PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

BYDUREON® BCise™

Exenatide prolonged-release injectable suspension

Prolonged-release injectable suspension, 2 mg/dose, subcutaneous use

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

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Hematologic	03/2022

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Monotherapy:
BYDUREON BCise (exenatide prolonged-release injectable suspension) is indicated for use as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM) for whom metformin is inappropriate due to contraindications or intolerance.

Add on combination:
BYDUREON BCise (exenatide prolonged-release injectable suspension) is indicated in adult patients with T2DM to improve glycemic control, in combination with:

- metformin
- sulfonylurea (alone or with metformin)

when the existing therapy (with or without metformin), along with diet and exercise, does not provide adequate glycemic control (see 14 CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY).

2 CONTRAINDICATIONS

BYDUREON BCise is contraindicated in patients with:

- known hypersensitivity to this product or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) (see 7 WARNINGS AND PRECAUTIONS).

- end-stage renal disease (ESRD) or severe renal impairment (creatinine clearance <30 mL/min), including patients on dialysis (see 7 WARNINGS AND PRECAUTIONS and Special Populations and Conditions).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Thyroid C-cell tumours

- BYDUREON BCise 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 2 CONTRAINDICATIONS).
- Exenatide prolonged-release causes an increased incidence of thyroid C-cell tumours at clinically relevant exposures in rats, compared to controls. It is unknown whether BYDUREON BCise cause thyroid C-cell tumours, including MTC, in humans (see Carcinogenicity).
- Patients should be counselled regarding the potential risk for MTC with the use of BYDUREON BCise, 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 BCise.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **Switching from BYETTA (exenatide twice daily) to BYDUREON BCise (exenatide prolonged-release injectable suspension):** Patients switching from BYETTA to BYDUREON BCise may experience transient elevations in blood glucose concentrations, which generally improve within two to four weeks after initiation of therapy.

- **Switching between BYDUREON (exenatide for extended-release injectable suspension) and BYDUREON BCise (exenatide prolonged-release injectable suspension):** Patients switching between BYDUREON and BYDUREON BCise may do so, with minimal expected effect on blood glucose concentrations.

- **Discontinuation of BYDUREON BCise:** After discontinuation of BYDUREON BCise, plasma levels of exenatide decline over 10 weeks (see General and 10 CLINICAL PHARMACOLOGY). Choice of other medicinal products and dose selection should be considered accordingly, as adverse reactions may continue and the anti-hyperglycemic effect may persist until exenatide levels decline.

The concurrent use of BYDUREON BCise with insulin has not been studied and is not recommended.

4.2 Recommended Dose and Dosage Adjustment

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

- When BYDUREON BCise is added to sulfonylurea therapy, a decrease in the dose of the sulfonylurea may be considered to reduce the risk of hypoglycemia (see Endocrine and Metabolism).

Special Populations:
Geriatrics (≥65 years of age)
A greater sensitivity of some older individuals cannot be ruled out. Use caution when initiating BYDUREON BCise in patients 65 years of age or older (see Special Populations and Conditions).

Pediatrics
Health Canada has not authorized an indication for pediatric use.

Hepatic Impairment
No dosage adjustment is required in patients with hepatic impairment (see Special Populations and Conditions).

Renal Impairment
BYDUREON BCise is contraindicated in patients with end-stage renal disease (ESRD) or severe renal impairment (creatinine clearance <30 mL/min), including patients on dialysis (see 2 CONTRAINDICATIONS).

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

4.4 Administration

Appropriate training is recommended for non-healthcare professionals administering BYDUREON BCise. 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 BCise is intended for subcutaneous (SC) self-administration by the patient, and must not be administered intravenously or intramuscularly. BYDUREON BCise 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 BCise is supplied as an autoinjector, containing a suspension of exenatide packaged in a 2-mL glass cartridge. The autoinjector contains an integrated needle.

BYDUREON BCise must be removed from the refrigerator 15 minutes before use. The suspension must be mixed by shaking hard for at least 15 seconds, and visually inspected prior to use. The suspension should only be used if it is evenly mixed and cloudy with no white medicine seen along the side, bottom or top of the autoinjector window. BYDUREON BCise must be injected immediately after the autoinjector is prepared.

4.5 Missed Dose

If a dose of BYDUREON BCise 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 BCise at the next usual weekly time. The patient should not take an extra dose of BYDUREON BCise to make up for the missed dose.

5 OVERDOSAGE

Signs and symptoms of overdose that may be observed with BYDUREON BCise 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Subcutaneous Use	Prolonged-release injectable suspension/ 2 mg/dose	Medium chain triglycerides (MCT) Poly (D,L-lactide-co-glycolide) Sucrose

Packaging
BYDUREON BCise is supplied in a carton containing:
- 4 single-dose autoinjectors
- Patient Medication Information
- Instructions for Use

BYDUREON BCise is supplied as an autoinjector, containing a suspension of exenatide in a MCT diluent vehicle, packaged in a 2-mL glass cartridge. The autoinjector is sealed at one end with a rubber seal/cap combination (combiseal), and at the other end with a rubber plunger. The autoinjector contains an integrated needle (23 gauge, 9/32").

Each autoinjector contains:
2 mg exenatide (as white to off-white microspheres suspended in a MCT vehicle)
Sufficient suspension to deliver 2 mg of exenatide prolonged-release in 0.85 mL vehicle

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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

BYDUREON (exenatide for extended-release injectable suspension), BYDUREON BCise, or BYETTA® (exenatide twice daily) should not be used concomitantly, as they contain the same medicinal ingredient and this could result in an overdose.

BYDUREON BCise 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.

The concurrent use of BYDUREON BCise with insulin has not been studied and is not recommended.

BYDUREON BCise 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 Post-Market Adverse Reactions and Drug-Drug Interactions).

After discontinuation of BYDUREON BCise, plasma levels of exenatide decline over 10 weeks (see 10 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 Dosing Considerations).

BYDUREON BCise must not be administered by intravenous or intramuscular injection (see 4 DOSAGE AND ADMINISTRATION).

Carcinogenesis and Mutagenesis
Risk of Thyroid C-cell tumours
BYDUREON BCise 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 2 CONTRAINDICATIONS).

Exenatide prolonged-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 prolonged-release at 25-times clinical exposure compared to controls, and higher incidences were noted in males compared to controls in all treated groups at ≥2-times clinical exposure. It is unknown whether BYDUREON BCise will cause thyroid C-cell tumours, including MTC, in humans, as the human relevance of exenatide prolonged-release-induced rodent thyroid C-cell tumours has not been determined (see 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 BCise.

Cardiovascular
Heart Rate Increase
Exenatide prolonged-release 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 8 ADVERSE REACTIONS, Drug-Drug Interactions and Cardiac Electrophysiology).

PR Interval Prolongation
Exenatide prolonged-release causes a prolongation of the heart rate-corrected PR interval of the electrocardiogram (see Drug-Drug Interactions and 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.

Driving and Operating Machinery
Patients should be advised to exercise caution when driving or operating a vehicle or potentially dangerous machinery under conditions where a risk of hypoglycemia is present (see Hypoglycemia).

Endocrine and Metabolism
Hypoglycemia
Use with a sulfonylurea
The risk of hypoglycemia was increased when BYDUREON BCise was used in combination with a sulfonylurea in clinical trials (see 8 ADVERSE REACTIONS). To reduce the risk of hypoglycemia associated with the use of a sulfonylurea, a decrease in the dose of sulfonylurea may be considered (see 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 BCise is not recommended in patients with severe gastrointestinal disease.

Hematologic
Post-marketing reports have associated BYDUREON BCise with serious bleeding, which may be fatal, from drug-induced thrombocytopenia (DITP) (see Post-Market Adverse Reactions). DITP is an immue-mediated reaction that is caused by drug-dependent platelet-reactive antibodies. These antibodies cause destruction of platelets in the presence of the sensitizing drug. Patients should be instructed to promptly report the development of signs and symptoms of thrombocytopenia, such as easy or excessive bruising or prolonged bleeding. If thrombocytopenia is suspected, direct platelet count should be performed. Management of DITP includes cessation of the suspect drug, to aid in drug clearance from the circulation and associated recovery from DITP. Drug-dependent platelet reactive antibodies can persist for many years, and patients of suspected DITP should be advised to indefinitely avoid the causative drug.

Hepatic/Biliary/Pancreatic
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 BCise, 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 BCise should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYDUREON BCise

should not be restarted. Antidiabetic therapies other than BYDUREON BCise 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 BCise, assess for other potential causes and institute alternative treatment for diabetes (see Post-Market Adverse Reactions).

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

In controlled studies with BYDUREON BCise, approximately 74% of patients developed antibodies (ranging from 71 to 76%), and at week 28, approximately 57% of patients had antibodies.

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

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 exenatide extended-release (BYDUREON). Isolated cases required surgical intervention.

The overall incidence of potentially immune-related injection site reactions (such as injection site pruritus, injection site erythema, and injection site nodule), for BYDUREON BCise, was higher in antibody-positive patients, compared with antibody negative patients, with a greater incidence in those with higher titer antibodies (see 8 ADVERSE REACTIONS).

Monitoring and Laboratory Tests
Renal Function
Assessment of renal function is recommended prior to initiation BYDUREON BCise and periodically thereafter, as appropriate (see 2 CONTRAINDICATIONS and 4 DOSAGE AND ADMINISTRATION).

Anticoagulation
INR should be monitored frequently until stable when BYDUREON BCise is co-administered with warfarin (see 9 DRUG INTERACTIONS).

Renal
BYDUREON BCise 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 2 CONTRAINDICATIONS).

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

Reproductive Health: Female and Male Potential
See 7.1.1 Pregnant Women.

- Fertility
  See Reproductive and Developmental Toxicology.

- Function
  No data exists.

- Teratogenic Risk
  BYDUREON BCise should not be used during pregnancy. See Reproductive and Developmental Toxicology.

7.1 Special Populations

7.1.1 Pregnant Women

BYDUREON BCise 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 prolonged-release to pregnant rats during organogenesis caused fetal growth retardation. Based on animal data, exenatide may cause fetal harm (see 16 NON-CLINICAL TOXICOLOGY).

The extent of exposure in pregnancy during clinical trials: No experience.

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

7.1.2 Breast-feeding

There are no adequate and well-controlled studies in women during breast-feeding. BYDUREON BCise should not be used by a woman during breast-feeding (see 16 NON-CLINICAL TOXICOLOGY).

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

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 BYDUREON BCise with caution in the elderly (see 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of BYDUREON BCise was assessed in one 28-week, comparator-controlled trial (n=229), and one 28-week, placebo- and comparator-controlled trial (n=181), with a total of 410 patients with type 2 diabetes.

In these trials, the most commonly observed adverse events in BYDUREON BCise-treated patients were: gastrointestinal disorders [nausea (9.3%), diarrhea (4.1%), vomiting (3.4%)] injection site reactions [nodules (12.2%), pruritis (3.7%)], and headache (5.1%).

Serious adverse events were reported in 2.4% of BYDUREON BCise-treated patients. No single SAE was reported with an incidence greater than 0.2%.

The incidence of discontinuation of treatment due to adverse events was 3.9% (n=16) for BYDUREON BCise-treated patients. The most common adverse events leading to discontinuation of treatment for BYDUREON BCise-treated patients were nausea (0.7%) and diarrhea (0.7%), vomiting (0.5%), and injection site nodule (0.5%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 2 summarizes the incidences of treatment-related adverse events with an incidence of ≥1% and reported in at least two BYDUREON BCise-treated patients in any of the studies within the table. These are provided for two placebo- and comparator-controlled 28-week trials of BYDUREON BCise used as monotherapy and in combination with metformin, a sulfonylurea, a thiazolidinedione, or a combination of any two of these therapies.

Table 2 Treatment-related[a] adverse events (excluding hypoglycemia[b]) reported in ≥1% and at least two BYDUREON BCise-treated patients in comparator-controlled trials in monotherapy and in combination with metformin, a sulfonylurea, a thiazolidinedione, or a combination of any two of these therapies

System Organ Class/Preferred Term	Study BCB118 (N=377) 28 weeks		Study BCB120 (N=364) 28 weeks		
	BYDUREON BCise 2 mg QW SC (N=229)	BYETTA 5 µg/10 µg BID (N=146)	BYDUREON BCise 2 mg QW SC (N=181)	Sitagliptin 100 mg/day (N=122)	Placebo (N=61)
	%		%		
Gastrointestinal disorders					
Abdominal distension	2.2	0	0	0	0
Diarrhea	2.6	4.1	1.7	0.8	1.6
Nausea	8.7	18.5	6.6	0.8	0
Vomiting	2.2	3.4	2.8	0	0
General disorders and administration site conditions					
Injection site bruising	2.6	0	2.8	0	0
Injection site erythema	3.5	0.7	1.7	0	0
Injection site induration	0	0	3.9	0	0
Injection site nodule	15.3	0.7	7.2	0	0
Injection site pain	2.6	0	0	0	0
Injection pruritus	4.4	0.7	2.8	0	0
Injection site swelling	0	0	1.1	0	0
Nervous system disorders					
Headache	1.3	2.1	0	0	0

[a] As assessed by the clinical investigator.
[b] See Hypoglycemia and Table 3.
QW Once Weekly; SC subcutaneous

Immunogenicity

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

Anti-exenatide antibodies were measured in 393 BYDUREON BCise-treated patients in two comparator-controlled 28-week studies of BYDUREON BCise. The incidence of treatment-emergent antibodies to BYDUREON BCise at the last treatment visit was approximately 57%. Approximately 42% of these patients developed low titer antibodies (<625) to exenatide and approximately 32% of patients developed high titer antibodies (≥625) at any time during the studies.

The level of glycemic control (i.e., reduction in HbA1c) in patients with low antibody titers (<625) (-1.1 to -1.5%) was generally comparable to that observed in patients negative for anti-exenatide antibodies (-1.1 to -1.4%). Patients with higher titer antibodies may have an attenuated HbA1c response (-0.6 to -0.7%). If there is worsening of glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered (see Immune).

Amongst BYDUREON BCise-treated patients evaluable for antibodies (N=393), the incidence of potentially immunogenic injection site reactions (including injection site nodule, pruritus, erythema and induration) during the two 28-week studies was approximately 21% for antibody-positive patients and 15.7% for antibody-negative patients (see Immune). These reactions were less commonly observed in antibody-negative patients (15.7%) and patients with low titer antibodies (16.3%) compared with those with high titer antibodies (27.2%).

Injection Site Reactions
Injection site reactions were observed more frequently in BYDUREON BCise-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 Immune).

Serious injection-site reactions have been reported with post-market use of exenatide extended-release (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 BCise was used in combination with a sulfonylurea (see Hypoglycemia). To reduce the risk of hypoglycemia associated with the use of a sulfonylurea, reduction in the dose of sulfonylurea may be considered (see Recommended Dose and Dosage Adjustment).

Table 3 summarizes the incidence and rate of minor hypoglycemia in the 2 comparator-controlled 28-week trials of BYDUREON BCise used as a monotherapy or as add-on to metformin, a sulfonylurea, a thiazolidinedione, or a combination of any two of these therapies. In these trials, a minor hypoglycemia event was defined as symptoms of hypoglycemia with a concomitant glucose <3 mmol/L prior to treatment.

Table 3 Incidence (% of subjects) and Rate (episodes/subject year) of Minor ϕ Hypoglycemia in the BYDUREON BCise Phase 3 Controlled Trials

Study	Incidence: % of subjects (Event rate episodes/subject year)
BCB118 (N=377); 28-week, comparator-controlled study comparing BYDUREON BCise (exenatide once weekly suspension) to BYETTA (exenatide twice daily) in patients who were inadequately treated with diet and exercise alone or with oral antidiabetic therapy, including metformin, a sulfonylurea, a thiazolidinedione, or a combination of any two of these therapies.	
With Concomitant Sulfonylurea Use	
BYDUREON BCise 2 mg QW SC (N=88)	26.1 (1.87)
BYETTA 5 ug BID, then 10 ug BID	17.7 (1.11)
Without Concomitant Sulfonylurea Use	
BYDUREON BCise 2 mg QW SC	2.1 (0.16)
BYETTA 5 ug BID, then 10 ug BID	4.8 (0.18)
BCB120 (N=364); 28-week, comparator-and placebo-controlled study comparing BYDUREON BCise (exenatide once weekly suspension) to sitagliptin and placebo in patients inadequately treated with metformin.	
BYDUREON BCise 2 mg QW SC	0 (0.0)
Sitagliptin 100 mg/day (N=122)	0.8 (0.02)

Placebo (N=61)	0 (0.0)

QW Once Weekly; SC subcutaneous; BID twice daily
ϕ Reported event that has symptoms consistent with hypoglycemia with a concomitant glucose <3 mmol/L
N = All treated.

There were no reported events of major hypoglycemia in BYDUREON BCise treated patients in the two 28-week comparator-controlled trials. 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. In addition, any event that required third-party assistance to resolve due to severe impairment in consciousness or behavior, and was associated with concomitant glucose <3 mmol/L, was also defined as major hypoglycemia.

Increased Heart Rate
A mean increase in heart rate (HR) of 2.4 beats per minute (bpm) from baseline (74 bpm) was observed in the pooled phase 3 BYDUREON BCise clinical studies, compared to 0.2 bpm (BYETTA) in BCB118, and 0.8 bpm (sitagliptin) and 0.6 bpm (placebo) in BCB120.

8.3 Less Common Clinical Trial Adverse 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 BCise-treated patients than in placebo-treated or comparator-treated patients in two 28-week studies, and which are not represented in Table 1.

Gastrointestinal disorders: Dyspepsia, Constipation, Gastrooesophageal reflux disease
General disorders and administration site conditions: Fatigue, Injection site reactions, Injection site swelling, Injection site haemorrhage, Injection site mass
Metabolism and nutrition disorders: Hyperlipidaemia, Hyperuricaemia
Musculoskeletal and connective tissue disorders: Muscle spasms
Nervous system disorders: Dizziness, Dysgeusia
Skin and subcutaneous tissue disorders: Urticaria

8.5 Post-Market Adverse Reactions

Additional adverse reactions have been reported with exenatide extended-release (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
Hematological: Drug-induced thrombocytopenia (see Hematologic)
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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

9.4 Drug-Drug Interactions

The following are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated.

Table 4 Established or Potential Drug-Drug Interactions

Drug	Source of Evidence	Effect	Clinical Comment
Drugs that Increase Heart Rate	Clinical Trial	Exenatide prolonged-release causes an increase in heart rate (see 8 ADVERSE REACTIONS and Cardiac Electrophysiology).	Caution should be observed if BYDUREON BCise is administered with other drugs that also increase heart rate, such as drugs with sympathomimetic or anticholinergic activity (see Cardiovascular).

Drug	Source of Evidence	Effect	Clinical Comment
Drugs that Cause PR Interval Prolongation	Clinical Trial	Exenatide prolonged-release causes an increase in the PR interval (see Cardiac Electrophysiology). The impact on the PR interval of co-administration of BYDUREON BCise 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.	Co-administration of BYDUREON BCise should be undertaken with caution (see Cardiovascular).
Orally administered drugs (e.g. acetaminophen)	Clinical Trial	In a study using 1000 mg acetaminophen as a marker of gastric emptying, either with or without a meal, following 14 weeks of exenatide extended-release (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). Exenatide extended-release (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 BCise. When exenatide is used in combination with a sulfonylurea, patients should be advised to take precautions to avoid hypoglycemia while driving or using machinery.

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

Table 5 Established or Potential Drug-Drug Interactions

Drug	Source of Evidence	Effect	Clinical Comment
Digoxin	Clinical Trial	Co-administration of repeated doses of exenatide 10 µg BID decreased the Cmax 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	Clinical Trial	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	Clinical Trial	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.	
Warfarin	Clinical Trial	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 General and Post-Market Adverse Reactions).

Drug	Source of Evidence	Effect	Clinical Comment
Combination Oral Contraceptives (ethinyl estradiol and levonorgestrel)	Clinical Trial	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.	

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 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).

BYDUREON BCise is a subcutaneously once-weekly injectable, exenatide prolonged-release non-aqueous suspension formulation developed as an extension to both the BYETTA exenatide immediate release injection, twice daily (BID) and BYDUREON subcutaneously once-weekly injectable, exenatide extended-release aqueous suspension product lines. BYDUREON BCise contains exenatide prolonged-release microspheres suspended in an oil-based vehicle of medium chain triglycerides (MCT), and does not require reconstitution.

10.1 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.

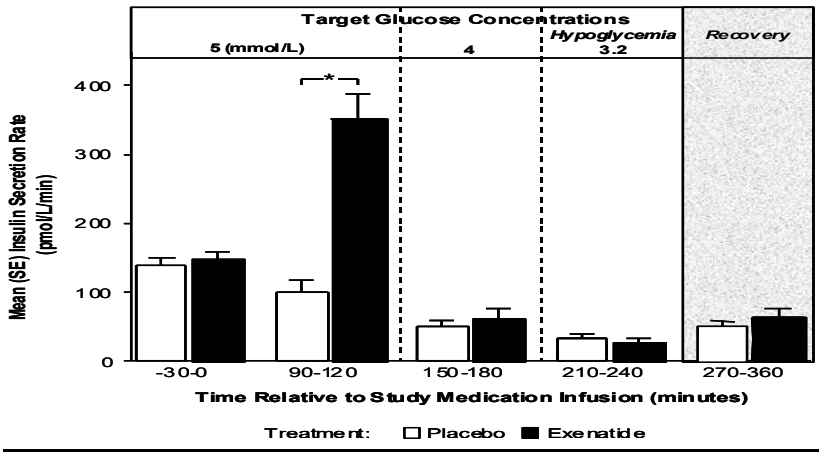
Exenatide is a GLP-1 receptor agonist that mimics several antihyperglycemic actions of incretins. Exenatide has been shown to bind to and activate the known human GLP-1 receptor *in vitro*. This leads to an increase in both glucose-dependent synthesis of insulin and *in vivo* secretion of insulin from 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.

10.2 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).

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 28-week controlled study of exenatide once weekly suspension (BYDUREON BCise) compared to exenatide twice daily (BYETTA), decreases in fasting plasma glucose concentrations were evident following two weeks of therapy, in both treatment groups. At Week 28, the mean change in fasting plasma glucose from baseline was -2.00 mmol/L for BYDUREON BCise and -1.70 mmol/L for BYETTA. The full effect on fasting glucose was not observed until approximately 8 weeks.

In a 12-week repeat dose pharmacokinetic study of exenatide microspheres suspended in MCT-oil in subjects with type 2 diabetes mellitus, reductions in fasting plasma glucose concentrations were seen by Week 4 compared to the placebo group. At the end of Week 12, the mean change in fasting plasma glucose from baseline was -1.8 mmol/L in the exenatide once weekly suspension-treated group compared to 0.4 mmol/L in the placebo group.

Postprandial Glucose
In patients with type 2 diabetes, exenatide reduces postprandial plasma glucose concentrations.

In a 28-week controlled study of exenatide once weekly (BYDUREON BCise) compared to exenatide twice daily (BYETTA), 2-hour postprandial glucose levels were measured during a mixed meal tolerance test in a subset of patients with type 2 diabetes mellitus. Following treatment for 16 weeks, after steady-state concentrations had been achieved, the LS mean change from baseline was greater with BYETTA (-6.31 mmol/L) than BYDUREON BCise (-4.83 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 Cardiovascular and 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 Cardiovascular and 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.

10.3 Pharmacokinetics

Table 6 Summary Statistics of Exenatide 2 mg Once Weekly (BYDUREON BCise) 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)	CL	Vd
Geometric Mean (CV %)	223.3 (29.4)	103.9 (12.5)	31325.7 (3937.4)	186.5 (23.4)	9.1 L/h	28.3 L

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; CL Clearance; Vd Volume of distribution; CV Coefficient of variation.

Absorption:
Following a single dose of BYDUREON BCise, there is an initial period of release of surface-bound exenatide followed by a gradual release of exenatide from the microspheres, which results in a peak of exenatide in plasma at weeks 6 to 7 representing the hydration and erosion of the microspheres. Following weekly administration of 2 mg BYDUREON BCise, mean drug concentrations exceeded minimal efficacious concentrations (~ 50 pg/mL) in 2 weeks with gradual increase in the average plasma exenatide concentration up to week 8.

Following initiation of once every 7 days (weekly) administration of 2 mg BYDUREON BCise, gradual increase in the plasma exenatide concentration is observed up to approximately week 8. From week 8 mean exenatide concentrations of approximately 208 pg/mL were maintained over once every 7 days (weekly) dosing intervals indicating that steady state was achieved.

Distribution:
The mean apparent volume of distribution of exenatide following subcutaneous administration of a single dose of 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. Exenatide extended-release (BYDUREON) has no clinically significant effect on acetaminophen pharmacokinetics.

Dose proportionality, Accumulation, Time-dependency:
The geometric mean C_{ssave} at steady state for BYDUREON BCise is about 8.6-fold higher than those observed after a single dose. Accumulation occurred gradually over the first 8 weeks of therapy for BYDUREON BCise, after which steady-state concentrations were maintained in the intended therapeutic range.

The exenatide C_{ssave} were comparable up to at least 28 weeks, indicating that exenatide clearance or absorption from BYDUREON BCise did not alter over time.

Special Populations and Conditions

- **Pediatrics:** BYDUREON BCise has not been studied in pediatric patients.

- **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 exenatide C_{ssave} for 2 mg BYDUREON BCise in patients ≥65 years of age was 44% higher than in patients <65 years of age.

- **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 exenatide C_{ssave} for 2 mg BYDUREON BCise in females was 10.6% higher than in males.

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

- **Ethnic Origin:** Population pharmacokinetic analysis of patients including Caucasian, non-Caucasian and Asian suggests that race has no significant influence on the pharmacokinetics of exenatide. The exenatide C_{ssave} for 2 mg BYDUREON BCise in Caucasian patients was 3% and 0.6% higher than in non-Caucasian and Asian patients, respectively.

- **Hepatic Insufficiency:** 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 4 DOSAGE AND ADMINISTRATION and Metabolism and Elimination).

- **Renal Insufficiency:** BYDUREON BCise 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 BCise indicate that a 69% and 28% higher systemic exposure to exenatide in moderate (N=24) and mild (N=96) renally-impaired patients, respectively, as compared to patients with normal renal function (N=70).
  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.

- **Body Mass Index:** The exenatide C_{ssave} for 2 mg BYDUREON BCise in patients with BMI <30 kg/m^2 was 12.8% higher than in patients with BMI ≥30 kg/m^2.

11 STORAGE, STABILITY AND DISPOSAL

BYDUREON BCise should be stored in the refrigerator at 2°C to 8°C, up to the expiration date or until preparing for use. BYDUREON BCise can be kept at room temperature (not to exceed 30°C) for no more than a total of 4 weeks, if needed. Store in the original packaging in order to

protect from light. BYDUREON BCise must be stored flat.

BYDUREON BCise should not be used past the expiration date. The expiration date for the autoinjector can be found on the carton, or on the autoinjector label.

Keep BYDUREON BCise out of reach of children and pets.

Care should be taken when discarding the BYDUREON BCise autoinjector after use. Place the used autoinjector in a closeable, puncture-resistant sharps container (biohazard container). Discard the sharps container according to the local policies.

12 SPECIAL HANDLING INSTRUCTIONS

BYDUREON BCise must be removed from the refrigerator 15 minutes before use. The suspension must be mixed by shaking hard for at least 15 seconds, and visually inspected prior to use. The suspension should only be used if it is evenly mixed and cloudy with no white powder seen along the side, bottom or top of the autoinjector window.

BYDUREON BCise must be administered immediately after mixing.

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

BYDUREON BCise must not be mixed with any other medicinal product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: exenatide

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

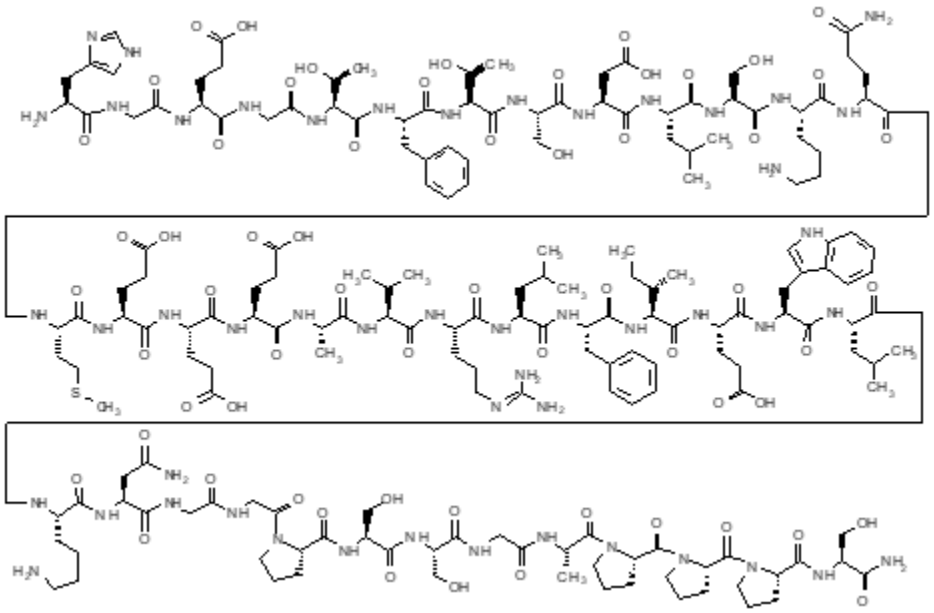
H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2

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.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Monotherapy, combination with metformin, combination with a sulfonylurea, combination with metformin and a sulfonylurea

Trial Design and Study Demographics

Table 7 Summary of patient demographics for clinical trials

Study design and duration	Dosage, route of administration and treatments	Study subjects per treatment arm N=number	Mean age (Range)	Gender (% M/F)
Study BCB118 – 28-week, comparator-controlled study comparing BYDUREON BCise (exenatide once weekly suspension) to BYETTA (exenatide twice daily) in patients who were inadequately treated with diet and exercise alone or with oral antidiabetic therapy, including metformin, a sulfonylurea, a thiazolidinedione, or a combination of any two of these therapies.[1]				
Phase 3, multicenter, randomized, open-label, parallel group, 28-week, comparator-controlled study, followed by 24-week uncontrolled extension	• BYDUREON BCise 2 mg QW SC • Byetta 5 µg BID for 4 weeks, then Byetta 10 µg BID for 24 weeks Subjects were randomized in a 3:2 ratio to receive BYDUREON BCise 2 mg QW SC or BYETTA, in addition to existing oral antidiabetic agents. Extension: • BYDUREON BCise 2 mg QW SC	BYDUREON BCise QW N=229 Byetta N=146 BYDUREON BCise QW N=309	56 years (26-80)	64/36
Study BCB120 – 28-week, comparator-and placebo-controlled study comparing BYDUREON BCise (exenatide once weekly suspension) to sitagliptin and placebo in patients inadequately treated with metformin.[2]				
Phase 3, randomized, open-label, 28-week, comparator- and placebo-controlled study	• BYDUREON BCise 2 mg QW SC • Sitagliptin 100 mg/day • Placebo Subjects were randomized to receive either BYDUREON BCise 2 mg QW SC, sitagliptin, or placebo in a ratio of 3:2:1. Subjects continued their existing metformin treatment (≥1500 mg metformin daily).	BYDUREON BCise QW N=181 Sitagliptin N=122 Placebo N=61	53 years (29-76)	53/47

BID Twice daily; QW Once Weekly, SC subcutaneous

Study Results

Comparator-Controlled Clinical Trials

BYDUREON BCise was studied as monotherapy and in combination with metformin, a sulfonylurea, a thiazolidinedione, or a combination of any two of these therapies

BYDUREON BCise vs. BYETTA as Add-On to Diet and Exercise Alone or in Combination with one or any two of Metformin, Sulfonylurea, or Thiazolidinedione (Study BCB118)

A 28-week, randomized open-label comparator-controlled trial with a 24-week open-ended extension period, compared BYDUREON BCise (n=229) to BYETTA (n=148). The majority of the patients in the study were Caucasian (74%, n=278), followed by Black or African American (16%, n=61), Asian (7%, n= 25), other (1%, n=5), American Indian or Alaska Native (1%, n=5), and Native Hawaiian or Other Pacific Islander (<1%, n=1).

Patients were treated with diet and exercise alone (13%), a single oral antidiabetic agent (49%), or combination therapy of oral antidiabetic agents (38%). The mean baseline HbA1c was 8.5%. Patients were randomly assigned to receive BYDUREON BCise 2 mg once every 7 days (weekly) or BYETTA (10 mcg twice daily), in addition to existing oral antidiabetic agents. Patients assigned to BYETTA initiated treatment with 5 mcg twice daily then increased the dose to 10 mcg twice daily after 4 weeks.

The primary endpoint was change in HbA1c from baseline to Week 28. Treatment with BYDUREON BCise achieved a statistically significantly larger reduction in HbA1c, compared to BYETTA (see Table 8)

Table 8 Results of 28-week trial of BYDUREON BCise versus BYETTA, both as monotherapy or as add-on to metformin, a sulfonylurea, a thiazolidinedione, or combination of oral agents (Modified intent-to-treat patients)

	BYDUREON BCise 2 mg QW	BYETTA 10 µg BID
N	229	146
HbA1c (%)		
Mean baseline	8.5	8.5
Mean change from baseline at week 28 [1]	-1.4	-1.0
Mean difference from BYETTA (95% CI)[†]	-0.37 (-0.63, -0.10)*	
Patients (%) achieving HbA1c <7% at Week 28 [2]	49	43
Fasting plasma glucose (mmol/L)		
Mean baseline	10	10
Mean change from baseline at week 28 [1]	-1.8	-1.3
Body weight (kg)		
Mean baseline	97.2	96.6

	BYDUREON BCise 2 mg QW	BYETTA 10 µg BID
N	229	146
Mean change from baseline at week 28[1]	-1.5	-1.9

N = number of patients in each treatment group, CI = unadjusted confidence interval, QW = once weekly.
*p-value <0.01.
†The non-inferiority margin was set at +0.4% in this study.
[1] Least squares means were obtained using a mixed model repeated measure analysis with treatment, diabetes management method at Screening (diet/exercise alone, SU use, or non-SU use), renal function (normal, mild renal impairment, or moderate renal impairment), week of visit, treatment-by-visit interaction, and HbA1c stratum (<9% or ≥9%) at Screening as fixed factors, and subject as random effect.
[2] Subjects with missing values at Week 28 counted as not achieving goal.

BYDUREON BCise versus Sitagliptin and Placebo, All as Add-on to Metformin Therapy (Study BCB120)

A 28-week open-label (oral medication blinded), comparator- and placebo-controlled trial, compared the safety and efficacy of BYDUREON BCise to sitagliptin and placebo. A total of 364 patients were studied, 296 (81%) were Caucasian, 49 (14%) Black or African American, 14 (4%) Asian, and 3(<1%) American Indian or Alaska Native, 1(<1%) Native Hawaiian or Other Pacific Islander and 1(<1%) was classified otherwise.

The mean baseline HbA1c was 8.5%. Patients were randomly assigned to receive BYDUREON BCise 2 mg once every 7 days (weekly), sitagliptin 100 mg/day or placebo (tablet), in addition to their existing metformin therapy.

The primary endpoint was change in HbA1c from baseline to week 28. Treatment with BYDUREON BCise 2 mg once weekly resulted in a statistically significant mean reduction in HbA1c compared to sitagliptin 100 mg/day and placebo (see Table 9).

Table 9 Results of 28-week trial of BYDUREON BCise versus Sitagliptin and Placebo, all as add-on to metformin therapy (Modified intent-to treat patients)

	BYDUREON BCise 2 mg QW	Sitagliptin 100 mg/day	Placebo Once Daily
N	**181**	**122**	**61**
HbA1c (%)			
Mean baseline	8.4	8.5	8.5
Mean change at week 28[1]	-1.1	-0.8	-0.4
Difference from sitagliptin (95% CI)[1†]	-0.38 (-0.70, -0.06)*		
Difference from placebo (95% CI)[1]	-0.72 (-1.15,-0.30)**		
Patients (%) achieving HbA1c <7% at Week 28 [2]	43	32	25
Fasting plasma glucose (mmol/L)			

	BYDUREON BCise 2 mg QW	Sitagliptin 100 mg/day	Placebo Once Daily
N	**181**	**122**	**61**
HbA1c (%)			
Mean baseline	9.9	9.8	9.6
Mean change from baseline at week 28[1]	-1.2	-0.6	0.5
Body weight (kg)			
Mean baseline	89.2	88.1	89.0
Mean change from baseline at week 28[1]	-1.1	-1.2	0.2

N = number of patients in each treatment group, CI = unadjusted confidence interval, QW = once weekly.
*p-value <0.05, **p-value <0.01.
†Sitagliptin 100 mg/day did not show superiority to placebo in this study.
[1] Least squares means were obtained using a mixed model repeated measure analysis with treatment, week of visit, treatment by week interaction, baseline HbA1c stratum (<9% or ≥9%) and baseline HbA1c stratum by week interaction as fixed factors, and subject as random effect. Baseline HbA1c and baseline HbA1c by week interaction were also included as covariates.
[2] Subjects with missing values at Week 28 counted as not achieving goal.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

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. *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. *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.

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. Beneficial actions of exenatide on glucose and HbA1c were consistent, whether dosed twice-daily with exenatide or dosed once over 4 weeks with exenatide prolonged-release in ZDF rats. 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.

Nonclinical Pharmacokinetics
Exenatide was absorbed over an extended period of time following a subcutaneous injection of exenatide extended-release (BYDUREON), with a relative bioavailability compared to exenatide twice daily (BYETTA) calculated to be approximately 63% in rat and 23% in monkey.

PK parameters for exenatide from BYDUREON BCise were determined in both the rat and monkey and showed, like BYDUREON, that exenatide is absorbed over an extended period of time following a SC injection with BYDUREON BCise. With the exception of the initial release of exenatide in the first few days following injection, the serum concentration time profile of BYDUREON BCise and PK parameters of BYDUREON BCise were similar to those observed for BYDUREON. 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.

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 (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.

General 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 extended-release (BYDUREON) 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.

Repeat-dose toxicity studies were conducted with BYDUREON BCise in cynomolgus monkeys (in 1 and 3 month studies). In the 1 month study, once weekly subcutaneous dosing of up to 1.1 mg/kg/dose was well tolerated, with no adverse systemic toxicity observed, corresponding to 4.2 times the human systemic exposure, based on AUC. In the 3 month study, once weekly subcutaneous dosing of up to 1.1 mg/kg/dose was well tolerated, with no adverse systemic toxicity observed, corresponding to 20 times the human systemic exposure, based on AUC.

Carcinogenicity:
A 104-week carcinogenicity study was conducted with exenatide extended-release (BYDUREON) in male and female rats at doses of 0.3, 1.0 and 3.0 mg/kg (2, 9, and 26-times human systemic exposure 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 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.

Genotoxicity:
Exenatide and exenatide extended-release (BYDUREON) were not mutagenic or clastogenic, with or without metabolic activation, in the Ames bacterial mutagenicity assay or chromosomal aberration assay in Chinese hamster ovary cells. Exenatide was negative in the *in vivo* mouse micronucleus assay.

Reproductive and Developmental Toxicology:
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.

Fetuses from pregnant rats given subcutaneous doses of exenatide extended-release (BYDUREON) 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. For BYDUREON BCise, doses of 0.3, 1 and 3 mg/kg correspond to systemic exposures of 2.8, 7.9, and 18.5 times respectively, the human exposure resulting from recommended dose of 2 mg/week based on AUC.

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 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). Systemic exposures were equivalent to the human exposure resulting from the recommended dose of 2 mg/week, based on AUC, for BYDUREON BCise.

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).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PBYDUREON® BCise™
Exenatide prolonged-release injectable suspension

Read this carefully before you start taking **BYDUREON BCise** 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 BCise**.

Serious Warnings and Precautions

Do NOT use BYDUREON BCise 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, prolonged-release exenatide causes a higher rate of thyroid tumours. It is not known if BYDUREON BCise causes thyroid tumours, including MTC, in people.

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

BYDUREON BCise 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)
  - or metformin and a SU

How does BYDUREON BCise work?
BYDUREON BCise 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 BCise?
Medicinal ingredients: prolonged-release exenatide
Non-medicinal ingredients: Medium chain triglycerides (MCT), poly (D,L-lactide-co-glycolide), sucrose.

BYDUREON BCise comes in the following dosage form:
Prolonged-release injectable suspension, 2 mg/dose

Do not use BYDUREON BCise if:

- 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 BCise will harm your unborn baby. Women who can have children should use effective means of birth control while they are taking BYDUREON BCise. BYDUREON BCise should be stopped 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 BCise. Talk about any health conditions or problems you may have, including if you:

- are taking other drugs to control blood sugar including insulin
- are taking a blood thinner such as warfarin
- have a high heart rate (fast pulse)
- have any heart disease, such as angina, history of a heart attack, or heart rhythm disturbances.
- have a condition called heart block
- are receiving treatment with a sulfonylurea (SU). Examples are glyburide, gliclazide, glimepride. These types of drugs can increase the risk of having low blood sugar if used in combination with BYDUREON BCise
- have severe problems with your stomach (gastroparesis) or food digestion
- 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 BCise passes into breast milk.
- are over 65 years old

Other warnings you should know about:
When using BYDUREON BCise with a sulfonylurea (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 BCise:

- a sulfonylurea (SU) such as glyburide, gliclazide, glimepiride. Taking BYDUREON BCise with 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).

How to take BYDUREON BCise:
Your doctor or pharmacist should give you training before you inject BYDUREON BCise. You should also read the "Instructions for Use" included at the end of this Patient Medication Information. A copy of the "Instructions for Use" is also included in the product packaging. These instructions will give you details on how to use and inject BYDUREON BCise.

Use BYDUREON BCise exactly as instructed by your doctor. Never take more than the dose your doctor has told you to use.

For subcutaneous use only. BYDUREON BCise is to be injected under the skin (subcutaneous injection) of your stomach area (abdomen), upper leg (thigh), or upper arm. If you inject in the same body part, you should choose a different spot each week.

Look at the solution prior to using BYDUREON BCise. The solution should be cloudy and evenly mixed, and not have any white medicine visible on the bottom, top, or sides of the autoinjector window. After BYDUREON BCise is evenly suspended in the diluent, it should be injected right away.

BYDUREON BCise must not be injected into a vein or muscle.

Do not share BYDUREON BCise with another person.

Do not mix BYDUREON BCise with any other medicines.

If you stop taking BYDUREON BCise, tell your healthcare professional. Do not start taking other drugs, vitamins, mineral supplements or alternative medicines on your own. This includes other drugs to treat diabetes. BYDUREON BCise drug levels, effects and side effects will slowly go down in your body. This continues for about 10 weeks after you stop using it.

Usual adult dose:
2 mg subcutaneous injection once every seven days. The dose can be administered at any time of day, with or without meals.

When you first take BYDUREON BCise with a sulfonylurea (SU), your doctor might lower the dose of the SU.

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

If you think you, or a person you are caring for, have taken too much BYDUREON BCise, contact a 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 BCise, 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 BCise at your next usual weekly time. Do not take an extra dose of BYDUREON BCise to make up for your missed dose.

What are possible side effects from using BYDUREON BCise?
These are not all the possible side effects you may have when taking BYDUREON BCise. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:
- nausea
- diarrhea
- vomiting
- injection site reactions such as lumps and itchy skin
- headache

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	
COMMON			
Hypoglycemia (low blood sugar) especially if you are also taking an SU. You may have headaches, feel sleepy, weak, dizzy, confused, hungry, jittery, or sweaty. Feel like your heart is beating fast.	✓		

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	
UNCOMMON			
Pancreatitis (swelling of the pancreas): long periods of pain in the stomach and/or intestine area which 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 BCise 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. This is 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, 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.		✓	
UNKNOWN			
Thrombocytopenia (low blood platelets): bleeding or bruising more easily than normal.			✓

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

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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 BCise flat in a refrigerator at 2°C to 8°C.
- Store BYDUREON BCise in the original packaging in order to protect from light.
- BYDUREON BCise can be stored at room temperature up to 30°C for 4 weeks if required.
- BYDUREON BCise should not be used after the expiration date printed on the product packaging (carton and autoinjector).
- BYDUREON BCise must be discarded after use in a puncture-resistant container.

Keep out of reach and sight of children.

If you want more information about BYDUREON BCise:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website: www.astrazeneca.ca, or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to-date version can be found at www.astrazeneca.ca.

This leaflet was prepared by AstraZeneca Canada Inc., Mississauga, Ontario L4Y 1M4

Last Revised: MAR 02, 2022

Important Instructions for Use, read carefully

How to use PrBYDUREON® BCise™

Exenatide Prolonged-release Injectable Suspension

For subcutaneous use only

Single-dose Autoinjector once weekly

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

Read these instructions before you start using Bydureon BCise 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 BCise is not recommended for people who are blind or cannot see well.

61XXXXY

Open here to begin

Before You Begin

The BYDUREON BCise autoinjector:

- Is a single use, fixed dose autoinjector that automatically injects your medicine.
- Comes in the locked position before you use it. Do not unlock the autoinjector until you are ready to inject it.
- Needle is hidden. You do not see it before, during, or after using the autoinjector.

- **Do not** use the autoinjector if any parts look to be broken or damaged.
- Store flat in the refrigerator between 2˚C to 8˚C.
- Never share your Bydureon BCise autoinjector with anyone else. You may give an infection to them or get an infection from them.
- Bydureon BCise should **not** be used by people who are blind or cannot see well, unless another person who is trained to use this device can help.
- Keep the autoinjector, and all medicines, out of the reach of children.

Before Use

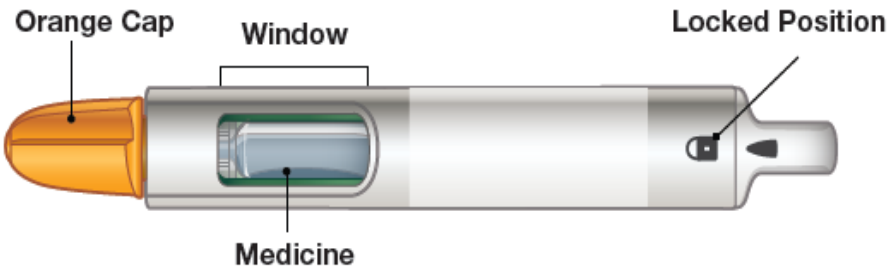


Figure A

Supplies needed to give your injection:

- Bydureon BCise autoinjector • Alcohol swab • A clean, flat surface
- Sharps container (see "disposal" instructions at the end of these instructions)

STEP 1: Prepare for Injection

A. Let your BYDUREON BCise autoinjector come to room temperature.

Remove 1 autoinjector from the refrigerator and rest it flat for 15 minutes.

Autoinjector can be kept at room temperature for up to 4 weeks.

Figure B

B. Check the expiration date (labeled EXP) printed on the autoinjector label.

Do not use the autoinjector past the expiration date.

Figure C

C. Wash your hands.

D. Choose your injection site.

In either your stomach, thigh, or back of the upper arm, see Figure D.

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

Clean the area with an alcohol swab.

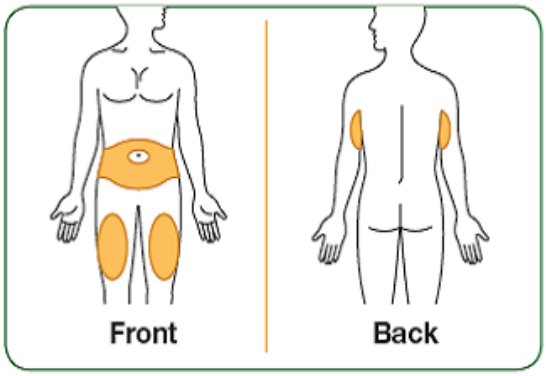


Figure D

STEP 2: Mix the medicine

A. Look in the window.
You may see white medicine along the sides, bottom or top. This means the medicine is not mixed evenly.

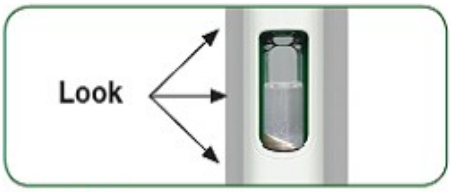


Figure E

B. Shake the BYDUREON BCise autoinjector hard, in an up-and-down motion, until the medicine is mixed evenly and you do not see any white medicine along the sides, bottom or top. Shake for at least 15 seconds.

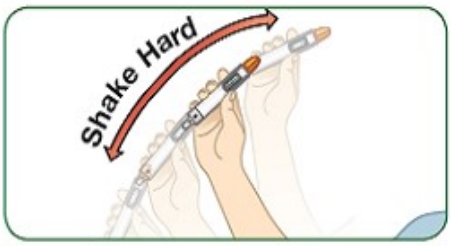


Figure F

C. Check the mix.
Hold the autoinjector up to the light and look through both sides and the bottom of the window. If not mixed well, repeat Step 2 and check again.

Figure G

Figure H

STOP

Do not go to the next step unless your medicine is mixed well.
To get a full dose, the medicine must be mixed well and look cloudy.
If not mixed well, continue to shake hard.

STEP 3: Prepare the BYDUREON BCise Autoinjector

Important: After the medicine is fully mixed, you must complete the preparation steps **right away**, and inject to get the full dose. Do not save it to use later.

Only unlock the autoinjector when you are ready to inject

A. Unlock the autoinjector.

Hold the autoinjector up straight with the orange cap toward the ceiling. Turn the knob from the Lock to the Unlock position until you hear a click.

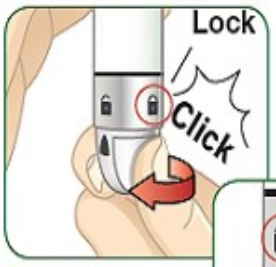


Figure I

Figure J

B. While still holding the autoinjector straight up, firmly unscrew the orange cap.

- You may need to turn the cap a few times before it loosens (if you hear clicking you are turning in the wrong direction).
- Continue holding the autoinjector upright to prevent the medicine from accidently leaking.
- A green shield will pop up after the cap is removed. The green shield hides the needle.

It is normal to see a few drops of liquid inside the cap. **Do not** recap the autoinjector.

Throw away the cap.

Hold **upright** & **firmly** unscrew

Figure K

Figure L

Removed Cap

Figure M

Green shield **pops** up

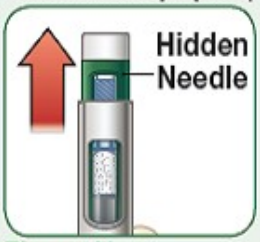


Figure N

STEP 4: Inject the Dose

A. Inject and hold:

- DO NOT inject through clothing. Lift or remove clothing.
- Push the BYDUREON BCise autoinjector against your skin. You will hear a "click" when the injection begins.
- Keep holding the autoinjector against the skin for 15 seconds. This is to make sure you get the full dose.

Figure O

B. Make sure you received your full dose.

After you receive your injection, you will see an orange rod in the window. After you lift the autoinjector from your skin, the green shield will move back up to lock over the needle. See the Common Questions & Answers for what to do if you do not see the orange rod in the window after injection.

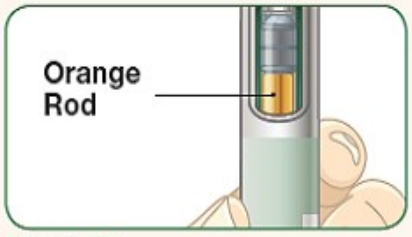


Figure P

STEP 4: Inject the Dose (continued)

C. Disposal.

Be careful when discarding the BYDUREON BCise autoinjector after use. Do not throw away your used autoinjector in your household trash or recycling bins.

Figure Q

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

See "Common Questions & Answers" for additional disposal information.

Common Questions and Answers

1. Where is the needle?

The needle is attached to the BYDUREON BCise autoinjector and covered by the orange cap. When you unscrew the orange cap, the green shield keeps the needle covered until you inject.

For more information, please see Figure N in Step 3B in the Instructions for Use.

2. How do I know if the medicine is fully mixed?

After shaking the autoinjector, look through both sides of the window. You should not see any white medicine along the bottom, top, or sides. If you see white medicine, it is unmixed. To mix, shake the autoinjector hard until the white medicine is no longer on the bottom, top, or sides. The medicine should look even throughout.

3. Why do I need to hold the BYDUREON BCise autoinjector upright while removing the orange cap?

Holding the autoinjector with the orange cap straight up helps prevent the medicine from leaking. It is normal to see a few drops of medicine inside the orange cap after you unscrew it.

4. Why should I inject my medicine right away after mixing it?

If you do not inject your medicine right away after mixing, the medicine may separate, and you will not get your full dose. You can re-mix your medicine if your autoinjector is in the locked position. However, after you unlock it, you must complete the preparation steps right away and inject to get the full dose. You cannot save it for later use.

Common Questions and Answers (continued)

5. How do I know I gave myself the full dose of medicine?

To be sure you get your full dose, press and hold the BYDUREON BCise autoinjector against your skin.

You will feel the needle go into your skin. Hold the needle against your skin for 15 seconds. This will allow enough time for all the medicine to go from the autoinjector to under your skin. After removing the needle, look for the orange rod in the window as a way to tell that the dose has been given. If the orange rod does not appear contact Medical Information at 1-800-668-6000.

6. Why should I store my autoinjectors flat in the refrigerator?

Autoinjectors stored vertically (with the needle up or down) are more difficult to mix. The medicine can still be fully mixed but it will take more shaking and more time.

7. What if I don't have a sharps disposal container?

Do not throw away (dispose of) the autoinjector in your household trash. Ask your healthcare provider about options available in your area to dispose of your autoinjector. Follow local, healthcare provider or institutional policies to dispose of your autoinjector.

Common Questions and Answers (continued)

8. What if the BYDUREON BCise device malfunctions and I cannot unlock it?

Review the Instructions for Use Step 3 to confirm the order of operations, then contact Medical Information at 1-800-668-6000 for help as needed. Do not try to unlock with excessive force or tools.

9. What if the BYDUREON BCise device malfunctions and I cannot remove the orange cap?

Review the Instructions for Use Step 3 to confirm the order of operations, also confirm that the knob is fully in the unlocked position, then contact Medical Information at 1-800-668-6000 for help as needed. Do not use tools or try to force the cap off.

10. For other questions about Bydureon BCise:

Questions or concerns: 1-800-668-6000

How to Store Bydureon BCise Autoinjector

- Store flat in the refrigerator between 2°C to 8°C.
- Each autoinjector can be kept at room temperature not to exceed 30°C for no more than a total of 4 weeks, if needed.
- Store in packaging provided to protect from light until you are ready to prepare and use your dose.
- Do not use past the expiration date. The expiration date is labeled EXP.
- Keep the autoinjector clean and away from spills.

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