2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of BYDUREON is 2 mg subcutaneously once every 7 days (weekly). The dose can be administered at any time of day, with or without meals.

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

2.2 Missed Dose

If a dose is missed, administer the dose 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, do not administer the missed dose and instead resume BYDUREON with the next regularly scheduled dose.

2.3 Administration Instructions

- There are two presentations of BYDUREON (i.e., a single dose tray and a single dose pen) *[see How Supplied/Storage and Handling (16)]*. The BYDUREON "Instructions for Use" for each presentation contains detailed instructions on the preparation and administration of BYDUREON *[see Instructions for Use]*.

- Each presentation of BYDUREON requires constitution prior to use to obtain a final concentration of 2 mg of exenatide per 0.65 mL of suspension.

- BYDUREON is intended for patient self-administration. Prior to initiation, train patients on proper mixing and injection technique to ensure the product is adequately mixed and a full dose is delivered.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. The suspension should appear white to off-white and cloudy. (BYDUREON contains microspheres which appear as white to off-white particles). Do not use if foreign particulate matter is present or if discoloration is observed. Refer patients to the accompanying Instructions for Use for disposal information *[see Instructions for Use]*.

- Administer BYDUREON immediately after the dose is prepared as a subcutaneous 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.

- Do not administer BYDUREON intravenously or intramuscularly.

- Refer patients to the accompanying Instructions for Use for complete administration instructions with illustrations *[see Instructions for Use]*.

2.4 Initiating BYDUREON Therapy

Prior treatment with an immediate- or extended-release exenatide product is not required when initiating BYDUREON therapy. Discontinue an immediate- or extended-release exenatide product prior to initiation of BYDUREON.

3 DOSAGE FORMS AND STRENGTHS

Extended-release for injectable suspension available as:

- Single-dose tray which contains one single dose vial of 2 mg exenatide white to off-white powder, one vial connector, one prefilled diluent syringe, and two needles (one provided as a spare).
- Single-dose pen which contains 2 mg of exenatide white to off-white powder, 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)* for additional information.

4 CONTRAINDICATIONS

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).
- A prior serious hypersensitivity reaction to exenatide or to any of the product components. Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with BYDUREON *[see Warnings and Precautions (5.7)]*.

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 has not been determined.

Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.

BYDUREON is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk of MTC with the use of BYDUREON and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with BYDUREON. Such monitoring may increase the risk of unnecessary procedures, due to the low specificity of serum calcitonin testing for MTC and a high background incidence of thyroid disease. Significantly elevated serum calcitonin may indicate MTC and patients with MTC usually have values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

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 with Concomitant Use of Insulin Secretagogues or Insulin

The risk of hypoglycemia is increased when exenatide is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. Patients may require a lower dose of the secretagogue or insulin to reduce the risk of hypoglycemia in this setting *[see Adverse Reactions (6.1)]*.

5.4 Acute Kidney Injury and Impairment of Renal Function

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.

BYDUREON is not recommended for use 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.

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 BYDUREON-treated patients in five of the six 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, consider alternative antidiabetic therapy *[see Adverse Reactions (6.1) and 6.2)]*.

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 promptly seek medical advice *[see Contraindications (4), Adverse Reactions (6.3)]*. Inform and closely monitor patients with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist for allergic reactions, because it is unknown whether such patients will be predisposed to anaphylaxis with BYDUREON.

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 (6.1)]*.

5.9 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYDUREON.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-cell Tumors *[see Warnings and Precautions (5.1)]*
- Acute Pancreatitis *[see Warnings and Precautions (5.2)]*
- Hypoglycemia *[see Warnings and Precautions (5.3)]*

- Acute Kidney Injury and Impairment of Renal Function *[see Warnings and Precautions (5.4)]*
- Gastrointestinal Disease *[see Warnings and Precautions (5.5)]*
- Immunogenicity *[see Warnings and Precautions (5.6)]*
- Hypersensitivity *[see Warnings and Precautions (5.7)]*
- Injection-Site Reactions *[see Warnings and Precautions (5.8)]*

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 six 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. In an open-label 26-week trial, patients on metformin, a sulfonylurea, metformin plus a sulfonylurea, or metformin plus pioglitazone were treated with BYDUREON 2 mg every 7 days (weekly) or liraglutide 1.8 mg once daily.

Common Adverse Reactions

Tables 1 and 2 summarize adverse reactions with an incidence ≥5% reported in the six 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 1: Adverse Reactions Reported in ≥5% of BYDUREON-Treated Patients with Type 2 Diabetes Mellitus in Monotherapy Trial

	26-Week Monotherapy Trial			
	BYDUREON 2 mg N = 248 %	**Sitagliptin 100 mg N = 163 %**	**Pioglitazone 30-45 (mean dose 40) mg N = 163 %**	**Metformin 1000-2500 (mean dose 2077) 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.

Table 2: Adverse Reactions Reported in ≥5% of BYDUREON-Treated Patients with Type 2 Diabetes Mellitus 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	
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			

Table 2: Adverse Reactions Reported in ≥5% of BYDUREON-Treated Patients with Type 2 Diabetes Mellitus in 24- to 30-Week Add-On Combination Therapy Trials

	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
26-Week Add-On to Metformin, a Sulfonylurea, Metformin + Sulfonylurea, or Metformin + Pioglitazone Trial		
	BYDUREON 2 mg N = 461 %	
Injection-site nodule	10.4	
Nausea	9.3	
Diarrhea	6.1	

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 a common adverse reaction associated with initiation of treatment with BYDUREON and usually decreased over time.

Adverse Reactions Leading to Study Withdrawal

The incidence of withdrawal due to adverse reactions was 4.1% (N=57) for BYDUREON-treated patients, 4.9% (N=13) for BYETTA-treated patients, and 2.9% (N=46) for other comparator-treated patients in the six comparator-controlled 24- to 30-week trials. The most common classes of adverse reactions (0.5%) leading to withdrawal for BYDUREON-treated patients were, Gastrointestinal Disorders 1.6% (N=22) versus 4.1% (N=11) for BYETTA and 1.9% (N=30) for other comparators, and Administration Site Conditions 0.8% (N=11) versus 0.0% for BYETTA and 0.2% (N=3) for other comparators. The most frequent adverse reactions within each of these respective classes were, nausea 0.4% (N=6) for BYDUREON versus 1.5% (N=4) for BYETTA and 0.8% (N=12) for other comparators, and injection-site nodule, 0.4% (N=6) for BYDUREON versus 0.0% for BYETTA and 0.0% for other comparators.

Hypoglycemia

Table 3 summarizes the incidence of minor hypoglycemia in the six 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 3: Incidence (% of Subjects) of Minor† Hypoglycemia in Clinical Trials in Patients with Type 2 Diabetes Mellitus

26-Week Monotherapy Trial	
BYDUREON 2 mg (N = 248)	2.0%
Sitagliptin 100 mg (N = 163)	0.0%
Pioglitazone 30-45 (mean dose 40) mg (N = 163)	0.0%
Metformin 1000-2500 (mean dose 2077) mg (N = 246)	0.0%
26-Week Add-On to Metformin Trial	
BYDUREON 2 mg (N = 160)	1.3%
Sitagliptin 100 mg (N = 166)	3.0%
Pioglitazone 45 mg (N = 165)	1.2%
26-Week Add-On to Metformin or Metformin + Sulfonylurea Trial	
With Concomitant Sulfonylurea Use (N = 136)	
BYDUREON 2 mg (N = 70)	20.0%
Titrated Insulin Glargine (N = 66)	43.9%
Without Concomitant Sulfonylurea Use (N = 320)	
BYDUREON 2 mg (N = 163)	3.7%
Titrated Insulin Glargine‡ (N = 157)	19.1%
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%
BYETTA 10 mcg (N = 34)	11.8%
Without Concomitant Sulfonylurea Use (N = 178)	
BYDUREON 2 mg (N = 89)	0.0%
BYETTA 10 mcg (N = 89)	0.0%
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%
BYETTA 10 mcg (N = 52)	15.4%
Without Concomitant Sulfonylurea Use (N = 186)	
BYDUREON 2 mg (N = 93)	0.0%
BYETTA 10 mcg (N = 93)	1.1%
26-Week as Add-On to Metformin, a Sulfonylurea, Metformin + Sulfonylurea, or Metformin + Pioglitazone Trial	
With Concomitant Sulfonylurea Use (N = 590)	
BYDUREON 2 mg (N = 294)	15.3%
Without Concomitant Sulfonylurea Use (N = 321)	
BYDUREON 2 mg (N = 167)	3.6%

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.

Injection-Site Adverse 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%) reported accompanying localized symptoms. The mean duration of events was 27 days. The formation of subcutaneous nodules is consistent with the known properties of the microspheres used in BYDUREON.

Increase in Heart Rate

Increases in heart rate from baseline ranging from 1.5 to 4.5 beats per minute have been observed in comparator-controlled clinical trials. The long-term effects of the increase in heart rate have not been established.

Other Adverse Reactions

The following adverse reactions were also reported in three 30-week controlled trials of BYETTA (N=963) add-on to metformin and/or sulfonylurea, with an incidence of ≥1% and reported more frequently than with placebo: feeling jittery (9% BYETTA, 4% placebo), dizziness (9% BYETTA, 6% placebo), asthenia (4% BYETTA, 2% placebo), and hyperhidrosis (3% BYETTA, 1% placebo).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to exenatide cannot be directly compared with the incidence of antibodies with other products.

Anti-exenatide antibodies were measured at prespecified intervals (4-14 weeks) in all BYDUREON-treated patients (N=918) in the five comparator-controlled studies of BYDUREON. In these five trials, 452 BYDUREON-treated patients (49%) had low titer antibodies (≤125) to exenatide at any time during the trials and 405 BYDUREON-treated patients (45%) had low titer antibodies to exenatide at study endpoint (24-30 weeks). The level of glycemic control in these patients was generally comparable to that observed in the 379 BYDUREON-treated patients (43%) without antibody titers. An additional 107 BYDUREON-treated patients (12%) had higher titer antibodies at endpoint. Of these patients, 50 (6%

overall) had an attenuated glycemic response to BYDUREON (<0.7% reduction in HbA_{1c}); the remaining 57 (6% overall) had a glycemic response comparable to that of patients without antibodies *[see Warnings and Precautions (5.6)]*. In the 30-week trial in which anti-exenatide antibody assessments were performed at baseline and at 4-week intervals from week 6 to week 30, the mean anti-exenatide antibody titer in the BYDUREON-treated patients peaked at week 6 then declined by 56% from this peak by week 30.

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

6.3 Postmarketing Experience

The following additional adverse reactions have been reported during post-approval use of another formulation of exenatide. 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.

Drug Interactions: increased international normalized ratio (INR), sometimes associated with bleeding, with concomitant warfarin use *[see Drug Interactions (7)]*.

Gastrointestinal: nausea, vomiting, and/or diarrhea resulting in dehydration; abdominal distension, abdominal pain, eructation, constipation, flatulence, acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death *[see Indications and Usage (1)*.

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.

Skin and Subcutaneous Tissue Disorders: alopecia

7 DRUG INTERACTIONS

Table 4: Clinically Relevant Interactions Affecting Drugs Co-Administered with BYDUREON and Other Exenatide-Containing Products

Orally Administered Drugs (e.g., acetaminophen)	
Clinical Impact	Exenatide slows gastric emptying. Therefore, BYDUREON has the potential to reduce the rate of absorption of orally administered drugs *[see Clinical Pharmacology (12.3)]*.
Intervention	Use caution when administering oral medications with BYDUREON where a slower rate of oral absorption may be clinically meaningful.
Warfarin	

Table 4: Clinically Relevant Interactions Affecting Drugs Co-Administered with BYDUREON and Other Exenatide-Containing Products

Clinical Impact	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 exenatide of increased INR with concomitant use of warfarin, sometimes associated with bleeding *[see Adverse Reactions (6.3)]*.
Intervention	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.
Concomitant Use of Insulin Secretagogues or Insulin	
Clinical Impact	Exenatide promotes insulin release from pancreatic beta-cells in the presence of elevated glucose concentrations. The risk of hypoglycemia is increased when exenatide is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin *[see Adverse Reactions (6.1)]*.
Intervention	Patients may require a lower dose of the secretagogue or insulin to reduce the risk of hypoglycemia in this setting.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data with exenatide, the active ingredient in BYDUREON, in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*. Based on animal reproduction studies, there may be risks to the fetus from exposure to BYDUREON during pregnancy. BYDUREON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproduction studies identified increased adverse fetal and neonatal outcomes from exposure to exenatide extended-release during pregnancy, or from exposure to exenatide, during pregnancy and lactation, in association with maternal effects. In rats, exenatide extended-release administered during the period of organogenesis reduced fetal growth and produced skeletal ossification deficits at doses that approximate clinical exposures at the maximum recommended human dose (MRHD) of 2 mg/week. In mice, exenatide administered during gestation and lactation caused increased neonatal deaths at doses that approximate clinical exposures at the MRHD *(see Data)*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with an HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

Pregnant rats given subcutaneous doses of 0.3, 1, or 3 mg/kg exenatide extended-release every 3 days during organogenesis had systemic exposures 3-, 7-, and 17-times human exposure, respectively, at the maximum recommended human dose (MRHD) of 2 mg/week BYDUREON based on plasma exenatide exposure (AUC) comparison. Reduced fetal growth at all doses and skeletal ossification deficits at 1 and 3 mg/kg occurred at doses that decreased maternal food intake and body weight gain.

In studies evaluating reproduction and development in pregnant mice and rabbits, maternal animals were administered exenatide, the active ingredient in BYDUREON, by subcutaneous injection twice a day. Differences in embryo-fetal developmental toxicity from subcutaneously injected exenatide extended-release and exenatide were not evaluated in mice, rats, or rabbits.

In pregnant mice given 6, 68, 460, or 760 mcg/kg/day exenatide during fetal organogenesis, skeletal variations associated with slowed fetal growth, including changes in number of rib pairs or vertebral ossifications sites, and wavy ribs were observed at 760 mcg/kg/day, a dose that produced maternal toxicity and yielded systemic exposure 200 times the human exposure resulting from the MRHD of BYDUREON based on AUC comparison.

In pregnant rabbits given 0.2, 2, 22, 156, or 260 mcg/kg/day exenatide during fetal organogenesis, irregular fetal skeletal ossifications were observed at 2 mcg/kg/day, a dose yielding systemic exposure up to 4 times the human exposure from the MRHD of BYDUREON based on AUC comparison.

In maternal mice given 6, 68, or 760 mcg/kg/day exenatide from gestation day 6 through lactation day 20 (weaning), an increased number of neonatal deaths were observed on postpartum days 2 to 4 in dams given 6 mcg/kg/day, a dose yielding a systemic exposure equivalent to the human exposure from the MRHD of BYDUREON based on AUC comparison.

8.2 Lactation

Risk Summary

There is no information regarding the presence of exenatide in human milk, the effects of exenatide on the breastfed infant, or the effects of exenatide on milk production. Exenatide, the active ingredient in BYDUREON, was present in the milk of lactating mice. However, due to species-specific differences in lactation physiology, the clinical relevance of these data is not clear *(see Data)*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for exenatide and any potential adverse effects on the breastfed child from exenatide or from the underlying maternal condition.

Data

In lactating mice subcutaneously injected twice a day with exenatide, the active ingredient in BYDUREON, the concentration of exenatide in milk was up to 2.5% of the concentration in maternal plasma.

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.

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)]*.

10 OVERDOSAGE

Effects of overdoses with BYETTA, another formulation of exenatide, 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 a GLP-1 receptor agonist 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) 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.

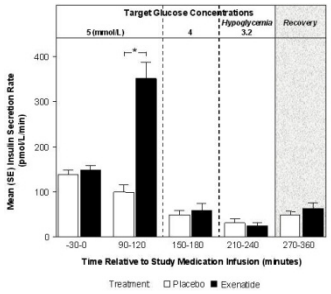
12.2 Pharmacodynamics

Exenatide improves glycemic control through the actions described below.

Glucose-Dependent Insulin Secretion

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

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.

Gastric Emptying

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

Fasting and Postprandial Glucose

In a clinical study in adults with type 2 diabetes mellitus, treatment with once weekly BYDUREON resulted in mean reductions in fasting plasma glucose of -45 mg/dL and 2-hour PPG concentrations of -95 mg/dL.

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

Absorption

Following a single dose of BYDUREON, exenatide is released from the microspheres over approximately 10 weeks. There is an initial period of release of surface-bound exenatide followed by a gradual release of

exenatide from the microspheres, which results in two subsequent peaks of exenatide in plasma at around week 2 and week 6 to 7, respectively, representing the hydration and erosion of the microspheres.

Following initiation of once every 7 days (weekly) administration of 2 mg BYDUREON, a 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

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 Interaction Studies

Acetaminophen

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

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

Digoxin

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

Lovastatin

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

Age, gender, race and body weight did not alter the pharmacokinetics of BYDUREON in population pharmacokinetic analyses.

Pediatric Patients

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

Thyroid C-cell tumors have been observed in rats and mice with GLP-1 receptor agonists.

A 2-year carcinogenicity study was conducted with exenatide extended-release, the active component of BYDUREON, 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 at the maximum recommended human dose (MRHD) of 2 mg/week BYDUREON based on plasma exenatide AUC, respectively) administered by subcutaneous injection every other week. In this study there was an increased incidence of C-cell adenomas and C-cell carcinomas at all doses. 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.

Carcinogenicity of exenatide extended-release has not been evaluated in mice.

Exenatide, the active ingredient in BYDUREON, was 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.

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, a combination of metformin and a thiazolidinedione, or in combination with a SGLT2 inhibitor on a background of metformin.

14.1 Monotherapy

BYDUREON Monotherapy versus Metformin, Sitagliptin, and Pioglitazone

A 26-week, randomized, comparator-controlled trial was conducted to compare the safety and efficacy of BYDUREON to metformin, sitagliptin, and pioglitazone in patients with type 2 diabetes whose glycemic control was inadequate with diet and exercise (NCT00676338).

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 has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) to their physician *[see Boxed Warning and Warnings and Precautions (5.1)]*.

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)]*.

Risk of Hypoglycemia

Inform patients that the risk of hypoglycemia is increased when BYDUREON is used in combination with an agent that induces hypoglycemia, such as a sulfonylurea or insulin *[see Warnings and Precautions (5.3)]*. Explain the symptoms, treatment, and conditions that predispose to the development of hypoglycemia. Review and reinforce instructions for hypoglycemia management when initiating BYDUREON therapy, particularly when concomitantly administered with a sulfonylurea or insulin *[see Warnings and Precautions (5.3)]*.

Risk of Acute Kidney Injury

Inform patients treated with BYDUREON of the potential risk for worsening kidney 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)]*.

Risk of Hypersensitivity Reactions

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

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)]*.

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 *[see Dosage and Administration (2)]*.

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. Inform patients formerly on BYETTA who start BYDUREON that they may experience transient elevations in blood glucose concentrations, which generally improve within the first 2 weeks after initiation of therapy *[see Dosage and Administration (2.4) 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 *[see How Supplied/Storage and Handling (16)]*.

Instruct the patient to review the BYDUREON Medication Guide and the Instructions for Use each time the prescription is refilled.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

By:
Amylin Ohio LLC
West Chester, OH 45071

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

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

What is the most important information I should know about BYDUREON?
BYDUREON may cause serious side effects, including:

- **Possible thyroid tumors, including cancer**. 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. In studies with rats or mice, BYDUREON and medicines that work like BYDUREON caused thyroid tumors, including thyroid cancer. It is not known if BYDUREON will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.
- Do not use BYDUREON if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

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 not recommended as the first choice of medicine for treating diabetes.
- BYDUREON is not a substitute for insulin and is not for use in people with type 1 diabetes or people with diabetic ketoacidosis.
- BYDUREON is a long-acting form of the medicine in BYETTA (exenatide). BYDUREON and BYETTA should not be used at the same time.
- It is not known if BYDUREON can be used in people who have had pancreatitis.
- It is not known if BYDUREON is safe and effective for use in children.

Who should not use BYDUREON?
Do not use BYDUREON if:

- you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- 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.

What should I tell my healthcare provider before using BYDUREON?
Before using BYDUREON, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had problems with your pancreas, kidneys, or liver.
- have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.
- are pregnant or plan to become pregnant. BYDUREON may harm your unborn baby. Tell your healthcare provider if you become pregnant while using BYDUREON. Talk to your healthcare provider about the best way to control your blood sugar if you plan to become pregnant or while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if BYDUREON passes into your breast milk. You should talk with your healthcare provider about the best way to feed your baby while using BYDUREON.

Tell your healthcare provider about all 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 medicines may affect the way BYDUREON works.
Before using BYDUREON, talk to your healthcare provider about low blood sugar and how to manage it. Tell your healthcare provider if you are taking other medicines to treat diabetes including insulin or sulfonylureas.

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

How should I use BYDUREON?

- Read the **Instructions for Use** that comes with BYDUREON.
- Use BYDUREON exactly as your healthcare provider tells you to.
- BYDUREON should be injected right away after you prepare your dose.
- **Your healthcare provider should show you how to use BYDUREON before you use it for the first time.**
- BYDUREON is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm. **Do not** inject BYDUREON into a muscle (intramuscularly) or vein (intravenously).
- **Use BYDUREON 1 time each week on the same day each week at any time of the day.**
- BYDUREON may be taken with or without food.
- If you miss a dose of BYDUREON, take the missed dose as soon as possible if there are at least 3 days (72 hours) until your next scheduled dose. If there are less than 3 days remaining, skip the missed dose and take your next dose on the regularly scheduled day. **Do not** take 2 doses of BYDUREON within 3 days of each other.
- You may change the day of the week as long as your last dose was given 3 or more days before.
- **Do not** mix insulin and BYDUREON together in the same injection.
- You may give an injection of BYDUREON and insulin in the same body area (such as, your stomach area), but not right next to each other.
- Change (rotate) your injection site with each weekly injection. **Do not** use the same site for each injection.
- **Do not share your BYDUREON pen, prefilled syringe, or needles with another person.** You may give another person an infection or get an infection from them.
- **Your dose of BYDUREON and other diabetes medicines may need to change because of:** change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of other medicines you take.

What are the possible side effects of BYDUREON?

BYDUREON may cause serious side effects, including:

- **See "What is the most important information I should know about BYDUREON?"**
- **inflammation of your pancreas (pancreatitis).** Stop using BYDUREON and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- **low blood sugar (hypoglycemia).** Your risk for getting low blood sugar may be higher if you use BYDUREON with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin. **Signs and symptoms of low blood sugar may include:**

o dizziness or light-headedness	o blurred vision	o anxiety, irritability, or mood changes
o sweating	o slurred speech	o hunger
o confusion or drowsiness	o shakiness	o weakness
o headache	o fast heartbeat	o feeling jittery

- **kidney problems (kidney failure).** In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse.
- **stomach problems.** Other medicines like BYDUREON may cause severe stomach problems. It is not known if BYDUREON causes or worsens stomach problems.

- **serious allergic reactions.** Stop using BYDUREON, and get medical help right away if you have any symptoms of a serious allergic reaction, including itching, rash, or difficulty breathing.
- **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 surgery. Call your healthcare provider if you have any symptoms of an injection-site reaction, including severe pain, swelling, blisters, an open wound, a dark scab.

The most common side effects of BYDUREON may include nausea, diarrhea, headache, vomiting, constipation, itching at the injection site, a small bump (nodule) at the injection site, indigestion.

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

Talk to your healthcare provider about any side effect that bothers you or does not go away. These are not all the possible 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.

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

General information about the 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.

You can ask your pharmacist or healthcare provider for information about BYDUREON that is written for health professionals.

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.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
By:
Amylin Ohio LLC
West Chester, OH 45071

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

1321141A0

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: October 2017

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.

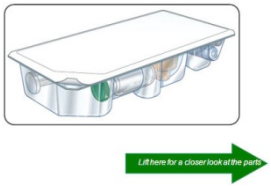
BYDUREON Single-Dose Tray is not for self-injection by people who are blind or cannot see well.

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

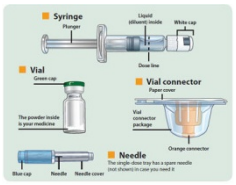
- 1 BYDUREON Single-Dose Tray that contains:
  - 1 BYDUREON vial
  - 1 Syringe
  - 2 Needles
  - 1 Vial connector
- alcohol swab
- a clean flat surface
- sharps container for throwing away used needles, vials, and syringes. See **Step 4h "Disposing of used Needles and Syringes."**

Your guide to your BYDUREON Single-Dose Tray

- Single-dose tray

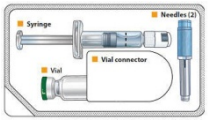


Keep this flap open so you can refer to it as you go through the steps.



Your guide to the parts

- Single-dose tray



What is 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.

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)**.

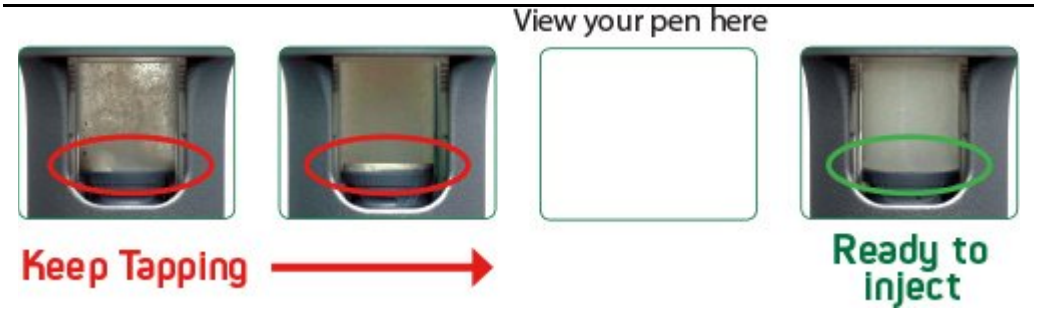


Figure C

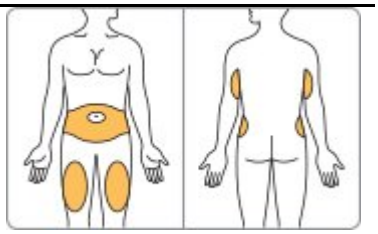
If you have any questions or are not sure if your Bydureon is mixed well, call 1-877-700-7365 for help.

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.

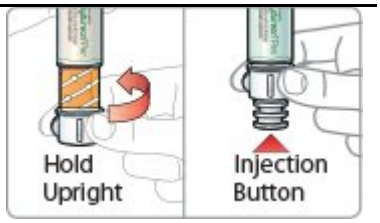
Choose your injection site.

- 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.
  - 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 used 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.

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

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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