PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

BYDUREON®

exenatide for extended-release injectable suspension

2 mg/dose once weekly

ATC Code: A10BJ01

Glucagon-like peptide-1 (GLP-1) analogues

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BYDUREON®
exenatide for extended-release injectable suspension

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous	Powder / 2 mg/dose (weekly)	Powder: Poly (D,L-lactide-co-glycolide) *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

Monotherapy:
BYDUREON is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance.

Combination with metformin:
BYDUREON is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin when metformin used alone, with diet and exercise, does not provide adequate glycemic control.

Combination with a sulfonylurea:
BYDUREON is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a sulfonylurea when the sulfonylurea used alone, with diet and exercise, does not provide adequate glycemic control.

Combination with metformin and a sulfonylurea:
BYDUREON is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulfonylurea when dual therapy with these two agents, with diet and exercise, does not provide adequate glycemic control.

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Combination with basal insulin (alone or with metformin):
BYDUREON is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with basal insulin (alone or with metformin) when therapy with these agents, with diet and exercise, does not provide adequate glycemic control.

Geriatrics (≥65 years of age):
Greater sensitivity of some older individuals cannot be ruled out. Clinical experience in patients 75 years of age and older is very limited. Therefore, use with caution in the elderly (see WARNINGS AND PRECAUTIONS; DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics (<18 years of age):
The safety and efficacy of BYDUREON have not been established in pediatric patients. Therefore, BYDUREON should not be used in pediatric patients.

CONTRAINDICATIONS

BYDUREON is contraindicated in patients with:

- known hypersensitivity to this product or any of its components. For a complete listing of ingredients, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

- a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) (see WARNINGS AND PRECAUTIONS).

- end-stage renal disease (ESRD) or severe renal impairment (creatinine clearance <30 mL/min), including patients on dialysis (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Thyroid C-cell tumours

- 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) (see CONTRAINDICATIONS).
- Exenatide extended-release causes an increased incidence of thyroid C-cell tumours at clinically relevant exposures in rats, compared to controls. It is unknown whether BYDUREON causes thyroid C-cell tumours, including MTC, in humans (see PART II: SCIENTIFIC INFORMATION, TOXICOLOGY, Carcinogenicity).

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- Patients should be counselled regarding the potential risk for MTC with the use of BYDUREON and informed of symptoms of thyroid tumours (e.g., mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with BYDUREON.

General

BYDUREON should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

BYDUREON and BYETTA® (exenatide twice daily) should not be used concomitantly, as they contain the same medicinal ingredient and this could result in an overdose.

BYDUREON should not be used in combination with other GLP-1 agonists or dipeptidyl peptidase-4 (DPP-4) inhibitors, as these have similar mechanisms of action and have not been studied together.

BYDUREON has not been studied with warfarin. There have been spontaneously reported cases of increased INR, sometimes associated with bleeding, with concomitant use of warfarin and exenatide. Closer monitoring of INR is recommended after initiation or alteration of exenatide therapy in patients taking warfarin (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions and DRUG INTERACTIONS, Drug-Drug Interactions).

After discontinuation of BYDUREON, plasma levels of exenatide decline over 10 weeks (see ACTION AND CLINICAL PHARMACOLOGY). Choice of other medicinal products and dose selection should be considered accordingly, as adverse reactions may continue and the anti-glycemic effect may persist until exenatide levels decline (see DOSAGE AND ADMINISTRATION, Dosing Consideration).

BYDUREON must not be administered by intravenous or intramuscular injection (see DOSAGE AND ADMINISTRATION).

Carcinogenesis and Mutagenesis

Risk of Thyroid C-cell tumours
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) (see CONTRAINDICATIONS).

Exenatide extended-release caused a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumours (adenomas and/or carcinomas) at clinically relevant exposures in rats, compared to controls. 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

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compared to controls in all treated groups at ≥2-times clinical exposure. It is unknown whether BYDUREON will cause thyroid C-cell tumours, including MTC, in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumours has not been determined (see TOXICOLOGY, Carcinogenicity).

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 or elevated levels of serum calcitonin should be evaluated. Routine monitoring of serum calcitonin or thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with BYDUREON.

Cardiovascular

Heart Rate Increase: BYDUREON causes an increase in heart rate, which may lead to worsening of cardiac conditions in patients with a history of ischemic heart disease or tachyarrhythmias. Caution should be observed in these patient populations (see ADVERSE REACTIONS; DRUG INTERACTIONS, Drug-Drug Interactions and ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology).

PR Interval Prolongation: BYDUREON causes a prolongation of the heart rate-corrected PR interval of the electrocardiogram (see DRUG INTERACTIONS, Drug-Drug Interactions and ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). Caution should be observed in patients with underlying structural heart disease, pre-existing conduction system abnormalities, ischemic heart disease, or cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities. Prolongation of the PR interval has also been associated with an increased risk of incident atrial fibrillation; therefore, caution is warranted in patients with a history of atrial fibrillation.

Endocrine and Metabolism

Hypoglycemia
Use with a sulfonylurea or insulin: The risk of hypoglycemia was increased when BYDUREON was used in combination with a sulfonylurea in clinical trials (see ADVERSE REACTIONS). To reduce the risk of hypoglycemia associated with the use of a sulfonylurea or insulin, a decrease in the dose of sulfonylurea or insulin may be considered (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Gastrointestinal

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

Hepatic/Biliary/Pancreas

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Pancreatitis
Based on post-market data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYDUREON, patients should be observed carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may 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. Antidiabetic therapies other than BYDUREON may be considered in patients with a history of pancreatitis or in patients with other risk factors for pancreatitis (e.g. gallstones, alcoholism, or hypertriglyceridemia).

Immune

Hypersensitivity
Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported post-market in patients treated with exenatide. If a hypersensitivity reaction is suspected, discontinue BYDUREON, assess for other potential causes and institute alternative treatment for diabetes (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Immunogenicity
Patients may develop antibodies to exenatide following treatment with BYDUREON. In controlled studies of BYDUREON, the incidence of anti-exenatide antibodies in BYDUREON treated patients ranged from 49.3 to 68.1 %.

High titers of anti-exenatide antibodies may result in an attenuated glycemic response to BYDUREON. If there is worsening glycemic control or failure to achieve targeted glycemic control with BYDUREON, alternative antidiabetic therapy should be considered.

Other than injection site reactions, patients positive for exenatide antibodies generally displayed similar rates and types of adverse events as antibody negative patients (see ADVERSE REACTIONS, Immunogenicity).

Injection-Site Reactions
Serious injection-site reactions (e.g., abscess, cellulitis, and necrosis), with or without subcutaneous nodules, have been reported post-market with the use of BYDUREON. Isolated cases required surgical intervention.

The overall incidence of potentially immune-related injection site reactions (including induration, pruritus erythema, and injection site nodule) was higher in antibody-positive patients, compared with antibody negative patients, with a greater incidence in those with higher titer antibodies (see ADVERSE REACTIONS).

Renal

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BYDUREON is contraindicated in patients with severe renal impairment (creatinine clearance <30mL/min) or end-stage renal disease (ESRD), including patients receiving dialysis, as it has not been investigated in this patient population (see CONTRAINDICATIONS).

Clinical experience in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) is very limited; therefore, BYDUREON should be used with caution in patients with moderate renal impairment. BYDUREON should be used with caution in renal transplant patients.

There have been spontaneously reported events 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/hydration status and/or in patients experiencing events that may affect hydration, including nausea, vomiting and/or diarrhea. Concomitant agents included angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, and diuretics. Reversibility of altered renal function has been observed with supportive treatment and discontinuation of exenatide and potentially causative agents.

Special Populations

Pregnant Women: BYDUREON should not be used during pregnancy. There are no adequate and well-controlled studies in pregnant women. The potential risk for humans is unknown.

Administration of exenatide extended-release to pregnant rats during organogenesis caused fetal growth retardation. Based on animal data, exenatide may cause fetal harm (see PART II: TOXICOLOGY).

Women of childbearing potential: Women of childbearing potential should use contraception during BYDUREON treatment. Due to its long washout period, BYDUREON should be discontinued at least 3 months before a planned pregnancy.

Nursing Women: There are no adequate and well-controlled studies in nursing women. BYDUREON is not recommended for use in nursing women (see PART II: TOXICOLOGY).

Pediatrics (<18 years of age): The safety and efficacy of BYDUREON have not been established in pediatric patients. BYDUREON should not be used in pediatric patients.

Geriatrics (≥65 years of age): Greater sensitivity of some older individuals cannot be ruled out. Clinical experience in patients 75 years of age and older is very limited. Therefore, use with caution in the elderly (see WARNINGS AND PRECAUTIONS; DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests

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Renal Function
Assessment of renal function is recommended prior to initiation of BYDUREON and periodically thereafter, as appropriate (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

Anticoagulation
INR should be monitored frequently until stable when BYDUREON is co-administered with warfarin (see DRUG INTERACTIONS).

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The safety of BYDUREON was assessed in nine 24 to 30 week comparator-controlled trials (n = 2045) and two 10 and 15 week placebo-controlled studies (n = 51), with a total of 2096 patients with type 2 diabetes.

In these trials, the most commonly observed adverse events in BYDUREON-treated patients were: gastrointestinal related [nausea (16.3%), diarrhea (10.8%), vomiting (7.0%) and constipation (6.5%)], injection site reactions [induration (6.8%), nodules (6.8%), pruritus (6.1%), erythema (3.3%)], hypoglycemia (1.9% without a sulfonylurea, 12.1% with a sulfonylurea, confirmed cases only), nasopharyngitis (10%) and headache (7.1%).

Serious adverse events were reported in 3.2% of BYDUREON-treated patients. No single SAE was reported with an incidence greater than 0.15%.

The incidence of withdrawal due to adverse events was 4.6% (n=97) for BYDUREON-treated patients. The most common adverse events leading to withdrawal for BYDUREON-treated patients were injection site nodule 0.4%, nausea 0.4%, diarrhea 0.2%, headache 0.2%, injection site pruritus 0.2%, and vomiting 0.2%.

When BYDUREON was administered with insulin glargine with or without metformin for 28 weeks in a placebo-controlled study, the most common adverse events reported in the BYDUREON group (n = 232) were urinary tract infection (7.8%), injection site nodule (5.2%), and nausea (5.2%). Serious adverse events were reported by 4.7% of BYDUREON-treated patients. No single serious adverse event was reported by more than 1 patient (0.4%) in the BYDUREON group. The incidence of withdrawal of BYDUREON treatment because of adverse events was 3.9% (n = 9). No single adverse event leading to withdrawal of BYDUREON treatment was reported by more than 1 patient (0.4%).

Clinical Trial Adverse Drug Reactions -
Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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Tables 1 - 3 summarize the incidences of treatment-related adverse events with an incidence of ≥1% and reported in at least two BYDUREON-treated patients in any of the studies within the table. These are provided for three comparator-controlled 24-30 week trials of BYDUREON used as monotherapy, or added on to oral antidiabetic agents and one 28-week placebo-controlled trial of BYDUREON added on to basal insulin glargine with or without metformin.

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Table 1 Incidence of treatment-related[a] adverse events (excluding hypoglycemia[b]) reported in ≥1% and at least two BYDUREON-treated patients in a monotherapy trial versus pioglitazone, sitagliptin and metformin

System Organ Class/Preferred Term	Study GWCH (N=820) 26 weeks			
	BYDUREON 2 mg QW (N=248)	pioglitazone 45 mg QD (N=163)	sitagliptin 100 mg QD (N=163)	metformin 2000 mg QD (N=246)
	%			
Gastrointestinal disorders				
Abdominal pain	2.4	0.6	1.8	1.2
Abdominal pain upper	1.2	1.2	0.6	1.2
Constipation	5.2	0.6	0.6	1.6
Diarrhea	4.0	2.5	3.1	11.0
Dyspepsia	4.0	1.8	1.2	1.2
Eructation	1.6	0	0	0
Flatulence	1.6	0.6	0.6	1.2
Nausea	12.9	3.7	3.1	7.7
Vomiting	2.8	1.8	1.2	2.4
General disorders and administration site conditions [c]				
Asthenia	1.6	0	0.6	0
Injection site bruising	1.2	0	0.6	0.8
Injection site erythema	3.2	0	1.8	1.2
Injection site induration	1.6	0.6	1.8	2.0
Injection site nodule	9.7	3.1	6.1	8.9
Injection site pain	2.0	1.2	1.8	0.4
Injection site pruritus	4.4	0.6	1.8	1.2
Injection site reaction	1.2	0.6	0.6	0
Nodule	3.6	1.2	0	2.0
Metabolism and Nutrition disorders				
Decreased appetite	1.6	0	0.6	1.6
Nervous system disorders				
Dizziness	1.2	1.2	0	0.8
Skin and subcutaneous tissue disorders				
Pruritus	1.6	0.6	0.6	0.4
Skin mass	2.4	0	0	2.0

[a] As assessed by the clinical investigator.
[b] See Hypoglycemia subsection of ADVERSE REACTIONS, and Table 4.
[c] Investigators were to report injection site nodules as adverse events only if associated with other symptoms (such as pain, induration, redness, bleeding, or inflammation).
N = The number of intent-to-treat patients

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Table 2 **Treatment-related[a] adverse events (excluding hypoglycemia[b]) reported in ≥1% and at least two BYDUREON-treated patients in comparator-controlled add-on combination trials versus BYETTA (exenatide twice daily) in patients on a background of diet and exercise with or without oral antidiabetic agents[c]**

System Organ Class/Preferred Term	Study 2993LAR-105 (N=295) 30 weeks		Study BCB108 (N=252) 24 weeks	
	BYDUREON 2 mg QW (N=148)	BYETTA 5 µg/10 µg BID (N=145)	BYDUREON 2 mg QW (N=129)	BYETTA 5 µg/10 µg BID (N=123)
	%		%	
Gastrointestinal disorders				
Abdominal distension	1.4	0.7	0	1.6
Constipation	7.4	2.8	0	0.8
Diarrhea	10.1	4.1	5.4	3.3
Dyspepsia	5.4	1.4	2.3	1.6
Eructation	2.7	0	0	0
Flatulence	2.7	0.7	0	1.6
Gastrointestinal sounds abnormal	2.0	0	0	0
Gastroesophageal reflux disease	4.7	0.7	0.8	0.8
Nausea	19.6	30.3	9.3	30.9
Vomiting	9.5	11.0	3.1	8.1
General disorders and administration site conditions [d]				
Fatigue	4.1	0.7	0.8	0.8
Injection site bruising	4.1	6.9	2.3	4.1
Injection site erythema	7.4	0	5.4	2.4
Injection site hematoma	1.4	0.7	1.6	0.8
Injection site hemorrhage	2.7	1.4	0	0
Injection site nodule	1.4	0	3.1	0
Injection site pain	2.7	3.4	0.8	0
Injection pruritus	18.2	1.4	4.7	0.8
Injection site rash	2.7	0.7	0	0
Malaise	1.4	0	0	0
Investigations				
Lipase increase	0	0	1.6	0.8
Metabolism and nutritional disorders				
Decreased appetite	3.4	1.4	2.3	0.8
Nervous system disorders				
Dizziness	1.4	1.4	0.8	1.6
Headache	2.0	0.7	0	4.1
Somnolence	1.4	0	0	0
Tremor	2.0	0	0	0

[a] As assessed by the clinical investigator.
[b] See Hypoglycemia subsection of ADVERSE REACTIONS, and Table 4.
[c] Oral antidiabetic agents included metformin and/or a sulfonylurea (see INDICATIONS and CLINICAL TRIALS).

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[d] Investigators were to report injection site nodules as adverse events only if associated with other symptoms (such as pain, induration, redness, bleeding, or inflammation).
N = The number of intent-to-treat patients

Table 3 Treatment-related[a] adverse events (excluding hypoglycemia[b]) reported in ≥1% and at least two BYDUREON-treated patients versus Placebo in patients on a background of diet and exercise and basal insulin with or without metformin[c]

System Organ Class/Preferred Term	Study D5553C00002 (N=463) 28 weeks	
	BYDUREON 2 mg QW (N=232)	PLACEBO (N=231)
	%	%
Gastrointestinal disorders		
Nausea	3.0	2.6
Diarrhea	2.2	1.3
Dyspepsia	1.7	0
General disorders and administration site conditions [c]		
Injection site nodule	5.2	0.4
Injection pruritus	1.7	1.3
Injection site erythema	1.3	0

[a] As assessed by the clinical investigator.
[b] See Hypoglycemia subsection of ADVERSE REACTIONS.
[c] Investigators were to report injection site nodules as adverse events only if associated with other symptoms (such as pain, induration, redness, bleeding, or inflammation).
N = The number of patients who received at least 1 dose of randomized medication; patients analyzed as treated (safety analysis set)

Less Common Clinical Trial Adverse Drug Reactions

The following is a list of less common treatment-related adverse events, reported in <1% of patients (and in at least 2 patients) and reported at a greater frequency in BYDUREON-treated patients than in comparator-treated patients in nine comparator-controlled 24-30 week trials, or placebo-treated patients in a 28-week placebo-controlled trial in combination with basal insulin with or without metformin and which are not represented in Tables 1, 2 or 3.

Eye disorders: Diabetic retinopathy
Gastrointestinal disorders: Abdominal discomfort, abdominal pain upper, eructation
General disorders and administration site conditions: Application site nodule, Induration, Infusion site induration, Injection site reactions (including discolouration, exfoliation, swelling), Malaise, Therapeutic response unexpected
Infections and infestations: Rhinoscleroma
Investigations: Lipase abnormal, Weight decreased
Nervous system disorders: Dizziness, Headache, Tremor
Skin and subcutaneous tissue disorders: Eczema, Rash, Skin induration, Skin mass
Vascular disorders: Hypertension, Intra-abdominal hematoma

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Immunogenicity
Patients may develop antibodies to exenatide following treatment with BYDUREON.

Anti-exenatide antibodies were measured in BYDUREON-treated patients in eight comparator-controlled 24-30 week studies of BYDUREON. The incidence of treatment-emergent antibodies to BYDUREON at the last treatment visit ranged from 49.3-68.1%. The majority of antibody-positive subjects had lower antibody titers. The level of glycemic control in patients with low antibody titers (<625) was generally comparable to that observed in patients negative for anti-exenatide antibodies. About 12% of the BYDUREON-treated patients had higher titer (≥625) antibodies. Of these patients, approximately half had an attenuated glycemic response to BYDUREON (reduction in HbA1c of less than 0.7% relative to baseline). If there is worsening of glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered (see WARNINGS AND PRECAUTIONS, Immune).

The incidence of potentially immunogenic injection site reactions (including injection site induration, injection site pruritus, nodule, and erythema) during the 30-week and 26-week studies was 23.6% for antibody positive patients and 12.4% for antibody negative patients (see WARNINGS AND PRECAUTIONS, Immune).

Injection Site Reactions
Injection site reactions were observed more frequently in BYDUREON-treated patients than in BYETTA (exenatide twice daily)-treated patients. Subcutaneous injection site nodules were observed very frequently; most were asymptomatic and resolved over 4 to 8 weeks (see WARNINGS AND PRECAUTIONS, Immune).

Serious injection-site reactions have been reported with post-market use of BYDUREON, including abscess, cellulitis, and necrosis, with or without subcutaneous nodules, and rare cases have required surgical treatment.

Hypoglycemia
The incidence of hypoglycemia was increased when BYDUREON was used in combination with a sulfonylurea (see WARNINGS AND PRECAUTIONS, Hypoglycemia). To reduce the risk of hypoglycemia associated with the use of a sulfonylurea or insulin, reduction in the dose of sulfonylurea or insulin may be considered (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Table 4 summarizes the incidence and rate of minor hypoglycemia in 3 comparator-controlled 24- to 30-week trials of BYDUREON used as monotherapy or as add-on to metformin, a sulfonylurea, pioglitazone, or a combination of these oral antidiabetic agents. In these trials, a minor hypoglycemia event was defined as symptoms of hypoglycemia with a concomitant glucose <2.5 mmol/L and the patient was able to self-treat.

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Table 4 Incidence (% of subjects) and Rate (episodes/subject year) of Minor [ϕ] Hypoglycemia in the Monotherapy Trial and Combination Therapy Trials

Study	Incidence: % of subjects (Event rate episodes/subject year)
GWCH (26 week monotherapy trial) (N=820)	
BYDUREON 2 mg QW (N=248)	2.0 (0.05)
Sitagliptin 100 mg/day (N=163)	0.0 (0.0)
Pioglitazone 30 - 45 mg/day (N=163)	0.0 (0.0)
Metformin 1000 – 2500 mg/day (N=246)	0.0 (0.0)
BCB108 (24 week add on to metformin, a sulfonylurea, pioglitazone or a combination of two of these oral agents trial) (N=252)	
With Concomitant Sulfonylurea Use	
BYDUREON 2 mg QW (N=40)	12.5 (0.75)
BYETTA 10 ug BID (N=34)	11.8 (0.31)
Without Concomitant Sulfonylurea Use	
BYDUREON 2 mg QW (N=89)	0.0 (0.0)
BYETTA 10 ug BID (N=89)	0.0 (0.0)
2993LAR-105 (30 week add on to with metformin, a sulfonylurea, pioglitazone or a combination of two of these oral agents trial) (N=293)	
With Concomitant Sulfonylurea Use	
BYDUREON 2 mg QW (N=55)	14.5 (0.57)
BYETTA 10 ug BID (N=52)	15.4 (0.38)
Without Concomitant Sulfonylurea Use	
BYDUREON 2 mg QW (N=93)	0.0 (0.0)
BYETTA 10 ug BID (N=93)	1.1 (0.02)

[ϕ] Reported event that has symptoms consistent with hypoglycemia with a concomitant glucose <2.5 mmol/L and the patient was able to self-treat.
N = The number of intent-to-treat patients. Note: Percentages are based on the number of intent-to-treat patients in each treatment group.

There were 3 reported events of major hypoglycemia in nine 24 to 30 week comparator-controlled trials, one each in the BYDUREON, BYETTA and insulin treatment groups; the BYDUREON treated subject was taking concomitant metformin, and the other 2 patients were taking concomitant sulfonylurea. Major hypoglycemia was defined as loss of consciousness, seizure, or coma (or other mental status change consistent with neuroglycopenia) which resolved after administration of glucagon or glucose, or required third-party assistance to resolve due to severe impairment in consciousness or behavior. Patients also had to have a concomitant glucose <2.5 mmol/L.

In a 28-week placebo-controlled trial of BYDUREON added to basal insulin glargine (alone or with metformin), there were no recorded episodes of major hypoglycemia in the study. Thirteen patients (5.6%) in the BYDUREON group and 13 patients (5.6%) in the placebo

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group experienced a minor hypoglycemic event and 68 patients (29.3%) in the BYDUREON group and 64 patients (27.7%) in the placebo group experienced other hypoglycemic events.

Increased Heart Rate
A mean increase in heart rate (HR) of 2.8 beats per minute (bpm) from baseline (74 bpm) was observed in the pooled BYDUREON clinical studies, compared to 1.5 bpm for the pooled incretin comparator group and a decrease of -0.4 bpm for the non-incretin comparator group.

Fifteen percent of BYDUREON treated patients had mean increases in heart rate of ≥10 bpm, compared to approximately 5% to 10% of subjects within the other treatment groups.

Loss of Body Weight
In a 52-week study, the proportion of BYDUREON treated patients with ≥5% and ≥10% weight loss from baseline was 31.1% and 12.2%, respectively, at last visit.

Post-Market Adverse Drug Reactions
Additional adverse reactions have been reported with BYDUREON. Because these reactions 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.

Gastrointestinal Disorders: Abdominal distension, Abdominal pain, Acute pancreatitis, Hemorrhagic and necrotizing pancreatitis (sometimes fatal), Constipation, Eructation, Flatulence
General Disorders and Administration Site Conditions: Injection-site reactions
Immune System Disorders: Anaphylactic reaction
Investigations: INR increased with concomitant warfarin use (some reports associated with bleeding)
Metabolism and Nutrition Disorders: Dehydration (generally associated with nausea, vomiting and/or diarrhea), Weight decreased
Nervous System Disorders: Dysgeusia, Somnolence
Renal and Urinary Disorders: Altered renal function, including acute renal failure (sometimes requiring hemodialysis), Worsened chronic renal failure, Renal impairment, Increased serum creatinine, Kidney transplant, Kidney transplant dysfunction
Skin and Subcutaneous Tissue Disorders: Alopecia, Angioedema, Generalized pruritus and/or urticaria, Macular or papular rash

DRUG INTERACTIONS

Overview
Drug interactions between BYDUREON and metformin or a sulfonylurea have not been studied in specific pharmacokinetic drug-drug interaction studies. The dose of a sulfonylurea or insulin may require adjustment due to the increased risk of hypoglycemia associated with sulfonylurea or insulin therapy (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism; ADVERSE REACTIONS, Hypoglycemia and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

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Drug-Drug Interactions

Drugs that Increase Heart Rate: BYDUREON causes an increase in heart rate (see ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). Caution should be observed if BYDUREON is administered with other drugs that also increase heart rate, such as drugs with sympathomimetic or anticholinergic activity (see WARNINGS AND PRECAUTIONS, Cardiovascular).

Drugs that Cause PR Interval Prolongation: BYDUREON causes an increase in the PR interval (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). The impact on the PR interval of co-administration of BYDUREON with other drugs that prolong the PR interval (including, but not limited to, antiarrhythmics, non-dihydropyridine calcium channel blockers, beta adrenoceptor blockers, digitalis glycosides, HIV protease inhibitors, and somatostatin analogues) has not been evaluated. As a result, co-administration of BYDUREON with these drugs should be undertaken with caution (see WARNINGS AND PRECAUTIONS, Cardiovascular).

Orally Administered Drugs: In a study using 1000 mg acetaminophen as a marker of gastric emptying, 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). BYDUREON has no clinically significant effect on acetaminophen pharmacokinetics.

However, exenatide slows gastric emptying which has the potential to reduce the rate of absorption of some orally administered drugs. Use with caution when administering oral medications with BYDUREON.

The following drug interaction studies have been conducted with exenatide BID (BYETTA) but not with BYDUREON.

Digoxin: Co-administration of repeated doses of exenatide 10 µg BID decreased the C_{max} of oral digoxin (0.25 mg QD) by 17% and delayed the T_{max} by approximately 2.5 h; however, the overall steady-state pharmacokinetic exposure (AUC) was not changed.

HMG CoA reductase inhibitors: Lovastatin AUC and C_{max} were decreased approximately 40% and 28%, respectively, and T_{max} was delayed about 4 h when exenatide 10 µg BID was administered concomitantly with a single dose of lovastatin (40 mg) compared with lovastatin administered alone.

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

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Warfarin: In a controlled clinical pharmacology study in healthy volunteers taking exenatide (5 µg BID daily on days 1-2 and 10 µg BID on days 3-9), a delay in warfarin T_{max} of about 2 hours was observed when warfarin was administered 35 minutes after exenatide administration on Day 4. No clinically relevant effects on C_{max} or AUC were observed and exenatide 10 µg BID did not have a significant effect on INR. However there have been spontaneously reported cases of increased INR, sometimes associated with bleeding, with concomitant use of warfarin and exenatide. Closer monitoring of INR is recommended after initiation or alteration of exenatide therapy in patients taking warfarin (see WARNINGS AND PRECAUTIONS, General and ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Combination Oral Contraceptives (ethinyl estradiol and levonorgestrel): In healthy females, the administration of a combination oral contraceptive, ethinyl estradiol and levonorgestrel, 30 min after exenatide 10 µg BID resulted in a 45% reduction of the C_{max} of ethinyl estradiol, a 27% to 41% reduction in C_{max} of levonorgestrel, and a delay in T_{max} of up to approximately 4.5 h; however, exenatide 10 µg BID did not affect AUC of ethinyl estradiol or levonorgestrel. When the oral contraceptive was administered 1 hour before exenatide BID, pharmacokinetic profiles of ethinyl estradiol or levonorgestrel were not altered.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
When exenatide is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycemia while driving or using machinery.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Switching from BYETTA (exenatide twice daily) to BYDUREON (exenatide for extended-release injectable suspension): Patients switching from BYETTA to BYDUREON may experience transient elevations in blood glucose concentrations, which generally improve within the first two weeks after initiation of therapy.

Discontinuation of BYDUREON: After discontinuation of BYDUREON, plasma levels of exenatide decline over 10 weeks (see WARNINGS AND PRECAUTIONS, General; DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY). Choice of other medicinal products and dose selection should be considered accordingly, as

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adverse reactions may continue and the anti-hyperglycemic effect may persist until exenatide levels decline.

Recommended Dose and Dosage Adjustment

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

When BYDUREON is added to a sulfonylurea or insulin, a decrease in the dose of the sulfonylurea or insulin may be considered to reduce the risk of hypoglycemia (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

BYDUREON and insulin must be administered as two separate injections.

Renal Impairment

BYDUREON is contraindicated in patients with end-stage renal disease (ESRD) or severe renal impairment (creatinine clearance <30 mL/min), including patients on dialysis (see CONTRAINDICATIONS).

No dosage adjustment of BYDUREON is required in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min). BYDUREON should be used with caution in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min). BYDUREON should be used with caution in renal transplant patients (see WARNINGS AND PRECAUTIONS, Renal and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Hepatic Impairment

No dosage adjustment is required in patients with hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Geriatrics (≥65 years of age)

A greater sensitivity of some older individuals cannot be ruled out. Use caution when initiating BYDUREON in patients 65 years of age or older (see WARNINGS AND PRECAUTIONS, Special Populations).

Missed Dose

If a dose of BYDUREON is missed, the patient should take it as soon as they remember within 3 days after the missed dose. The patient can take the next dose at the usual weekly time.

If it has been longer than 3 days after the missed dose, the patient should skip the dose and take BYDUREON at the next usual weekly time. The patient should not take an extra dose of BYDUREON to make up for the missed dose.

Administration

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Appropriate training is recommended for non-healthcare professionals administering the product. The "Instructions for Use", which are attached to the PATIENT MEDICATION INFORMATION and also provided in the carton, must be followed carefully by the patient.

BYDUREON is intended for subcutaneous (SC) self-administration by the patient. BYDUREON must not be administered intravenously or intramuscularly. BYDUREON is administered as a 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 is provided in a pen injector consisting of a dual chamber glass cartridge (containing 2 mg exenatide in the front chamber and diluent in the rear chamber) with a bypass channel and one injection needle (one spare needle is provided in the carton). **Do not substitute or reuse needles or any other components in the pen injector.**

The diluent should be visually inspected prior to use. Use the diluent only if it is clear and free of particulate matter. After suspension, use only if the mixture is white to off-white and cloudy. BYDUREON must be injected immediately after the powder is suspended in the diluent.

OVERDOSAGE

Signs and symptoms of overdose that have been observed with BYDUREON include severe nausea, severe vomiting and rapidly declining blood glucose concentrations. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms and should include close monitoring of blood glucose, hydration status and renal function.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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ACTION AND CLINICAL PHARMACOLOGY

Exenatide, a GLP-1 receptor agonist, is a 39 amino acid peptide amide. The amino acid sequence of exenatide partially overlaps that of the endogenous incretin glucagon-like peptide 1 (GLP-1). Exenatide once weekly (BYDUREON) is a subcutaneously injectable extended-release formulation developed as an extension to the approved BYETTA immediate-release, twice-daily (BID) product line.

Mechanism of Action

Incretins, such as GLP-1, enhance glucose-dependent insulin secretion and exhibit other glucoregulatory actions following their release into the circulation from the gut.

Exenatide is a GLP-1 receptor agonist that mimics several antihyperglycemic actions of incretins. Exenatide has been shown to bind to and activate the known 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. As blood glucose concentrations decrease, insulin secretion subsides.

Pharmacodynamics

Exenatide improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes through multiple mechanisms of action. Exenatide enhances glucose-dependent insulin secretion and restores first-phase insulin secretion. Exenatide suppresses glucagon secretion during periods of hyperglycemia in patients with type 2 diabetes. Exenatide also slows gastric emptying. These actions work together to reduce fasting and postprandial glucose concentrations by modulation of both glucose appearance and glucose disposal.

Glucose-dependent insulin secretion: The effect of exenatide infusion on glucose-dependent insulin secretion rate was investigated in 11 healthy subjects. On average, the insulin secretion rate response was glucose-dependent (Figure 1).

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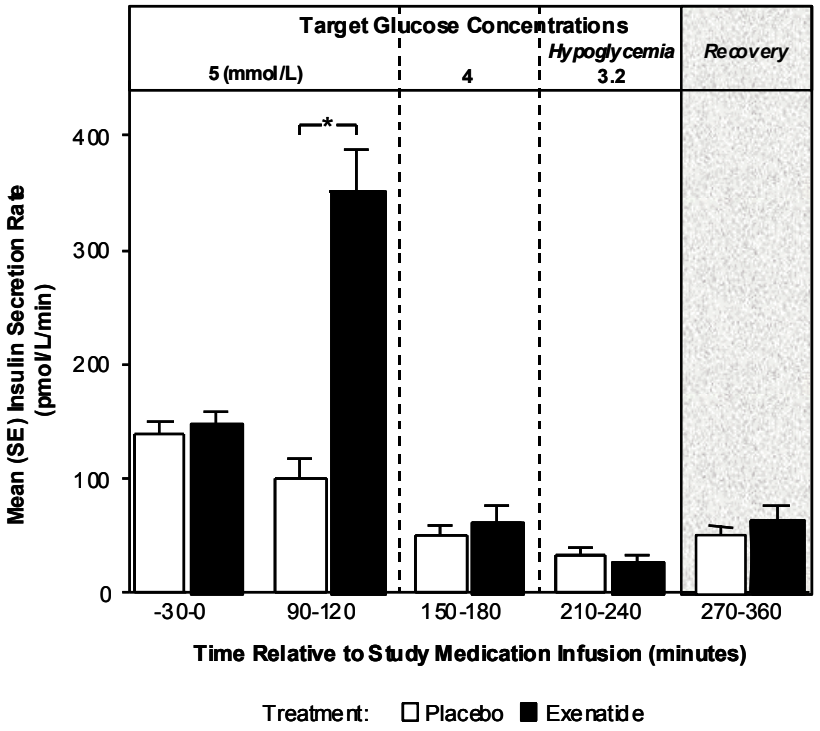
Figure 1 Insulin secretion rates (pmol/L/min) by treatment, time, and glycemic condition in healthy subjects (N=11)



Subjects underwent a stepwise insulin-induced hypoglycemic clamp during IV infusion of exenatide or placebo in a cross-over study design. Study medication infusion was started at time = 0 min. Statistical assessments were for the last 30 min of each glycemic step, during which the target glucose concentrations were maintained. * $p<0.05$, exenatide treatment relative to placebo. min Minute(s); SE Standard error.

Glucagon secretion: In patients with type 2 diabetes, exenatide moderates glucagon secretion and lowers serum glucagon concentrations during periods of hyperglycemia. Lower glucagon concentrations lead to decreased hepatic glucose output and decreased insulin demand. However, exenatide does not impair the normal glucagon response to hypoglycemia.

Gastric emptying: Exenatide slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.

Fasting and Postprandial Glucose: Exenatide improves glycemic control through the immediate and sustained effects of lowering both fasting and postprandial glucose concentrations in patients with type 2 diabetes.

Fasting Glucose
In a single-dose crossover trial in patients with type 2 diabetes, plasma glucose concentrations under fasting conditions were significantly reduced with exenatide compared with placebo. In a separate 15-week controlled study, where fasting glucose was assessed on a weekly basis,

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exenatide once weekly (BYDUREON) treatment resulted in a mean reduction in fasting glucose of 0.94 mmol/L following two weeks of therapy. The full effect on fasting glucose was not observed until approximately 9 weeks.

Postprandial Glucose
In patients with type 2 diabetes, exenatide reduces postprandial plasma glucose concentrations. In a 30-week controlled study of exenatide once weekly (BYDUREON) compared to exenatide twice daily (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, the LS mean change from baseline was significantly greater with BYETTA (-7.0 mmol/L) than BYDUREON (-5.3 mmol/L).

Cardiac Electrophysiology: A randomised, 3-period, placebo- and positive-controlled, double-blind, crossover study was performed to assess the electrophysiological effects of exenatide at therapeutic concentrations on the 12-lead electrocardiogram in healthy subjects (N=74). Exenatide was administered by continuous intravenous infusion at rates selected to maintain plasma concentrations of 200 pg/mL (Day 1), 300 pg/mL (Day 2), and 500 pg/mL (Day 3).

Heart Rate: Exenatide was associated with concentration-related increases in heart rate. All comparisons of change from baseline heart rate between exenatide and placebo were positive on days 1, 2, and 3, with 90% confidence intervals excluding zero. The maximum mean difference from placebo in heart rate was 12.88 bpm (90% CI 11.48, 14.28) on day 1, 14.06 bpm (90% CI 12.74, 15.37) on day 2, and 15.09 bpm (90% CI 13.66, 16.52) on day 3 (see WARNINGS AND PRECAUTIONS, Cardiovascular and DRUG INTERACTIONS, Drugs that Increase Heart Rate).

PR Interval: Exenatide resulted in prolongation of the heart rate-corrected PR interval (PRc) at all time points on days 1, 2, and 3, with 90% CIs excluding zero at most time points. The maximum mean difference from placebo in PRc was 5.91 ms (90% CI 3.71, 8.12) on day 1, 4.17 ms (90% CI 1.66, 6.68) on day 2, and 6.20 ms (90% CI 3.67, 8.72) on day 3 (see WARNINGS AND PRECAUTIONS, Cardiovascular and DRUG INTERACTIONS, Drugs that Cause PR Interval Prolongation).

QTc Interval: No sustained or concentration-related effect on the QTcP ($QTcP=QT/RR^{0.332}$) interval was observed on days 1 to 3.

Pharmacokinetics

Table 5 Summary Statistics of Exenatide 2 mg Once Weekly Pharmacokinetic Parameters at Steady-state in Patients with Type 2 Diabetes Mellitus

Pharmacokinetic Parameters	C_{ssmax} (pg/ml)	T_{ssmax} (h)	AUC_{ss} (pg*h/ml)	C_{ssave} (pg/ml)

Geometric Mean (CV %)	432.7 (86.3)	6.0	50484 (69.7)	300.2 (69.8)

C_{ssmax} Steady-state maximum concentration; T_{ssmax} Time to maximum steady-state concentration; AUC_{ss} Steady-state area under the time-concentration curve during a dosing interval (one week); C_{ssave} Steady-state average concentration; $T_{ss\ max}$ median and range is displayed instead of mean; CV Coefficient of variation.

The pharmacokinetics of BYDUREON was comparable between healthy volunteers and Type 2 Diabetes Mellitus patients. After discontinuation of BYDUREON, plasma levels of exenatide decline over 10 weeks to below minimal detectable concentrations of 10 pg/mL (see WARNINGS AND PRECAUTIONS, General and DOSAGE AND ADMINISTRATION).

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

Following weekly administration of BYDUREON, mean drug concentrations exceed minimal efficacious concentrations (~ 50 pg/mL) in 2 weeks. A gradual increase in the average plasma exenatide concentration occurs over 6 to 7 weeks, after which steady-state concentrations (approximately 300 pg/mL) are achieved. At steady-state, peak to trough fluctuation (78%) is minimal. Once weekly dosing of BYDUREON, achieves concentrations similar to the peak concentration attained with exenatide 10 µg twice daily (BYETTA).

Distribution: The mean apparent volume of distribution of exenatide following subcutaneous administration of a single dose of exenatide 10 µg BID (BYETTA) is 28.3 L.

Metabolism and Elimination: Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/h and is independent of dose.

Dose proportionality, Accumulation, Time-dependency: The mean C_{ssave} for BYDUREON is approximately dose proportional between the doses of 0.8 to 2 mg administered once weekly.

The geometric mean C_{ssave} at steady state for exenatide 2 mg once weekly is about 8.6-fold higher than those observed after a single dose. Accumulation occurred gradually over the first 6 to 7 weeks of therapy, after which steady state C_{ssave} concentrations were maintained in the intended therapeutic range.

The exenatide C_{ssave} were comparable up to at least 52 weeks, indicating that exenatide clearance or absorption from BYDUREON did not alter over time.

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Special Populations and Conditions

Geriatrics: Population pharmacokinetic analysis of patients (range from 19 to 83 years) suggests that age does not influence the pharmacokinetic properties of exenatide to a clinically meaningful extent. The C_{ssave} for 2 mg BYDUREON in patient ≥65 years of age was 24.2% higher than in patients <65 years of age.

Pediatrics: BYDUREON has not been studied in pediatric patients

Sex: Population pharmacokinetic analysis of male and female patients suggests that sex has no clinically relevant influence on the steady state concentrations of exenatide. The C_{ssave} for 2 mg BYDUREON in females was 9.2% higher than in males.

Race: Population pharmacokinetic analysis of patients including Caucasian, non-Caucasian and Asian suggests that race has no significant influence on the pharmacokinetics of exenatide. The C_{ssave} for 2 mg BYDUREON in Caucasian patients was 5.6% and 7.1% higher than in non-Caucasian and Asian patients, respectively.

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. The C_{ssave} for 2 mg BYDUREON in patients with BMI <30 kg/m^2 was 5.6% higher than in patients with BMI ≥30 kg/m^2.

Hepatic Impairment: No pharmacokinetic study has been performed in patients with acute or chronic hepatic insufficiency. Because exenatide is cleared primarily by the kidney, hepatic impairment is not expected to affect blood concentrations of exenatide (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism and Elimination).

Renal Impairment: BYDUREON has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease (ESRD), including patients on 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) (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

In a study of BYETTA in subjects with ESRD on dialysis, mean exenatide exposure increased by 3.4-fold compared to that of subjects with normal renal function.

Genetic polymorphism: The influence of genetic polymorphism on the pharmacokinetics of BYDUREON has not been evaluated.

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STORAGE AND STABILITY

BYDUREON should be stored in the refrigerator at 2°C to 8°C, up to the expiration date or until preparing for use. The pen injector can be kept at room temperature (not to exceed 30°C) for no more than a total of 4 weeks, if needed. Do not freeze BYDUREON. Do not use BYDUREON if it has been frozen. Protect from light.

BYDUREON should not be used past the expiration date. The expiration date for the pen injector can be found on the carton and pen injector.

Keep BYDUREON out of reach of children and pets.

The BYDUREON pen must be discarded after use in a puncture-resistant container, with the needle attached.

SPECIAL HANDLING INSTRUCTIONS

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.

The "Instructions for Use", which are attached to the PATIENT MEDICATION INFORMATION and also included in the carton, must be carefully followed.

Do not substitute needles or any other components in the product packaging.

BYDUREON must not be mixed with other medicinal products.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

BYDUREON is a sterile powder which is combined with a diluent to formulate an extended release suspension of exenatide (2 mg/dose) for once every seven days (weekly) subcutaneous administration.

Packaging

BYDUREON is supplied as a kit which contains:

- 4 single dose pens
- One extra needle (23 gauge, 9/32")
- Patient Medication Information
- Instructions for Use

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BYDUREON is supplied in a pen injector containing a dual-chamber glass cartridge injector with a bypass channel and injection needle. Each pen injector contains:

- 2 mg exenatide (as a white to off-white powder) filled into the front chamber of the glass cartridge pen injector
- Sufficient diluent filled in the rear chamber of the glass cartridge injector pen to deliver 0.65 mL after reconstitution
- One injection needle (23 gauge, 9/32")

Composition

Powder: Exenatide, poly (D,L-lactide-co-glycolide), sucrose

Diluent: Carboxymethylcellulose sodium, dibasic sodium phosphate heptahydrate, monobasic sodium phosphate monohydrate, polysorbate 20, sodium chloride, water for injection

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PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: exenatide

Chemical name: Exenatide is a 39-amino acid peptide amide. The amino acid sequence of exenatide is as follows:

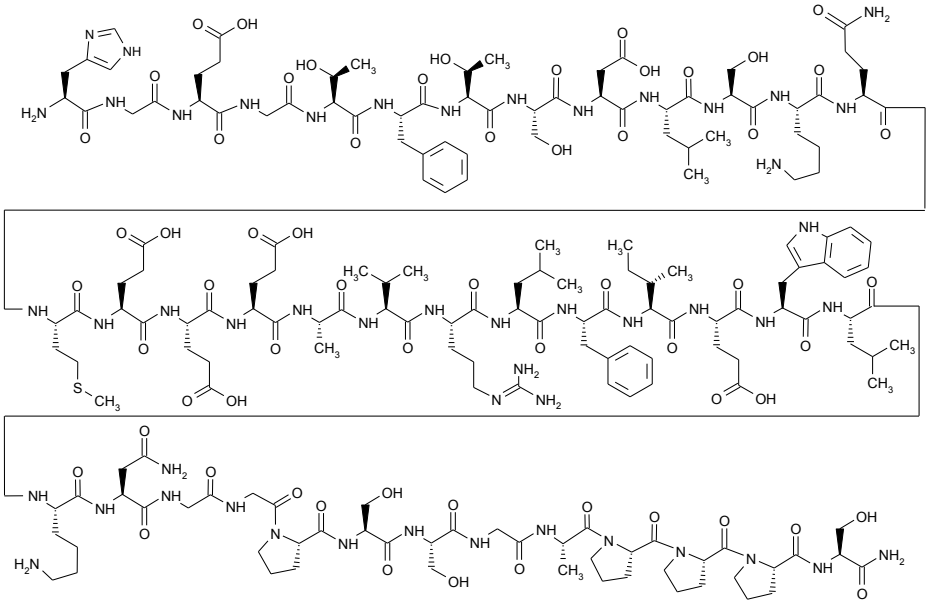
H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2

Chemical name (USAN):

L-histidylglycyl-L-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-leucyl-L-seryl-L-lysyl-L-glutaminyl-L-methionyl-L-glutamyl-L-glutamyl-L-glutamyl-L-alanyl-L-valyl-L-arginyl-L-leucyl-L-phenylalanyl-L-isoleucyl-L-glutamyl-L-tryptophanyl-L-leucyl-L-lysyl-L-asparaginylglycylglycyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl-L-serinamide

Molecular formula and molecular mass: $C_{184}H_{282}N_{50}O_{60}S$, 4186.6 Daltons

Structural formula:



Physicochemical properties: Exenatide drug substance is a white to off-white powder. Exenatide is freely soluble in water and pH 4.5 acetate buffer.

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CLINICAL TRIALS

Study demographics and trial design

Table 6 Summary of patient demographics for clinical trials in specific indication

Trial design and duration	Dosage, route of administration and treatments	Study subjects per treatment arm N=number	Mean age (Range)	Gender (% M/F)
Study GWCH - 26-week comparator-controlled study comparing BYDUREON (as monotherapy) versus metformin, sitagliptin and pioglitazone in patients who were inadequately treated with diet and exercise.				
Phase 3, multicenter, randomized, 26-week, comparator-controlled monotherapy study, followed by a 10 week off-treatment follow-up period	• Exenatide 2 mg QW SC • Metformin 1000-2500 mg/day PO • Pioglitazone 30-45 mg/day PO • Sitagliptin 100 mg/day PO Subjects randomized in a 3:3:2:2 ratio to exenatide QW + placebo PO, Met + exenatide QW placebo, Pio + exenatide QW placebo, and Sita + exenatide QW placebo.	Exenatide QW N=248 Metformin N=246 Pioglitazone N=163 Sitagliptin N=163	54 years (20-82)	59/41
Study BCB108 - 24 week comparator-controlled study comparing BYDUREON (exenatide once weekly) versus BYETTA (exenatide twice daily) in patients inadequately treated with diet and exercise or inadequately treated with one or two oral antidiabetic agents, including metformin and/or a sulfonylurea.				
Phase 3, randomized, 24-week, 2-arm, open-label, comparator-controlled study	• Exenatide 2 mg QW SC • Exenatide 5 µg BID SC for 4 weeks, then Exenatide 10 µg BID SC Subjects continued their usual diabetes treatment throughout the 24-week treatment period.	Exenatide QW N=129 Exenatide BID N=123	56 years (23-83)	57/43
Study 2993LAR-105 - 30-week comparator-controlled study comparing BYDUREON (exenatide once weekly) versus BYETTA (exenatide twice daily) in patients inadequately treated with diet and exercise or inadequately treated with one or two oral antidiabetic agents, including metformin and/or a sulfonylurea.				
Phase 3, randomized, 30-week, 2-arm, open-label, comparator-controlled study; followed by an open-ended uncontrolled assessment period	• Exenatide 2 mg QW SC • Exenatide 5 µg BID SC for 4 weeks, then Exenatide 10 µg BID SC Subjects continued their usual diabetes treatment throughout the 30-week treatment period and the open-ended assessment period. After 30 weeks of treatment, all subjects received Exenatide QW 2 mg.	Exenatide QW N=148 Exenatide BID N=147	55 years (19-80)	53/47
Study GWBR - 26-week comparator-controlled study comparing BYDUREON versus insulin glargine in patients inadequately treated with metformin or with metformin + sulfonylurea.				

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Trial design and duration	Dosage, route of administration and treatments	Study subjects per treatment arm N=number	Mean age (Range)	Gender (% M/F)
Phase 3, randomized, 26-week, 2-arm, open-label, comparator-controlled study; followed by a 130-week, open-label comparator-controlled assessment period, plus a 10-week off-treatment follow-up period	• Exenatide 2 mg QW SC • Insulin glargine (titrated) Subjects continued their usual diabetes treatment throughout the 26-week treatment period and the open-ended assessment period. After Week 48, addition of OADs or change to the dose of MET or SU were permitted as needed.	Exenatide QW N=233 Insulin glargine N=223	58 years (26-84)	53/47
Study D5553C00002 – 28 week placebo controlled study comparing BYDUREON versus placebo in patients inadequately treated with basal insulin with or without metformin				
Phase 3, randomized, double-blind, 28-week, placebo-controlled study; plus a 10-week off-treatment follow-up period	• Exenatide 2 mg QW SC • Placebo Subjects continued on titrated basal insulin glargine with or without metformin treatment throughout the 28-week treatment period.	Exenatide QW N=231 Placebo N=230	58 years (20-80)	48/52

BID Twice daily; OAD Oral antidiabetes drug; Met metformin; Pio pioglitazone; PO Per oral; QAM Every morning; QW Once weekly; SC Subcutaneous; Sita sitagliptin; T2DM Type 2 diabetes mellitus.

Study Results

Comparator-Controlled Clinical Trials

BYDUREON was studied as monotherapy and in combination with oral anti-diabetic agents, including metformin and/or a sulfonylurea.

BYDUREON monotherapy versus sitagliptin, pioglitazone or metformin in patients inadequately treated with diet and exercise

In the double-blind Study GWCH (n=820), BYDUREON was compared to sitagliptin (100 mg/day), titrated pioglitazone (30-45 mg/day) and titrated metformin (1000-2500 mg/day) over a 26-week treatment period followed by a 10-week off-treatment follow-up period. Approximately 13% of patients in this study were aged ≥65 years. The majority of patients in this study were Caucasian (67%), followed by East Asian (12%), West Asian (9%), Hispanic (8%) and Black (3%). The mean duration of diabetes was 2.7 years (median: 1.3 years), and the mean body mass index (BMI) was 31.2 kg/m^2 (range: 21.2 to 45.3 kg/m^2), with 54% having a BMI ≥30 kg/m^2. BYDUREON demonstrated non-inferiority to metformin regarding mean reduction in HbA1c at 26 weeks of treatment. Approximately 94% of patients in this comparator arm were on ≥1500

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mg/day metformin from Week 16. Treatment with BYDUREON showed a statistically significant reduction (p<0.01) in HbA1c relative to baseline, when compared with sitagliptin (see Table 7). Non-inferiority of BYDUREON to pioglitazone was not demonstrated.

Table 7 Results of 26-week trial of BYDUREON monotherapy versus sitagliptin, pioglitazone and metformin in patients inadequately treated with diet and exercise (intent-to-treat patients)

Study GWCH	BYDUREON 2 mg QW	Sitagliptin 100 mg/day	Metformin 1000-2500 mg/day
N	**248**	**163**	**246**
HbA1c (%)			
Mean baseline	8.4	8.4	8.6
Mean change from baseline at week 26[ϕ]	-1.6	-1.2	-1.5
Mean difference from sitagliptin (98.3% CI)[∞ϕ†]	-0.39* (-0.63, -0.16)		
Mean difference from metformin (98.3% CI)[∞ϕ†]	-0.05 (-0.26, 0.17)		
Patients (%) achieving HbA1c <7%	63*	43	55
Fasting serum glucose (mmol/L)			
Mean baseline	9.8	9.7	9.9
Mean change from baseline at week 26[ϕ]	-2.3	-1.1	-2.0
Mean difference from sitagliptin (95% CI)[ϕ]	-1.12* (-1.56, -0.68)		
Mean difference from metformin (95% CI)[ϕ]	-0.28 (-0.66, 0.10)		
Body weight (kg)			
Mean baseline	87.5	88.6	85.9
Mean change from baseline at week 26[ϕ]	-2.0	-0.8	-2.0
Mean difference from sitagliptin (95% CI)[ϕ]	-1.28* (-1.92, -0.63)		
Mean difference from metformin (95% CI)[ϕ]	-0.04 (-0.61, 0.53)		

CI = confidence interval, N= number of patients in each treatment group, QD = Once daily, QW = Once weekly, [*]p<0.01, BYDUREON versus sitagliptin, [∞] The primary efficacy analysis was adjusted for multiple comparisons and a two-sided 98.3% confidence interval was utilized to assess difference between treatments (Bonferroni adjustment), [ϕ] Least squares means were obtained using a mixed model repeated measure analysis with treatment, pooled country, visit, baseline HbA1c and treatment as fixed effects and patient as random effects. [†]The non-inferiority margin was set at +0.3% in this study.

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BYDUREON (exenatide once weekly) versus BYETTA (exenatide twice daily) in patients inadequately treated with diet and exercise or inadequately treated with one or two oral diabetic agents, including metformin and/or a sulfonylurea

BYDUREON was compared to BYETTA 5 µg twice daily for 4 weeks followed by BYETTA 10 µg twice daily in two open-label studies. One study (Study BCB108, n=252) was of 24 weeks in duration. The other was 30 weeks (Study 2993LAR-105, n= 295), followed by an open-ended uncontrolled extension where all patients were treated with BYDUREON 2 mg once weekly.

In study BCB108, 19% of patients were aged ≥65 years. The majority of patients in this study were Caucasian (61%), followed by Hispanic (28%), Black (7%) and Asian (4%). The mean duration of diabetes was 7.0 years (median: 6.0), and the mean body mass index was 33.3 kg/m^2 (range: 23.2 to 45.1), with 66% having a BMI ≥30 kg/m^2. Of randomized patients, 19% were on a background of diet and exercise alone and 68% were on a treatment background of metformin and/or a sulfonylurea. The remaining patients were on oral antidiabetic treatment backgrounds not approved for use with BYDUREON. Among patients on a background that included metformin, 96% were on metformin ≥1500 mg/day.

In study 2993LAR-105, 17% of patients were aged ≥65 years. The majority of patients in this study were Caucasian (78%), followed by Hispanic (12%) and Black (10%). The mean duration of diabetes was 6.7 years (median: 5.8), and the mean body mass index was 34.9 kg/m^2 (range: 25.0 to 52.8), with 84% having a BMI ≥30 kg/m^2. Of randomized patients, 15% of patients were on a background of diet and exercise alone and 69% were on a treatment background of metformin and/or a sulfonylurea. The remaining patients were on oral antidiabetic treatment backgrounds not approved for use with BYDUREON. Among patients on a background that included metformin, 76% were on metformin ≥1500 mg/day.

BYDUREON resulted in a statistically significant reduction in HbA1c compared to patients receiving BYETTA (Table 8).

A greater proportion of subjects on BYDUREON compared to subjects on BYETTA achieved an HbA1c of <7.0 % in Study BCB108 and ≤7.0% in Study 2993LAR-105 (Table 8).

In Study BCB108, the average baseline body weight in the BYDUREON group was 97.0 kg. At Week 24, the least squares mean difference (95% CI) from baseline was -2.3 (-3.1, -1.6) kg in the exenatide QW arm. This endpoint was not tested against the comparator.

In Study 2993LAR-105, the average baseline body weight in the BYDUREON group was 102 kg. At Week 30, the least squares mean difference (95% CI) from baseline was -3.7 (-4.59, -2.75) kg in the exenatide QW arm. This difference from baseline was not significantly different from that observed with BYETTA.

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Table 8 **Results of two trials of BYDUREON versus BYETTA (exenatide twice daily) in combination with diet and exercise alone, or oral antidiabetic agents, including metformin and/or a sulfonylurea (intent-to-treat patients)**

	BYDUREON 2 mg QW	BYETTA 10 µg BID
Study BCB108 (24 weeks)		
N	129	123
HbA1c (%)		
Mean baseline	8.5	8.4
Mean change from baseline at week 24 ϕ	-1.6	-0.9
Mean difference between treatments (95% CI) ϕ	-0.67** (-0.94, -0.39)	
Patients (%) achieving HbA1c <7%	58**	30
Fasting serum glucose (mmol/L)		
Mean baseline	9.6	9.3
Mean change from baseline at week 24 ϕ	-1.4	-0.3
Mean difference between treatments (95% CI)ϕ	-1.11** (-1.72, -0.56)	
Study 2993LAR-105 (30 weeks)		
N	148	147
HbA1c (%)		
Mean baseline	8.3	8.3
Mean change from baseline at week 30 ϕ	-1.9	-1.5
Mean difference between treatments (95% CI) ϕ	-0.33* (-0.54, -0.12)	
Patients (%) achieving HbA1c ≤7%	73	57
Fasting serum glucose (mmol/L)		
Mean baseline	9.6	9.2
Mean change from baseline at week 30 ϕ	-2.3	-1.4
Mean difference between treatments (95% CI)ϕ	-0.94** (-1.35, -0.52)	

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CI= confidence interval, N= number of patients in each treatment group, QW = Once weekly, BID= twice daily, ϕ Least squares (LS) means are adjusted for baseline HbA1c strata, background antihyperglycemic therapy, and baseline value of the dependent variable (if applicable), *p<0.05 treatment vs comparator, **p<0.01 treatment vs comparator

BYDUREON versus insulin glargine QD in patients inadequately treated with metformin or with metformin and a sulfonylurea

In Study GWBR (n=456), BYDUREON was compared to insulin glargine QD over an open-label 26-week treatment period followed by a 130-week open-labelled comparator-controlled assessment period plus a 10-week off-treatment follow-up period. The results demonstrated a decrease in mean HbA1c from baseline to Week 26 of -1.48% for BYDUREON and -1.32% for insulin glargine [least square mean difference of -0.16 (p=0.047)]. BYDUREON treatment significantly lowered mean body weight from baseline to Week 26 (-2.63 kg), compared with insulin glargine (+1.42 kg), and was associated with fewer hypoglycemic events.

Combination with Basal Insulin

BYDUREON versus Placebo as add-on to basal insulin alone or in combination with metformin

A 28-week, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of BYDUREON (n=231) versus placebo (n=230) when added to titrated basal insulin glargine, with or without metformin, in patients with type 2 diabetes with inadequate glycemic control.

All patients initially entered an 8 week insulin dose optimization phase. Patients on sulfonylurea therapy discontinued sulfonylurea. The dose of insulin glargine was titrated according to the INITIATE algorithm[1] to a target fasting plasma glucose of 4.0 to 5.5 mmol/L. Patients with HbA1c ≥7.0% and ≤10.5% were then randomly assigned to receive either BYDUREON or placebo. Insulin glargine dose titration continued throughout the treatment phase of the study. Patients who had been on metformin at baseline (≥1,500 mg/day) continued on the same type and dose of metformin therapy throughout the study.

The majority of the patients (87%) were White, 10% Black or African American, 1% Asian, 1% Other, <1% American Indian or Alaska Native, and <1% Pacific Islander.

The primary endpoint was the change in HbA1c from baseline to Week 28. BYDUREON achieved a significantly greater reduction in HbA1c at Week 28 than that observed with placebo (Table 9).

[1] Yki-Järvinen H, Juurinen L, Alvarsson M, et al. Initiate Insulin by Aggressive Titration and Education (INITIATE): a randomized study to compare initiation of insulin combination therapy in type 2 diabetic patients individually and in groups. Diabetes Care 2007 Jun;30(6):1364-9.

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Table 9 28-week placebo-controlled trial of BYDUREON as add-on to insulin glargine alone or in combination with metformin (intent-to-treat patients)

	BYDUREON 2 mg QW + Titrated Insulin Glargine	Placebo + Titrated Insulin Glargine
Study D5553C00002 (28 weeks)		
N	231	230
HbA1c (%)		
Mean baseline	8.5	8.5
Mean change from baseline at week 28 ϕ	-1.0	-0.2
Mean difference between treatments (95% CI) ϕ	-0.73* (-0.93, -0.53)	
Patients (%) achieving HbA1c <7%	33*	7
Body weight (kg)		
Mean baseline	94	94
Mean change from baseline at week 28 ϕ	-1.0	0.5
Mean difference between treatments (95% CI)ϕ	-1.50* (-2.17, -0.84)	

CI= confidence interval, N= number of patients in each treatment group, QW = Once weekly, ϕ Least squares (LS) means and treatment group difference(s) in the change from baseline values at Week 28 are modeled using a mixed model with repeated measures (MMRM) including treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), baseline SU-use stratum (yes vs. no), week and treatment by week interaction as fixed factors, and baseline value as a a covariate. *p<0.001 treatment vs comparator (adjusted for multiplicity), Analyses exclude measurements post rescue therapy and post premature discontinuation of study medication

The change from baseline to Week 28 in fasting plasma glucose was -0.7 mmol/L for the BYDUREON group and -0.1 mmol/L for the placebo group.

DETAILED PHARMACOLOGY

Exenatide is a 39-amino acid peptide amide that exhibits approximately 50% sequence identity with that of the mammalian endogenous incretin glucagon-like peptide-1 (GLP-1) secreted in response to a meal by intestinal L-cells.[4] *In vitro* pharmacology studies have shown that exenatide can bind and activate the human GLP-1 receptor leading to an increase in both synthesis and secretion of insulin from pancreatic beta-cells.[6] *In vitro* studies have also demonstrated that exenatide is not substantially degraded by the protease dipeptidyl peptidase-4 (DPP-4), which explains the longer duration of pharmacologic effects observed with exenatide, when compared to native GLP-1.

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Nonclinical Pharmacodynamics
Nonclinical pharmacology studies support the concept that exenatide is a GLP-1 receptor agonist that acts through multiple mechanisms to promote lowering of plasma glucose concentrations and to lower HbA1c. Exenatide decreases fasting glucose concentrations in animal models of type 2 diabetes (rat, mouse, and monkey) and exhibits a durable effect to lower HbA1c in diabetic mice and rats.[7] Beneficial actions of exenatide on glucose and HbA1c were consistent, whether dosed twice-daily with exenatide or dosed once over 4 weeks with exenatide extended-release in ZDF rats.[5, 7] Improvements in glycemic control are achieved via modulation of both the rate of glucose appearance in the circulation (slowing of gastric emptying, reduced food intake, and suppression of inappropriately elevated glucagon secretion) and the rate of glucose clearance (enhanced glucose-dependent insulin secretion, improved insulin sensitivity, and increased beta-cell mass). Reduced food intake in animal models of type 2 diabetes was associated with reduced weight gain.[10]

Nonclinical Pharmacokinetics
Exenatide was absorbed over an extended period of time following a subcutaneous injection of BYDUREON, with a relative bioavailability compared to BYETTA calculated to be approximately 63% in rat and 23% in monkey. Treatment-emergent antibodies to exenatide developed over time in both rats and monkeys and impacted the measured plasma concentrations. Exenatide was eliminated primarily by the kidney. Studies performed in rats, mice, rabbits, and humans to evaluate the potential for exenatide to cross the placental barrier provide support that the fetal to maternal ratio is low.

Clinical Pharmacodynamics
BYDUREON treatment resulted in a mean reduction in fasting glucose following two weeks of therapy with the full effect observed at approximately 9 weeks. Data from a mixed meal tolerance test in patients with type 2 diabetes show a mean change from baseline in 2 hour postprandial plasma glucose of -5.3 mmol/L following 14 weeks of once weekly BYDUREON treatment.

Clinical Pharmacokinetics
There is an initial release of exenatide within hours following a single subcutaneous dose of BYDUREON followed by a gradual release of exenatide from the microspheres resulting in two subsequent peaks at approximately week-2 and weeks 6 to 7. Accumulation occurs gradually over the first 6 to 7 weeks of once weekly administration, after which steady state is achieved with a 8.6-fold accumulation of exenatide C_{ssave} compared to the first dose. The mean apparent volume of distribution of exenatide following subcutaneous administration of a single dose of exenatide 10 µg BID (BYETTA) is 28.3 L. Exenatide is primarily cleared via passive renal mechanisms. The mean apparent clearance of exenatide in humans is 9.1 L/h. BYDUREON has no clinically significant effect on acetaminophen pharmacokinetics.

Safety Pharmacology
Safety pharmacology studies examined exenatide-related cardiovascular, renal, nervous, and endocrine system effects. Exenatide produced acute, dose-dependent hemodynamic effects including increases in mean arterial blood pressure and heart rate in rats. These effects appeared to be transient and were not observed in other species. Exenatide at nominal concentrations of 5.9 and 91.1 µM did not affect hERG currents in HEK293 cells stably transfected with hERG DNA

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(N=3/treatment). No differences from vehicle in heart rate or electrocardiogram changes were detected in an escalating dose cardiovascular safety pharmacology study performed in free-moving conscious telemetry monkeys (N=3), receiving single subcutaneous doses of 30, 300, and 1000 µg/kg exenatide. Exenatide produced an acute, profound diuresis and natriuresis in rats, and a mild diuresis in mice. No exenatide-related effects on renal function were detected in monkeys.

TOXICOLOGY

Acute Toxicity

Single-dose toxicity studies were conducted with exenatide in mice, rats, and monkeys. No lethality or serious toxicity was observed in mice, rats, or monkeys at doses up to 1500 µg/kg (intravenous), 30,000 µg/kg (subcutaneous), or 5000 µg/kg (subcutaneous) respectively.

Repeat-Dose Toxicity

Repeat-dose toxicity studies were conducted with exenatide for extended-release injectable suspension in rats and monkeys. Decreased body weight gain and food consumption, a known pharmacologic effect of exenatide, were observed in rats. Reversible, dose-related injection site reactions (erythema, swelling, inflammation, thickening, and granulomas associated with the presence of microspheres) were observed in placebo microsphere- and exenatide-treated groups in both species. No target organ toxicities occurred in rats or monkeys at subcutaneous doses up to 9 mg/kg Q2W (18 weeks) or 1.1 mg/kg Q1W (39 weeks), respectively, with corresponding systemic exposures of up to 27 and 14 times the human exposure resulting from the recommended dose of 2 mg/week based on plasma area under the curve (AUC), respectively.

Repeat-dose toxicity studies were conducted with exenatide in mice, rats, and monkeys. Decreased body weight gain and food consumption, a known pharmacologic effect of exenatide, were observed in all repeat-dose toxicity studies. No target organ toxicities occurred in mice, rats, or monkeys at subcutaneous doses up to 760 µg/kg/day (182 days), 250 µg/kg/day (91 days), or 150 µg/kg/day (273 days), respectively, with corresponding systemic exposures of up to 157, 37, and 183 times the human exposure resulting from the recommended dose of 2 mg/week based on AUC, respectively.

Carcinogenicity

A 104-week carcinogenicity study was conducted with exenatide for extended-release injectable suspension 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 tumour incidence was observed in both males and females. The incidence of C-cell adenomas was statistically significantly increased at all doses (27% to 31%) in females and at 1.0 and 3.0 mg/kg (46% and 47%, respectively) in males compared with the control group (13% for males and 7% for females). A statistically significantly higher incidence of C-cell carcinomas occurred in the high dose group females (6%), while numerically higher incidences of 3%, 7%, and 4% (non-statistically significant versus controls) were noted in the low, mid, and high dose group males compared with the control group (0% for both males and females). An increase in benign fibromas was seen in

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the skin subcutis at injection sites of males given 3 mg/kg. No treatment-related injection site fibrosarcomas were observed at any dose. The no-observed-adverse-effect level (NOAEL) for carcinogenicity was less than 0.3 mg/kg (<2 times human exposure resulting from the recommended dose of 2 mg/week, based on AUC).

A 104-week carcinogenicity study was conducted with exenatide in male and female rats at doses of 18, 70, or 250 µg/kg/day administered by bolus subcutaneous injection. An apparent numerical increase in benign thyroid C-cell adenomas was observed in female rats given the high dose of 250 µg/kg/day. This dose has a systemic exposure 37 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. This increased incidence was not statistically significant when adjusted for survival. There was no tumourigenic response in male rats.

In a 104-week carcinogenicity study conducted with exenatide in mice at doses of 18, 70, or 250 µg/kg/day administered by bolus subcutaneous injection, no evidence of tumours was observed at doses up to 250 µg/kg/day, a systemic exposure up to 23 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC.

Mutagenicity
Exenatide and exenatide for extended-release injectable suspension 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.

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

Development
Fetuses from pregnant rats given subcutaneous doses of exenatide for extended-release injectable suspension 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. Both the maternal and developmental NOAELs for exenatide extended-release in rats were less than 0.3 mg/kg.

In pregnant mice given subcutaneous doses of 6, 68, 460, or 760 µg/kg/day exenatide from Gestation Day 6 through 15 (organogenesis), fetal growth was slowed at doses ≥68 µg/kg/day exenatide. Administration of higher doses of exenatide (≥460 µg/kg/day) was associated with skeletal effects known to be associated with slowed fetal growth. The NOAEL for developmental

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effects in mice was 6 µg/kg/day (1.2 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC).

In pregnant rabbits given subcutaneous doses of 0.2, 2, 22, 156, or 260 µg/kg/day exenatide from Gestation Day 6 through 18 (organogenesis), fetal growth was slowed at doses greater than or equal to 22 µg/kg/day. The NOAEL for developmental effects in rabbits was 2 µg/kg/day (4.8 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC).

In pregnant mice given subcutaneous doses of 6, 68, or 760 µg/kg/day exenatide from Gestation Day 6 through Lactation Day 20 (weaning), slowed neonatal growth was observed in the F1 offspring at doses ≥68 µg/kg/day. Increased perinatal and neonatal mortality occurred in the F1 offspring at 760 µg/kg/day. The NOAEL for developmental toxicity in mice was 6 µg/kg/day (1.2 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC).

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

BYDUREON®
exenatide for extended-release injectable suspension

Read this carefully before you start taking **BYDUREON** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **BYDUREON**.

Serious Warnings and Precautions

Do NOT use BYDUREON if you:

- or a family member has ever had medullary **thyroid** cancer (MTC).
- have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). This is a disease where people have tumours in more than one gland in their body.

In rats, BYDUREON causes a higher rate of thyroid tumours. It is not known if BYDUREON causes thyroid tumours, including MTC, in people.

What is BYDUREON used for?
BYDUREON along with diet and exercise is used to improve control of blood sugar levels in adults with type 2 diabetes.

BYDUREON can be used:

- alone, if you cannot take metformin,
  OR
- in combination with these drugs. The combination is used when these drugs no longer provide enough control of blood sugar levels on their own.
  - metformin
  - a sulfonylurea (SU)
  - metformin and a SU
  - basal insulin
  - basal insulin and metformin

How does BYDUREON work?
BYDUREON helps your body release more insulin when your blood sugar is high. This helps to improve your blood sugar control.

What are the ingredients in BYDUREON?
Medicinal ingredients: extended release exenatide

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Non-medicinal ingredients: carboxymethylcellulose sodium, dibasic sodium phosphate heptahydrate, monobasic sodium phosphate monohydrate, poly (D,L-lactide-co-glycolide), polysorbate 20, sodium chloride, sucrose, water for injection.

BYDUREON is supplied as:
A kit which contains:

- 4 single dose pens
- One extra needle (23 gauge, 9/32")
- Patient Medication Information
- Instructions for Use

Each pen contains:

- 2 mg exenatide (as a white to off-white powder) in the front chamber of the pen injector
- Diluent in the rear chamber of the injector pen. It delivers 0.65 mL after reconstitution.
- One injection needle (23 gauge, 9/32")

Do not use BYDUREON if you:

- are allergic to exenatide or to any of the ingredients in this drug.
- have severe kidney disease or are on dialysis.
- have diabetic ketoacidosis. This is an accumulation of ketones in the blood and urine.
- have type 1 diabetes.
- are pregnant or planning to have a baby. It is not known if BYDUREON will harm your unborn baby. Women who can have children should use effective means of birth control while they are taking BYDUREON. Stop BYDUREON at least 3 months before planning to become pregnant.
- are under 18 years old.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BYDUREON. Talk about any health conditions or problems you may have, including if you:

- are taking other drugs to control blood sugar.
- are taking a blood thinner such as warfarin.
- have a high heart rate (fast pulse).
- have a condition called heart block.
- have any heart disease, such as angina, history of a heart attack, or heart rhythm disturbances.
- have severe problems with your stomach (gastroparesis) or food digestion. BYDUREON slows the emptying of your stomach so food passes more slowly.
- have severe vomiting and/or diarrhea and/or dehydration.
- have a history of problems with your pancreas, stones in your gallbladder (gallstones), alcohol abuse, or high levels of fat in your blood.
- have kidney problems or a kidney transplant.
- are breast feeding or plan to breastfeed. It is not known if BYDUREON passes into breast milk.
- are over 65 years old.

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Other warnings you should know about:
When using BYDUREON with an SU take precautions to avoid having low blood sugar while driving or using machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BYDUREON:
- insulin or an SU such as glyburide, gliclazide, glimepiride. Taking BYDUREON with insulin or an SU can make your blood sugar too low.
- certain other kinds of drugs used to control blood sugar, including all drugs that contain exenatide.
- drugs that increase heart rate or that affect your heart rhythm.
- other drugs taken by mouth.
- a birth control pill (oral contraceptive).
- blood thinner (warfarin).
- heart medication (digoxin).
- blood pressure medication (lisinopril).
- cholesterol medication (lovastatin).

Before you inject BYDUREON:
- Get training from your healthcare professional. Use BYDUREON exactly as instructed by your doctor. Never take more than the dose your doctor has told you to use.
- When you first take BYDUREON with an SU, your doctor might lower the dose of the SU.
- If you use insulin and BYDUREON, you must take them as two separate injections.
- Read and follow the "Instructions for Use". They are included at the end of this Patient Medication Information and in the product packaging.

Do NOT do the following actions:
- Do not mix BYDUREON with any other medicines.
- Do not take BYDUREON if it is discolored, contains solid particles or if there are any signs of leakage. Look through the Inspection Window. Before mixing, the solution should be clear.
- Do not inject through clothing.
- Do not inject into a vein or muscle.
- Do not share with another person.
- Do not reuse or substitute needles or other parts of the pen injector.
- Do not start taking other drugs, vitamins, mineral supplements or alternative medicines on your own. This includes other drugs to treat diabetes.

If you stop taking BYDUREON:
- Tell your healthcare professional. BYDUREON drug levels will slowly go down in your body. The effects and side effects will continue for about 10 weeks after you stop using it.

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How to use BYDUREON:

- at any time of day, with or without meals.
- Follow the "Instructions for Use". They will tell you how to prepare your pen, and how to mix and inject your dose.
- **Inject BYDUREON under the skin. This is called a subcutaneous injection.**

Recommended Adult dose: 2 mg (one injection) subcutaneously every seven days.

Overdose:
Too much BYDUREON can give you nausea, vomiting or make you feel like you have low blood sugar.

If you think you have taken too much BYDUREON, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of BYDUREON, you should take it as soon as you remember if it is within 3 days after the missed dose. You can take your next dose at your usual weekly time.

If it has been longer than 3 days after the missed dose, skip the dose and wait to take BYDUREON at your next usual weekly time. Do not take an extra dose of BYDUREON to make up for your missed dose.

What are possible side effects from using BYDUREON?
These are not all the possible side effects you may feel when taking BYDUREON. If you experience any side effects not listed here, contact your healthcare professional. Please also see the Serious Warnings and Precautions box.

Side effects may include:

- nausea, vomiting, diarrhea, constipation, pain in stomach area (abdomen), decreased appetite, burping
- injection site reactions such as lump, redness, itchiness, bruising and/or pain
- dizziness, headache, common cold, cough
- joint and muscle pain
- weight loss. If you are concerned talk to your health care professional
- rash

BYDUREON can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them		
Symptom/effect	Talk to your healthcare professional	Stop taking drug

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	Only if severe	In all cases	and get immediate medical help
COMMON			
Hypoglycemia (low blood sugar) especially if you are also taking an SU or insulin. You may have headaches, feel sleepy, weak, dizzy, confused, hungry, jittery, or sweaty. Feel like your heart is beating fast.	✓		
UNCOMMON			
Pancreatitis (swelling of the pancreas): long periods of pain in the stomach and/or intestine area may go around to your back. You may also vomit.			✓
Dehydration. (It can be from nausea, vomiting and/or diarrhea, or not taking enough liquids by mouth): If this happens while on BYDUREON it may cause new or worsening problems with kidney function. This includes kidney failure.	✓		
Increase heart rate or changes in heart rhythm: dizziness, fainting. Feel a rapid, pounding, or irregular heartbeat. They are more likely if you, have heart disease, take certain other drugs, or are more than 65 years old.		✓	
Injection Site Reactions: Swelling, hardness, itching, redness, dark discoloration or bruising. This can be with or without lumps under the skin. There can be intense pain, pus, or an open wound, fever and fatigue. Surgery may be required.	✓		
RARE			
Angioedema or Severe Allergic Reactions, including Anaphylaxis: severe rash,			✓

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Serious side effects and what to do about them			
Symptom/effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
hives, or itching. Sudden swelling of the face, lips, tongue or throat. Difficulty breathing or swallowing. Fainting and a very fast heartbeat.			
Kidney Disorders: nausea, vomiting, diarrhea. Muscle cramps. Swelling of the legs, ankles, feet, face and/or hands. Shortness of breath due to extra fluid on the lungs. More frequent urination, or in greater amounts than usual, with pale urine. Or, less frequent urination, or in smaller amounts than usual, with dark coloured urine.			✓
Thyroid Cancer: a lump or swelling in your neck, hoarseness, or trouble swallowing.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

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Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:
- Online at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html)

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
- Store BYDUREON in the original carton in a refrigerator at 2°C to 8°C. Protect from light. Do not freeze. Throw away any BYDUREON that has been frozen.
- BYDUREON can be stored at room temperature up to 30°C for 4 weeks if required.
- Do not use BYDUREON after the expiration date printed on the product packaging (carton and pen injector).
- Dispose of your pen, with the needle attached, in a puncture-resistant container.
- Do not recap or reuse the needle.
- Keep BYDUREON, the needles and all medicines out of reach and sight of children and pets.

If you want more information about BYDUREON:
- Talk to your healthcare professional
- Find the current full Product Monograph that is prepared for healthcare professionals and includes the current Patient Medication Information and Instructions for Use by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the AstraZeneca website: www.astrazeneca.ca,
  or by calling AstraZeneca Canada Inc. at:
  Questions or concerns: 1-800-668-6000

NOTE: This PATIENT MEDICATION INFORMATION leaflet provides you with the most current information at the time of printing.

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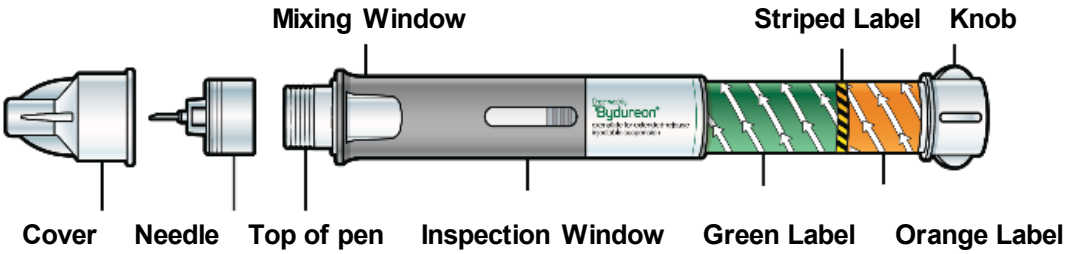
Date of Revision: December 24, 2018

Instructions for Use, read carefully

How to use BYDUREON®
(exenatide for extended-release injectable suspension)



Prior to using BYDUREON you should be trained on its proper use by a healthcare professional.

Read these instructions 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 to your healthcare provider about your medical condition or your treatment. Unless a trained person can help, BYDUREON is not recommended for people who are blind or cannot see well.

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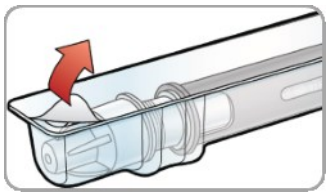
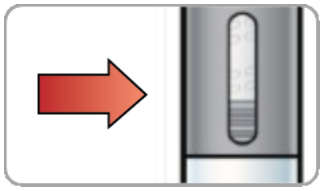
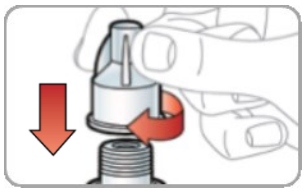
Step 1: Prepare Your Pen	
Let your pen warm up. Remove one pen from the refrigerator and let it stand at room temperature for at least 15 minutes. **DO NOT** use a pen past its expiration date. **Be sure to wash your hands while the pen is warming up.**	
Open the tray by pulling on the corner tab. Then remove the pen and needle. **DO NOT** use your pen or needle if any parts are broken or missing.	
Check the liquid inside the inspection window. It should be clear and free of particles. It's okay if you see bubbles.	
Completely peel off the paper tab from the needle cover.	
Attach the needle to the pen by pushing and screwing it onto the top of the pen until it is tight. **DO NOT** remove the needle cover yet.	

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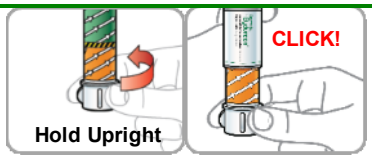
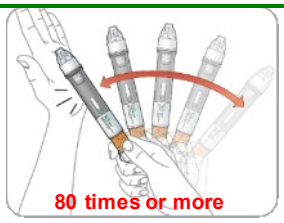
Step 2: Mix Your Dose

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 the pen to mix. Hold the pen by the end with the orange label and **tap the pen firmly against the palm of your hand.**

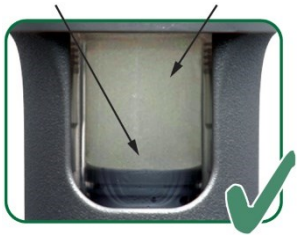
WITHOUT twisting the knob, **ROTATE** the pen every few taps. You may need to tap 80 times or more.



Check the mix. Hold the pen up to the light and look through both sides of the mixing window. The solution should have **NO CLUMPS** and be uniformly cloudy.

Not Mixed Well
Clumps, non-uniform solution

Mixed Well
NO clumps, uniformly cloudy solution



To get your full dose the medicine must be mixed well.

If it's not mixed well, tap longer and more firmly.

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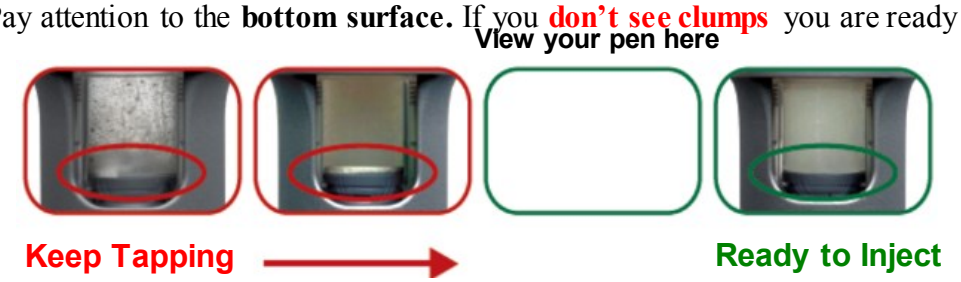
DO NOT proceed unless your medicine is mixed well

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

Compare both sides of the mixing window to the photos below by holding the pen against the page. Pay attention to the **bottom surface.** If you **don't see clumps** you are ready to inject.



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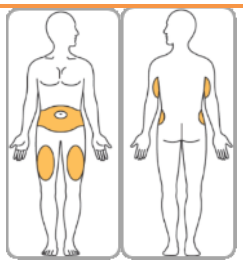
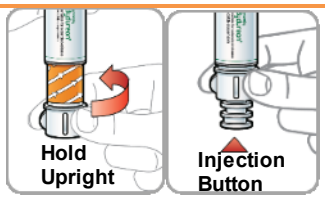
Step 3: Inject Your Dose

IMPORTANT Once the medicine is mixed well, you must inject the dose immediately. You cannot save it for later use.

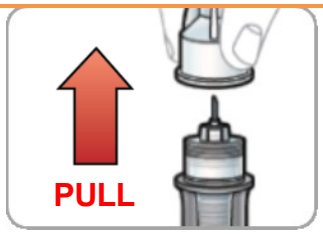
Choose your injection site in either your stomach, thigh, or back of the arm. Each week you can use the same area of your body but choose a different injection site in that area. **Gently clean the area** with soap and water or an alcohol swab.



Twist knob to release injection button. While holding the **pen straight up,** turn the knob until the orange label disappears and the injection button is released. **DO NOT** push the injection button yet.



Remove the needle cover by pulling straight off. **DO NOT** twist. You may see a few drops of liquid on the needle or in the cover.



Inject the medicine. DO NOT inject through clothing. Lift or remove clothing. Insert the needle into your skin. Press the injection button with your thumb until you hear a click. **Hold for 10 seconds** to make sure you get the full dose.

Properly dispose of your pen, with the needle attached, in a puncture-resistant container. **DO NOT** try to recap or reuse the needle.

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Common Questions and Answers

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

The medicine 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 the pen up to the light to see in the window. If you see clumps of any size keep tapping the 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 the pen out of the refrigerator for at least 15 minutes. This will let the pen warm up to room temperature. It will be easier to mix the medicine if the pen is at room temperature.

Be sure you are holding the pen at the end with the knob and the orange label. This will help you grip the 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 the medicine, 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 BYDUREON right away, small clumps of medicine may form in the pen and you may not get your full dose.

4. I'm 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 the 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.

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 all the medicine to go from the pen to under your skin.

7. How do I dispose of BYDUREON?

Be careful when discarding the pen after use. Do not throw away your used prefilled pens in your household trash or recycling bins.

- Put the Pen in a closeable, puncture-resistant sharps container (like a biohazard container).

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- Do not recycle the filled sharps container.
- Ask your healthcare provider about options available in your area to dispose of the sharps container properly.
- The directions regarding Pen handling and disposal are not intended to replace local, healthcare provider or institutional policies.

Always keep your sharps container out of reach of children and animals.

To make sure you receive your full dose, follow these do's and don'ts:

- **DO take the pen out of the refrigerator 15 minutes before you inject. Letting the pen warm up will make the medicine easier to mix**
- **DO hold the pen in the correct orientation throughout the injection process**
- **DON'T inject unless the medicine is well mixed with no clumps. (It should look cloudy)**
- **DON'T remove the needle from the injection site until 10 seconds after the click**

Questions or concerns: 1-800-668-6000

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