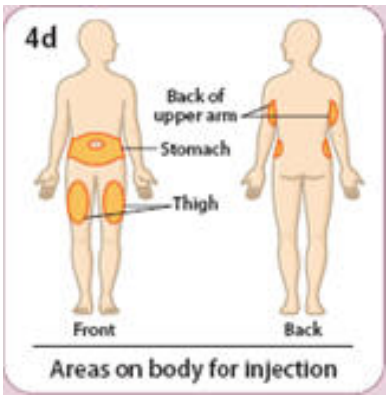
Then, take your thumb off the plunger.

The top of the plunger must stay lined up with the black dashed Dose Line as you go through the next steps. This will help you get the correct dose of medicine.

Put aside the syringe with the needle attached.

IMPORTANT:

It is normal to see a few bubbles in the mixture. The bubbles will not harm you or affect your dose.

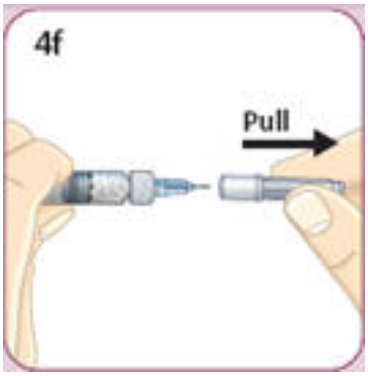


You can inject the medicine in your stomach area (abdomen), your thigh, or the back of your upper arm.

Each week you can use the same area of your body but choose a different injection site in that area.

Gently clean the site you choose with soap and water or an alcohol swab.

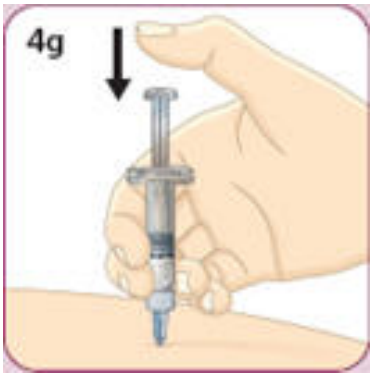
Now, pick up the syringe and hold it near the black dashed Dose Line.



Pull the needle cover straight off. Do not twist.

Be careful not to push in the plunger.

When you remove the cover, you may see 1 or 2 drops of liquid. This is normal.



Insert the needle into your skin (subcutaneously). To inject your full dose, push down on the plunger with your thumb until it stops.

Withdraw the needle.

Be sure to use the injection technique recommended by your healthcare provider.

Disposing of used Needles and Syringes:

- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) loose needles and syringes in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic,
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
    - upright and stable during use,
    - leak-resistant, and
    - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and pens. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

Please keep these Instructions for Use for your next dose.

Common Questions and Answers

If your question is about:	See question number:
How soon to inject after mixing	**1**
Mixing the medicine	**2**
Air bubbles in syringe	**3**
Attaching the needle	**4**
Removing the needle cover	**5**
Plunger not lining up with black dashed Dose Line	**6**
Being unable to push the plunger down when injecting	**7**

1. **After I mix the medicine, how long can I wait before taking the injection?**

   You must take your injection of BYDUREON right after mixing it. If you do not inject BYDUREON right away, the medicine will start to form small clumps in the syringe. These clumps can clog the needle when you take the injection (see question 7).

2. **How do I know that the medicine is mixed well?**

   When the medicine is mixed well, it should look cloudy. There should not be any dry powder on the sides or bottom of the vial. **If you do see any dry powder, shake hard while continuing to push down on the plunger with your thumb.** (This question relates to the steps shown on pages X through X.)

Reference ID: 3511713

3. **I'm ready to take the injection. What should I do if I see air bubbles in the syringe?**

   It is normal for air bubbles to be in the syringe. The air bubbles will not harm you or affect your dose. BYDUREON is injected into your skin (subcutaneously). Air bubbles are not a problem with this type of injection. (This question relates to step 3f shown on page X and step 4c shown on page X.)

4. **What should I do if I have trouble attaching the needle?**

   First, be sure you have removed the blue cap. Then, **twist** the needle onto the syringe until snug. To prevent losing medicine, do not push in the plunger while attaching the needle. (This question relates to step 4a on page X.)

5. **What should I do if I have trouble removing the needle cover?**

   With one hand, hold the syringe near the black dashed Dose Line. With your other hand, hold the needle cover. **Pull the needle cover straight off.** Do not twist it. (This question relates to step 4f on page X.)

6. **I am at step 4c. What should I do if the top of the plunger has been pushed past the black dashed Dose Line?**

   The black dashed Dose Line shows the correct dose. If the top of the plunger has been pushed past the line, you should continue from step 4d and take the injection. Before your next injection in 1 week, carefully review the instructions on pages X through X.

7. **When I inject, what should I do if I cannot push the plunger all the way down?**

   This means the needle has become clogged. Remove the needle from your skin and replace it with the spare needle from your tray. Then choose a different injection site and finish taking the injection.

   To review how to:

   - Remove the blue cap of the needle, see page X
   - Attach the needle, see page X
   - Remove the needle cover and give the injection, see pages X and X

Reference ID: 3511713

If you still cannot push the plunger all the way down, remove the needle from your skin. Use a puncture-resistant container to throw away the syringe with the needle still attached. It is important that you then call 1-877-700-7365.

To help prevent a clogged needle, always mix the medicine very well and inject right after mixing.

Where to learn more about BYDUREON

- **Talk with your healthcare provider**
- **Read the Medication Guide that came with your BYDUREON.** The Medication Guide can help answer your questions about BYDUREON, such as what it is used for, possible side effects, and when to take BYDUREON.
- Enroll in BYDUREON Support for FREE ongoing help managing your diabetes. **Visit www.BYDUREON.com or call 1-877-700-7365.**

These Instructions for Use have been approved by the U.S. Food and Drug Administration.

BYDUREON® is a registered trademark of the AstraZeneca group of companies.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

By:
Amylin Ohio LLC
West Chester, OH 45071

Approved: May 2014

Instructions for Use

BYDUREON® (by-DUR-ee-on) Pen

(exenatide extended-release for injectable suspension)

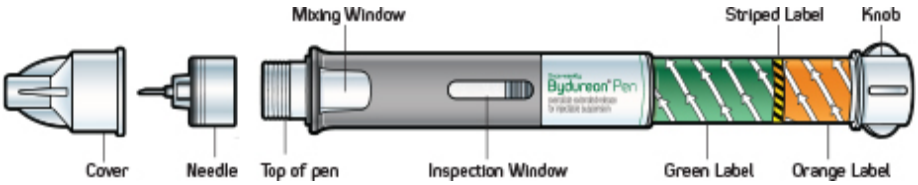


Figure A

Before using Bydureon Pen, your healthcare provider should show you how to use it the right way.

Read the Instructions for Use before you start using Bydureon Pen and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Getting ready

Never share your Bydureon Pen or needles with anyone else. You may give an infection to them or get an infection from them.

Bydureon Pen is not for self-injection by people who are blind or cannot see well.

Supplies needed to give your Bydureon Pen injection (not all supplies are included):

- 1 Bydureon single-use "Pen" tray that contains:
  - 1 Bydureon Pen
  - 1 custom needle
- a clean flat surface
- alcohol swab
- sharps container for throwing away used needles and Pens. See "**Disposing of used needles and Pens**" at the end of these instructions.

Reference ID: 3511713

How should I store Bydureon?

- Store your Bydureon Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Protect pens from light until you are ready to prepare and use your dose.
- **DO NOT** use pens past the expiration date printed on the paper cover of each Bydureon Pen tray.
- **DO NOT** freeze Bydureon. **DO NOT** use Bydureon if it has been frozen.
- Keep Bydureon in its sealed tray until ready for use.

Keep Bydureon Pen, and all medicines, out of the reach of children.

Step 1: Prepare your Bydureon Pen

Let your Pen warm up.

- Remove 1 Pen from the refrigerator and let it stand at room temperature for at least 15 minutes.

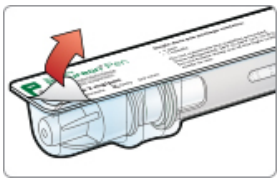
Check the expiration date printed on your Pen tray.

- **Do not** use a Pen past the expiration date printed on your Pen tray.

Wash your hands.

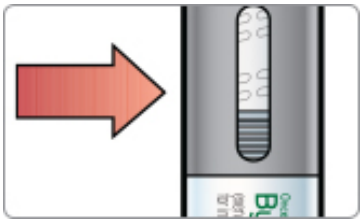
Open the tray.

- Pull up on the corner tab.
- Remove the Pen and needle.
  - **Do not** use your Pen or needle if any parts are broken or missing.



Check the liquid in your Pen.

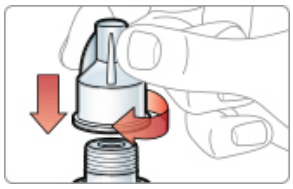
- **Check the liquid** inside the inspection window. It should be clear and free of particles. **Do not** use the Pen if the liquid is colored, has particles, or is not clear. Throw it away and get a new one.
  - You may see bubbles in the liquid, this is normal.



Peel off the paper tab from the needle cover.

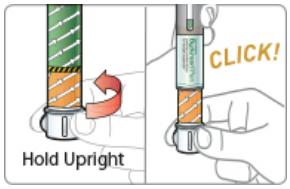
Attach the needle to the Pen.

- Screw the needle onto the Pen by pushing and twisting clockwise until it is tight. **Do not** remove the needle cover yet.



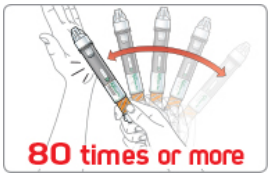
Step 2: Mix your dose

Combine the medicine.



- While holding the pen straight up, **slowly** turn the knob. **Stop** when you hear the click and the green label disappears.

Firmly tap your Pen to mix.



- Hold your Pen by the end with the orange label and **tap the Pen firmly against the palm of your hand**.
  - **DO NOT** twist the white knob.
  - **ROTATE** your Pen every 10 taps.
  - **You may need to tap your Pen 80 times or more.**

Check the Bydureon mix.

- **Hold your Pen up to the light and look through both sides of the mixing window.** The solution should have **NO CLUMPS** and be uniformly cloudy **(see Figure B)**.

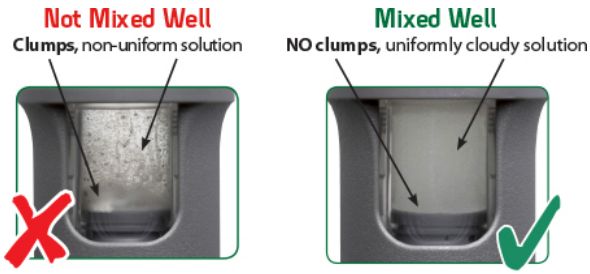


Figure B

- **To get your full dose, Bydureon must be mixed well.**
- **If Bydureon is not mixed well, keep tapping your Pen longer and more firmly until it is mixed well.**
- **Do not give your Bydureon injection unless your Bydureon is mixed well.**

STOP. Do Not proceed unless your medicine is mixed well.

To get your full dose the medicine must be mixed well. If it's not mixed well, tap longer and more firmly.

Check the Bydureon mix again.

- **Compare both sides of the mixing window to the photos below** by holding your Pen against the page. Pay attention to the **bottom surface.** If you **do not see clumps** you are ready to inject **(see Figure C)**.

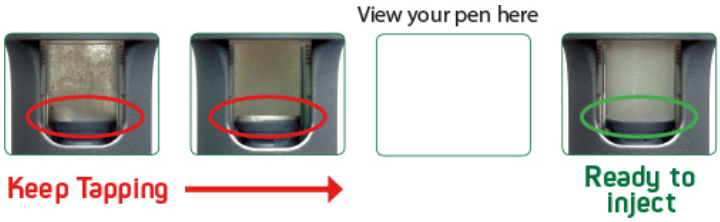


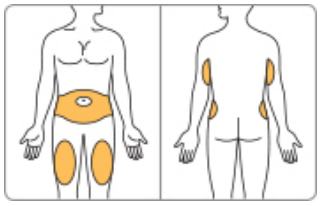
Figure C

If you have any questions or are not sure if your Bydureon is mixed well, call 1-877-700-7365 for help.

Step 3: Inject your dose

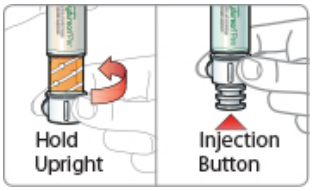
IMPORTANT: After the medicine is mixed well, you must inject your dose right away. You cannot save it for later use.

Choose your injection site.



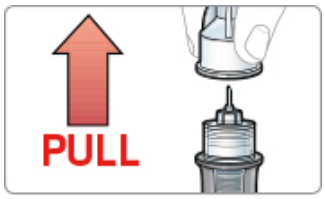
- The recommended injection sites for Bydureon are your stomach (abdomen), thigh, or back of the arm.
  - Each week you can use the same area of your body but choose a different injection site in that area.
  - Gently wipe the site you choose with an alcohol swab (not included).

Twist knob to release injection button.



- Hold your **Pen with the needle pointing straight up** and turn the white knob until the orange label disappears and the injection button is released. **DO NOT** push the injection button yet.

Remove the needle cover.



- Pull the needle cover straight off. **DO NOT** twist the needle cover.
  - o You may see a few drops of liquid on the needle or in the cover.

Inject your Bydureon.

- Insert the needle into your skin.
- Press the injection button with your thumb until you hear a "click." Keep holding **the button down and slowly count to 10 to get your full dose.**

Properly dispose of your Pen.

- Put your used needles and Pens in an FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) loose needles and Pens in your household trash. See **Common Questions and Answers** for additional disposal information.

Common Questions and Answers:

1. How do I know that the Bydureon is mixed well?

The Bydureon is mixed well when the liquid looks cloudy from both sides of the window. You should not see any clumps in the liquid. It may help to hold your Pen up to the light to see in the window. If you see clumps of any size keep tapping your Pen firmly against the palm of your hand until mixed.

2. I am having trouble mixing my dose. What should I do?

Remember, before preparing your dose, leave your Pen out of the refrigerator for at least 15 minutes. This will let your Pen warm up to room temperature. It will be easier to mix Bydureon if your Pen is at room temperature.

Be sure you are holding your Pen at the end with the knob and the orange label. This will help you grip your Pen better and tap it more firmly against your palm.

It may also help to tap the mixing window on both sides against your palm. If you see any clumps, keep tapping.

3. After I mix Bydureon, how long can I wait before taking the injection?

You must inject your dose of Bydureon right after mixing it. If you do not inject your Bydureon right away, small clumps of medicine may form in your Pen and you may not get your full dose.

4. I am ready to inject my dose. What should I do if I see air bubbles in the Pen?

It is normal for air bubbles to be in your Pen. Bydureon is injected into your skin (subcutaneously). Air bubbles will not harm you or affect your dose with this type of injection.

Reference ID: 3511713

5. What should I do if I cannot push the injection button all the way in when trying to inject my dose?

Check that you have fully screwed on the pen needle. Also be sure you twisted the knob until it stopped, the orange label disappeared, and the injection button appears.

If you still cannot push the button in, this may mean that the needle is clogged. Remove the needle from your skin and replace it with the spare needle from the carton. Review how to attach the needle. Then choose a different injection site and finish taking the injection.

If you still cannot push the button all the way in, remove the needle from your skin. Use a puncture-resistant container to throw away the pen with the needle still attached.

If you have problems giving your Bydureon Pen injection or have any questions call 1-877-700-7365 for more instructions.

6. How do I know if I injected my full dose?

To be sure you get your full dose, press the injection button with your thumb until you hear a “click.” After the “click,” continue to hold the needle in your skin for 10 seconds. This will allow enough time for you to get your full dose.

7. What if I do not have an FDA-cleared sharps disposal container?

Do not throw away (dispose of) loose needles and Pens in your household trash.

- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and Pens. For more

information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal

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BYDUREON® is a registered trademark of the AstraZeneca group of companies.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

By:
Amylin Ohio LLC
West Chester, OH 45071

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