HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BYDUREON BCISE safely and effectively. See full prescribing information for BYDUREON BCISE.

BYDUREON BCISE® (exenatide) extended-release injectable suspension, for subcutaneous use
Initial U.S. Approval: 2005

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- **Exenatide extended-release causes thyroid C-cell tumors at clinically relevant exposures in rats. It is unknown whether BYDUREON BCISE causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors has not been determined. (5.1, 13.1)**
- **BYDUREON BCISE is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors. (4, 5.1)**

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

Warnings and Precautions, Pulmonary Aspiration During General Anesthesia or Deep Sedation (5.11)	11/2024

---------- INDICATIONS AND USAGE ----------

BYDUREON BCISE is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus. (1)

Limitations of Use:
- Coadministration with other exenatide-containing products is not recommended. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Administer 2 mg by subcutaneous injection once every seven days (weekly), at any time of day and with or without meals. (2.1)
- Administer immediately after the dose is prepared. See full prescribing information for additional administration instructions. (2.2)

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

Extended-release injectable suspension: 2 mg of exenatide in a 0.85 mL single-dose autoinjector. (3)

---------- CONTRAINDICATIONS ----------
- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2. (4)
- Prior serious hypersensitivity reaction to exenatide or any of the product components. (4)
- History of drug-induced immune-mediated thrombocytopenia from exenatide products. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Acute Pancreatitis: Has been observed in patients treated with GLP-1 receptor agonists, including BYDUREON BCISE. Discontinue if pancreatitis is suspected. (5.2)
- Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin: Patients taking an insulin secretagogue or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. Reduction in the dose of insulin secretagogues or insulin may be necessary. (5.3)
- Acute Kidney Injury Due to Volume Depletion: Monitor renal function in patients reporting adverse reactions that could lead to volume depletion. (5.4)
- Severe Gastrointestinal Adverse Reactions: Use has been associated with gastrointestinal adverse reactions, sometimes severe. BYDUREON BCISE is not recommended in patients with severe gastroparesis. (5.5)
- Immunogenicity-Associated Decreased Glycemic Control: Patients may develop antibodies to exenatide. If there is worsening glycemic control or failure to achieve target glycemic control, consider alternative antidiabetic therapy. (5.6)
- Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) have been reported. Discontinue BYDUREON BCISE and promptly seek medical advice. (5.7)
- Drug-induced Immune-mediated Thrombocytopenia: Serious bleeding which may be fatal has been reported. Discontinue BYDUREON BCISE promptly and avoid re-exposure to exenatide. (5.8)
- Serious Injection-site Reactions: Serious injection-site reactions with or without subcutaneous nodules have been reported. (5.9)
- Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated. (5.10)
- Pulmonary Aspiration During General Anesthesia or Deep Sedation: Has been reported in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures. Instruct patients to inform healthcare providers of any planned surgeries or procedures. (5.11)

---------- ADVERSE REACTIONS ----------

Most common (≥5%) in clinical trials: injection-site nodule, nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 and www.bydureonbcise.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------
- May impact absorption of orally administered medications. (7)
- Warfarin: Postmarketing reports with exenatide of increased international normalized ratio (INR) sometimes associated with bleeding. Monitor INR frequently until stable upon initiation of BYDUREON BCISE therapy. (7)

---------- USE IN SPECIFIC POPULATIONS ----------

Pregnancy: Use during pregnancy only if the potential benefit justifies the risk to the fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

- **Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether BYDUREON BCISE causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.**
- **BYDUREON BCISE is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of BYDUREON BCISE and inform them of symptoms of thyroid tumors (e.g., mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for detection of MTC in patients treated with BYDUREON BCISE *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

BYDUREON BCISE is indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus.

Limitations of Use

- BYDUREON BCISE contains exenatide. Coadministration with other exenatide-containing products is not recommended.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- The recommended dosage of BYDUREON BCISE is 2 mg subcutaneously once every 7 days (weekly). The dose can be administered at any time of day, with or without meals.
- Discontinue an immediate- or extended-release exenatide product prior to initiation of BYDUREON BCISE. Patients changing from another extended-release exenatide product to BYDUREON BCISE may do so at the next regularly scheduled dose. Patients changing from immediate-release exenatide to BYDUREON BCISE may experience transient (approximately 2 to 4 weeks) elevations in blood glucose concentrations.
- The day of weekly administration can be changed if necessary, as long as the last dose was administered 3 or more days before the new day of administration.

Recommendations Regarding Missed Dose

- If a dose is missed, administer the dose as soon as noticed, provided the next regularly scheduled dose is due at least 3 days later. Thereafter, administer subsequent doses once every 7 days (weekly).

- If a dose is missed and the next regularly scheduled dose is due 1 or 2 days later, do not administer the missed dose and instead resume BYDUREON BCISE with the next regularly scheduled dose.

2.2 Administration Instructions

- Prior to initiation, train patients and caregivers on proper mixing and injection *[see Instructions for Use]*. Instruct caregivers to assist pediatric patients with mixing and administration.
- Remove the autoinjector from the refrigerator 15 minutes prior to mixing the injection, in order to reach room temperature.
- Mix by shaking vigorously for at least 15 seconds.
- Inspect BYDUREON BCISE visually before use. After mixing, BYDUREON BCISE should appear as an opaque, cloudy, white to off-white suspension, evenly mixed with no residual medicine along the side, bottom or top of the inspection window. Do not use if particulate matter is present or if discoloration is observed.
- Administer BYDUREON BCISE immediately after the autoinjector is prepared as a subcutaneous injection in the abdomen, thigh, or upper arm region. Advise patients to use a different injection site each week when injecting in the same region.
- When using BYDUREON BCISE with insulin, instruct patients to administer as separate injections and to never mix the products. It is acceptable to inject BYDUREON BCISE and insulin in the same body region, but the injections should not be adjacent to each other.

3 DOSAGE FORMS AND STRENGTHS

Extended-release injectable suspension: 2 mg of exenatide per 0.85 mL suspension, in a pre-filled single-dose autoinjector. Redispersion by mixing provides a white to off-white, opaque, suspension.

4 CONTRAINDICATIONS

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).
- Prior serious hypersensitivity reaction to exenatide or to any of the excipients of BYDUREON BCISE. Serious hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with exenatide *[see Warnings and Precautions (5.7)]*.
- History of drug-induced immune-mediated thrombocytopenia from exenatide products. Serious bleeding, which may be fatal, from drug-induced immune-mediated thrombocytopenia has been reported with exenatide use *[see Warnings and Precautions (5.8)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-cell Tumors

In both genders of rats, exenatide extended-release caused a dose-related and treatment-duration–dependent increase in the incidence of thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures compared to controls *[see Nonclinical Toxicology (13.1)]*. A statistically significant increase in malignant thyroid C-cell carcinomas was observed in female rats receiving exenatide extended-release at 27-times clinical exposure compared to controls and higher incidences were noted in males above controls in all treated groups at ≥2-times clinical exposure. The potential of exenatide extended-release to induce C-cell tumors in mice has not been evaluated. Other glucagon-like peptide-1 (GLP-1) receptor agonists have also induced thyroid C-cell adenomas and carcinomas in male and female mice and rats at clinically relevant exposures. It is unknown whether BYDUREON BCISE will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of exenatide extended-release–induced rodent thyroid C-cell tumors has not been determined.

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

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

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

5.2 Acute Pancreatitis

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists, including BYDUREON BCISE *[see Adverse Reactions (6)]*. After initiation of BYDUREON BCISE, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, discontinue BYDUREON BCISE and initiate appropriate management.

5.3 Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Patients receiving BYDUREON BCISE in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia *[see Adverse Reactions (6.1) and Drug Interactions (7)]*.

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

5.4 Acute Kidney Injury Due to Volume Depletion

There have been postmarketing reports of acute kidney injury, in some cases requiring hemodialysis, in patients treated with GLP-1 receptor agonists, including BYDUREON BCISE *[see Adverse Reactions (6.2)]*. The majority of the reported events occurred in patients who experienced gastrointestinal reactions leading to dehydration such as nausea, vomiting, or diarrhea *[see Adverse Reactions (6)]*. Monitor renal function in patients reporting adverse reactions to BYDUREON BCISE that could lead to volume depletion, especially when initiating BYDUREON BCISE.

BYDUREON BCISE is not recommended for use in patients with an eGFR below 45 mL/min/1.73 m^2 *[see Use in Specific Populations (8.6)]*.

5.5 Severe Gastrointestinal Adverse Reactions

Use of GLP-1 receptor agonists, including BYDUREON BCISE, has been associated with gastrointestinal adverse reactions, sometimes severe *[see* Adverse Reactions (6)*]*. BYDUREON BCISE is not recommended in patients with severe gastroparesis.

5.6 Immunogenicity-Associated Decreased Glycemic Control

In the 28-week treatment period in Trials 1 and 2 in adult patients with type 2 diabetes mellitus *[see Clinical Studies (14.2)]*, BYDUREON BCISE-treated patients who had high titer anti-exenatide antibodies (defined as ≥625) had a lower glycemic response compared to BYDUREON BCISE-treated patients who did not have anti-exenatide antibodies *[see Clinical Pharmacology (12.6)]*.

In the 24-week treatment period in Trial 9 in pediatric patients with type 2 diabetes mellitus *[see Clinical Studies (14.6)]*, BYDUREON-treated patients who had high titer anti-exenatide antibodies (≥625) appeared to have had a lower glycemic response compared to BYDUREON-treated patients who did not have anti-exenatide antibodies. At Week 24, the mean change in HbA_{1c} from baseline in BYDUREON-treated patients was greater (-0.73%) in those with low titer anti-exenatide antibodies (<625) compared to +0.07% in those with high titer anti-exenatide antibodies *[see Clinical Pharmacology (12.6)]*.

If there is worsening glycemic control or failure to achieve targeted glycemic control, consider stopping BYDUREON BCISE and using alternative antidiabetic therapy.

5.7 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) in patients treated with exenatide. If a hypersensitivity reaction occurs, the patient should discontinue BYDUREON BCISE and promptly seek medical advice *[see Contraindications (4) and Adverse Reactions (6.2)]*. Inform and closely monitor patients with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist for allergic reactions, because it is unknown whether such patients will be predisposed to anaphylaxis with BYDUREON BCISE.

5.8 Drug-Induced Thrombocytopenia

Serious bleeding, which may be fatal, from drug-induced immune-mediated thrombocytopenia has been reported in the postmarketing setting with exenatide use. Drug-induced thrombocytopenia is an immune-mediated reaction with exenatide-dependent anti-platelet antibodies. In the presence of exenatide, these antibodies cause platelet destruction. If drug-induced thrombocytopenia is suspected, discontinue BYDUREON BCISE immediately and do not re-expose the patient to exenatide. Upon discontinuation, thrombocytopenia can persist due to the prolonged exenatide exposure from BYDUREON BCISE (about 10 weeks) *[see Adverse Reactions (6.2)]*.

5.9 Serious Injection-Site Reactions

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

5.10 Acute Gallbladder Disease

Acute events of gallbladder disease, such as cholelithiasis or cholecystitis, have been reported in GLP-1 receptor agonist trials and postmarketing. In the EXSCEL trial *[see Clinical Studies (14.5)]*, 1.9% of BYDUREON-treated patients and 1.4% of placebo-treated patients reported an acute event of gallbladder disease, such as cholelithiasis or cholecystitis. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

5.11 Pulmonary Aspiration During General Anesthesia or Deep Sedation

BYDUREON BCISE delays gastric emptying *[see Clinical Pharmacology (12.2)]*. There have been rare postmarketing reports of pulmonary aspiration in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation who had residual gastric contents despite reported adherence to preoperative fasting recommendations.

Available data are insufficient to inform recommendations to mitigate the risk of pulmonary aspiration during general anesthesia or deep sedation in patients taking BYDUREON BCISE, including whether modifying preoperative fasting recommendations or temporarily discontinuing BYDUREON BCISE could reduce the incidence of retained gastric contents. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking BYDUREON BCISE.

6 ADVERSE REACTIONS

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

- Risk of Thyroid C-cell Tumors *[see Warnings and Precautions (5.1)]*
- Acute Pancreatitis *[see Warnings and Precautions (5.2)]*
- Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin *[see Warnings and Precautions (5.3)]*
- Acute Kidney Injury Due to Volume Depletion *[see Warnings and Precautions (5.4)]*
- Severe Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.5)]*
- Immunogenicity-Associated Decreased Glycemic Control *[see Warnings and Precautions (5.6)]*

- Hypersensitivity Reactions *[see Warnings and Precautions (5.7)]*
- Drug-Induced Thrombocytopenia *[see Warnings and Precautions (5.8)]*
- Serious Injection-Site Reactions *[see Warnings and Precautions (5.9)]*
- Acute Gallbladder Disease *[see Warnings and Precautions (5.10)]*
- Pulmonary Aspiration During General Anesthesia or Deep Sedation [*see Warnings and Precautions (5.11)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in this section are derived from pooled data from the controlled period of the 2 comparator-controlled trials (Trials 1 and 2) in adults as well as data from the extension phase of one of these trials *[see Clinical Studies (14.2)]*. There were 410 patients exposed to BYDUREON BCISE 2 mg for 28 weeks during the controlled phases, and an additional 116 patients exposed to BYDUREON BCISE 2 mg during an uncontrolled extension for an additional 24 weeks. Overall, there were 526 patients exposed to BYDUREON BCISE 2 mg with a mean duration of exposure of 35 weeks in the controlled and extension phases of the two trials. Across the treatment arms in the controlled periods, the mean age of patients was 55 years, 2% were 75 years or older and 59% were male. The population in these studies was 78% White, 15% Black or African American, 5% Asian; 1% American Indian or Alaska Native; <1 % were Native Hawaiian or Pacific Islander; and <1% were other races. This population included 42% of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 8.3 years and had a mean HbA_{1c} of 8.5%. Baseline estimated renal function was normal or mildly impaired (eGFR $\geq$60 mL/min/1.73 m^2) in 93% of the pooled study populations.

The safety of BYDUREON, another formulation of exenatide extended-release, in pediatric patients age 10 to less than 18 years with type 2 diabetes was similar to that observed in the adults *[see Clinical Studies (14.6)]*.

Common Adverse Reactions

Table 1 summarizes the adverse reactions with an incidence ≥5% occurring in BYDUREON BCISE-treated adult patients in the pooled data from the controlled and extension phases, including 10 weeks of follow-up, of the two comparator-controlled 28-week clinical trials. Adverse reactions were identified based on known adverse reactions associated with BYDUREON.

Table 1: Adverse Reactions Reported in ≥5% of BYDUREON BCISE-Treated Patients from Pooled Clinical Trial Data in Patients with Type 2 Diabetes Mellitus (Trials 1 and 2)

	BYDUREON BCISE 2 mg N=526 %
Injection site nodule	10.5
Nausea	8.2

Note: Percentages are based on the number of patients who were randomized and received at least one dose of BYDUREON BCISE.

Nausea was a common adverse reaction associated with initiation of treatment with BYDUREON BCISE and usually decreased over time with continued use. The incidence of nausea and/or vomiting was 2% in the first week of therapy compared to 1% in the 4th week of therapy.

Less Common Adverse Reactions

Adverse reactions that occurred in >2% and <5% of adult patients receiving BYDUREON BCISE during the controlled and extension phases, including 10 weeks of follow-up, of the two comparator-controlled 28-week clinical trials include: headache (4.4%), diarrhea (4.0%), vomiting (3.4%), injection site pruritus (3.2%), dizziness (2.5%), injection site erythema (2.3%), constipation (2.1%).

Adverse Reactions Leading to Discontinuation of Therapy

The incidence of discontinuation of therapy due to adverse reactions was 3.9% for BYDUREON BCISE-treated patients in the two comparator-controlled 28-week trials in adults. The most common classes of adverse reactions leading to discontinuation of therapy for BYDUREON BCISE-treated patients were Gastrointestinal Disorders 2.0% and General Disorders and Administration Site Conditions 1.2%. For BYDUREON BCISE-treated patients, the most frequent adverse reactions leading to discontinuation of therapy within each of these respective classes were diarrhea (0.7%), nausea (0.7%), vomiting (0.5%) and injection-site nodule (0.5%).

Hypoglycemia

Table 2 summarizes the incidence of glucose level <54 mg/dL regardless of hypoglycemia clinical symptoms and the incidence of severe hypoglycemia in the two comparator-controlled 28-week trials of BYDUREON BCISE in adults.

Table 2: Incidence (% of Subjects) of Hypoglycemia (glucose <54 mg/dL) and Severe Hypoglycemia in Clinical Trials in Patients with Type 2 Diabetes Mellitus

Incidence of Hypoglycemia (glucose <54 mg/dL)	
Mono- or Combination Therapy with One or Two OADs Trial (28 weeks)	
With Concomitant Sulfonylurea Use	
BYDUREON BCISE 2 mg (N=88)	25%
Without Concomitant Sulfonylurea Use	
BYDUREON BCISE 2 mg (N=141)	2.1%
Add-On to Metformin Trial (28 weeks)	
All treated subjects	
BYDUREON BCISE 2 mg (N=181)	0.0%
Incidence of Severe Hypoglycemia	
Mono- or Combination Therapy with One or Two OADs Trial (28 weeks)	
With Concomitant Sulfonylurea Use	
BYDUREON BCISE 2 mg (N=88)	2.3%
Without Concomitant Sulfonylurea Use	
BYDUREON BCISE 2 mg (N=141)	0.7%
Add-On to Metformin Trial (28 weeks)	
All treated subjects	
BYDUREON BCISE 2 mg (N=181)	0.0%

Note: N and percentages are based on the number of patients who were randomized and received at least one dose of BYDUREON BCISE.

Severe hypoglycemia was defined as clinical symptoms that were considered to result from hypoglycemia in which the patient required the assistance of another person and associated with recovery after oral carbohydrates, intravenous glucose or glucagon administration if no plasma glucose was available.

In the 24-week pediatric placebo-controlled clinical trial *[see Clinical Studies (14.6)]*, 2 (3.4%) of BYDUREON-treated patients with type 2 diabetes had hypoglycemia with a blood glucose <54 mg/dL with or without symptoms and 1 (1.7%) had severe hypoglycemia (defined as an episode with severe cognitive impairment requiring external assistance for recovery.

Injection-Site Adverse Reactions Including Nodules

In the two comparator-controlled 28-week trials in adults, injection site reactions (including injection site nodule, injection site pruritus, injection site bruising) were observed in 23.9% of patients treated with BYDUREON BCISE.

Immunogenicity: Anti-Drug Antibody-Associated Adverse Reactions

Injection site reactions for BYDUREON BCISE-treated patients were more commonly observed in those with high titer anti-exenatide antibodies (≥625) (27%) compared to those with low titer anti-exenatide antibodies (<625) (16%) or those who did not develop anti-exenatide antibodies (16%) *[see Clinical Pharmacology (12.6)]*.

Increase in Heart Rate

In clinical trials of BYDUREON BCISE in adults, the mean increase from baseline in heart rate was 2.4 beats per minute.

Acute Pancreatitis

In clinical trials of BYDUREON BCISE acute pancreatitis occurred in 0.4% of patients.

Cholelithiasis and cholecystitis

In the EXSCEL trial *[see Clinical Studies (14.5)],* 1.9% of BYDUREON-treated patients and 1.4% of placebo-treated patients reported an acute event of gallbladder disease, such as cholelithiasis or cholecystitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of BYDUREON BCISE or other formulations of exenatide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal

Blood: Drug-induced thrombocytopenia.

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

Gastrointestinal: Nausea, vomiting, and/or diarrhea resulting in dehydration; abdominal distension, abdominal pain, eructation, constipation, flatulence, ileus, acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death.

Hepatobiliary: Cholecystitis, cholelithiasis requiring cholecystectomy.

Hypersensitivity: Injection-site reactions (e.g., abscess, cellulitis, and necrosis, with or without subcutaneous nodules), generalized pruritus and/or urticaria, macular or papular rash, angioedema; anaphylactic reaction.

Neurologic: Dysgeusia, somnolence, dysesthesia.

Pulmonary: Pulmonary aspiration has occurred in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation.

Renal: Altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure or acute renal failure (sometimes requiring hemodialysis), kidney transplant and kidney transplant dysfunction.

Skin and Subcutaneous Tissue: Alopecia.

7 DRUG INTERACTIONS

Table 3: Clinically Relevant Interactions with BYDUREON BCISE

Concomitant Use of Insulin Secretagogues or Insulin	
Clinical Impact	Exenatide promotes insulin release from pancreatic beta-cells in the presence of elevated glucose concentrations. The risk of hypoglycemia is increased when exenatide is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin *[see Adverse Reactions (6.1)]*.
Intervention	When initiating BYDUREON BCISE, consider reducing the dose of concomitantly administered insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Warfarin	
Clinical Impact	BYDUREON BCISE has not been studied with warfarin. However, in a drug interaction study, BYETTA did not have a significant effect on INR *[see Clinical Pharmacology (12.3)]*. There have been postmarketing reports for exenatide of increased INR with concomitant use of warfarin, sometimes associated with bleeding *[see Adverse Reactions (6.2)]*.
Intervention	In patients taking warfarin, the INR should be monitored more frequently after initiating BYDUREON BCISE. Once a stable INR has been documented, the INR can be monitored at the intervals recommended for patients taking warfarin.
Orally Administered Drugs (e.g., acetaminophen)	
Clinical Impact	Exenatide slows gastric emptying. Therefore, BYDUREON BCISE has the potential to reduce the rate of absorption of orally administered drugs *[see Clinical Pharmacology (12.3)]*.
Intervention	Use caution when administering oral medications with BYDUREON BCISE where a slower rate of oral absorption may be clinically meaningful.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with an HbA_{1c} >7 and has been reported to be as high as 20-25% in women with HbA_{1c} >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryofetal Risk

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

Data

Animal Data

Pregnant rats given subcutaneous doses of 0.3, 1, or 3 mg/kg exenatide extended-release every 3 days during organogenesis had systemic exposures 3-, 8-, and 19-times human exposure, respectively, at the MRHD of 2 mg/week BYDUREON BCISE based on plasma exenatide exposure (AUC) comparison. Reduced fetal growth at all doses and skeletal ossification deficits at 1 and 3 mg/kg occurred at doses that decreased maternal food intake and body weight gain.

In studies evaluating reproduction and development in pregnant mice and rabbits, maternal animals were administered exenatide, the active ingredient in BYDUREON BCISE, by subcutaneous injection twice a

day. Differences in embryofetal developmental toxicity from subcutaneously injected exenatide extended-release and exenatide were not evaluated in mice, rats, or rabbits.

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

In pregnant rabbits given 0.2, 2, 22, 156, or 260 mcg/kg/day exenatide during fetal organogenesis, irregular fetal skeletal ossifications were observed at 2 mcg/kg/day, a dose yielding systemic exposure up to 6-times the human exposure from the MRHD of BYDUREON BCISE based on AUC comparison.

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of exenatide, in human milk, the effects of exenatide on the breastfed infant, or the effects of exenatide on milk production. Exenatide, the active ingredient in BYDUREON BCISE was present in the milk of lactating mice. However, due to species-specific differences in lactation physiology, the clinical relevance of these data is not clear *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for exenatide and any potential adverse effects on the breastfed child from exenatide or from the underlying maternal condition.

Data

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

8.4 Pediatric Use

The safety and effectiveness of BYDUREON BCISE as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus have been established in pediatric patients aged 10 years and older. Use of BYDUREON BCISE for this indication is supported by a 24-week placebo-controlled trial with BYDUREON with 28-week open-label uncontrolled extension (Trial 9) in 82 pediatric patients 10 years of age and older with type 2 diabetes, a pediatric pharmacokinetic study, and studies in adults with type 2 diabetes mellitus *[see Clinical Pharmacology (12.3) and Clinical Studies (14.2, 14.3, 14.4, 14.6)]*.

Safety and effectiveness of BYDUREON BCISE have not been established in pediatric patients less than 10 years of age.

8.5 Geriatric Use

In two comparator-controlled 28-week trials, BYDUREON BCISE was studied in 74 patients (18%) who were at least 65 years of age and 10 (2.4%) patients who were at least 75 years of age. In these studies, no meaningful differences in safety and effectiveness were observed between patients ≥65 years of age and younger adult patients, but these studies did not include sufficient numbers of patients ≥75 years of age to determine whether they respond differently from younger adult patients.

In a large cardiovascular outcomes trial *[see Clinical Studies (14.5)]*, BYDUREON was studied in 2,959 patients (40%) who were at least 65 years old and of those, 605 patients (8%) were at least 75 years old.

Use caution when initiating BYDUREON BCISE in geriatric patients because they are more likely to have decreased kidney function *[see Use in Specific Populations (8.6)]*.

8.6 Renal Impairment

Pharmacokinetic studies of adult patients with renal impairment who received BYDUREON BCISE indicate that there is an increase in exenatide exposure in those with mild and moderate renal impairment as compared to patients with normal kidney function. BYDUREON BCISE may induce nausea and vomiting with transient hypovolemia and may worsen kidney function in patients with renal impairment.

Monitor patients with mild renal impairment for adverse reactions that may lead to hypovolemia. BYDUREON BCISE is not recommended for use in patients with eGFR below 45 mL/min/1.73 m^2 or end-stage renal disease. If BYDUREON BCISE is used in patients with renal transplantation, closely monitor for adverse reactions that may lead to hypovolemia *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Effects of overdoses with BYETTA, another exenatide product, included severe nausea, severe vomiting, and rapidly declining blood glucose concentrations, including severe hypoglycemia requiring parenteral glucose administration. In the event of overdose, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations. Initiate appropriate supportive treatment according to the patient's clinical signs and symptoms.

11 DESCRIPTION

BYDUREON BCISE (exenatide) extended-release injectable suspension is a GLP-1 receptor agonist supplied as a sterile suspension of exenatide extended-release microspheres in an oil-based vehicle of medium chain triglycerides (MCT), in a single-dose autoinjector. Redispersion by mixing provides a white to off-white, opaque, suspension to be administered by subcutaneous injection. Each autoinjector contains sufficient suspension to deliver 2 mg of exenatide extended-release in a volume of 0.85 mL.

Exenatide is a 39-amino acid synthetic peptide amide with an empirical formula of $C_{184}H_{282}N_{50}O_{60}S$ and a molecular weight of 4186.6 Daltons. The amino acid sequence for exenatide is shown below.

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

Exenatide is incorporated in an extended-release microsphere formulation containing the 50:50 poly (D,L-lactide-co-glycolide) polymer (37.2 mg per dose) along with sucrose (0.8 mg per dose), suspended in the vehicle, MCT (774.4 mg per dose).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

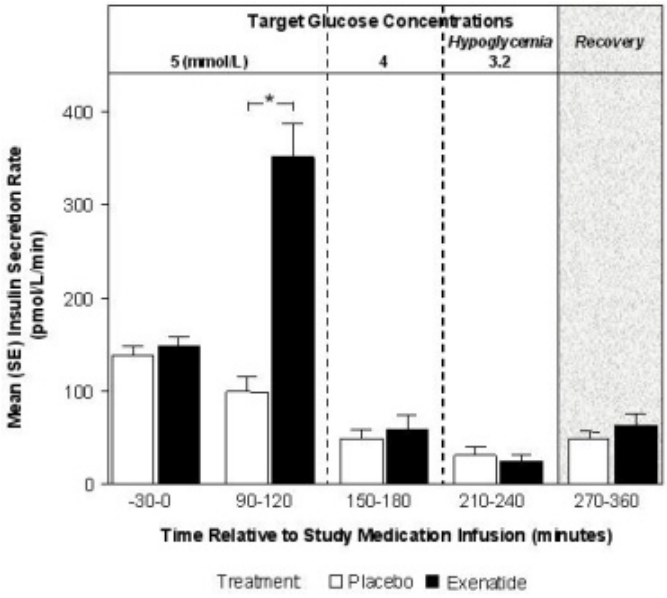
12.2 Pharmacodynamics

Exenatide improves glycemic control through the actions described below.

Glucose-Dependent Insulin Secretion

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

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



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

Glucagon Secretion

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

Gastric Emptying

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

Fasting and Postprandial Glucose

In a 12-week clinical pharmacology study of exenatide microspheres suspended in MCT-oil in adults with type 2 diabetes mellitus, reductions in fasting plasma glucose were evident after 2 weeks of treatment, and after 12 weeks resulted in a reduction of fasting plasma glucose concentrations of -40.4 mg/dL, when compared to placebo.

In a clinical study of BYDUREON BCISE, 2-hour postprandial glucose levels were measured at Week 16, during a mixed meal tolerance test, in a subset of patients with type 2 diabetes mellitus. The mean change from baseline was −78 mg/dL.

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

Absorption

Following a single subcutaneous dose of exenatide microspheres suspended in MCT-oil, 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 plasma exenatide concentration at around Week 6 to Week 7 representing the hydration and erosion of the microspheres.

Following initiation of once every 7 days (weekly) administration of 2 mg BYDUREON BCISE, a gradual increase in the plasma exenatide concentration is observed up to approximately Week 10. From Week 10 mean plasma 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 BYETTA is 28.3 L and is expected to remain unchanged for BYDUREON BCISE.

Metabolism

Elimination

Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/hour and is independent of the dose. Approximately 10 weeks after discontinuation of BYDUREON BCISE therapy, plasma exenatide concentrations generally fall below the minimal quantifiable concentration of 20 pg/mL.

Specific Populations

Patients with Renal Impairment

BYDUREON BCISE has not been studied in patients with severe renal impairment (CrCL <30 mL/min, eGFR <30 mL/min/1.73m^2) or end-stage renal disease receiving dialysis. Pharmacokinetic analysis of patients receiving 2 mg BYDUREON BCISE indicated that there was a 28% and 69% higher systemic exposure to exenatide in patients with mild (N=96) or moderate (N=24) renal impairment, respectively, as compared to patients with normal renal function (N=70) *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)]*. In a study of BYETTA in subjects with end-stage renal disease receiving

dialysis, mean exenatide exposure increased by 3.4-fold compared to that of subjects with normal renal function *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

BYDUREON BCISE has not been studied in patients with acute or chronic hepatic impairment.

Age, Male and Female Patients, Race or Ethnic Groups, and Body Weight

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

Pediatric Patients

The pharmacokinetics of BYDUREON BCISE has not been studied in pediatric patients *[see Use in Specific Populations (8.4)]*. The clinical pharmacology of BYDUREON, another formulation of exenatide extended-release, has been evaluated in the population pharmacokinetic study in adolescent patients with type 2 diabetes mellitus between age 11 and age less than 18 years old. The pharmacokinetic profile of BYDUREON in the pediatric population is consistent with that of BYDUREON and BYDUREON BCISE in adults. The pharmacokinetic behavior of BYDUREON BCISE is expected to be consistent with that of BYDUREON in adolescent patients.

Drug Interaction Studies

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

Acetaminophen

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

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

Warfarin

Administration of warfarin (25 mg) 35 minutes after repeated doses of BYETTA (5 mcg twice daily on days 1-2 and 10 mcg twice daily on days 3-9) in healthy volunteers delayed warfarin T_{max} by approximately 2 hours. No clinically relevant effects on C_{max} or AUC of *S*- and *R*-enantiomers of warfarin were observed. BYETTA did not significantly alter the pharmacodynamic properties (e.g., international normalized ratio) of warfarin *[see Drug Interactions (7)]*.

Digoxin

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

Lovastatin

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

Lisinopril

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

Oral Contraceptives

The effect of BYETTA (10 mcg twice daily) on single and on multiple doses of a combination oral contraceptive (30 mcg ethinyl estradiol plus 150 mcg levonorgestrel) was studied in healthy female subjects. Repeated daily doses of the oral contraceptive (OC) given 30 minutes after BYETTA administration decreased the C_{max} of ethinyl estradiol and levonorgestrel by 45% and 27%, respectively, and delayed the T_{max} of ethinyl estradiol and levonorgestrel by 3.0 hours and 3.5 hours, respectively, as compared to the oral contraceptive administered alone. Administration of repeated daily doses of the OC one hour prior to BYETTA administration decreased the mean C_{max} of ethinyl estradiol by 15%, but the mean C_{max} of levonorgestrel was not significantly changed as compared to when the OC was given alone. BYETTA did not alter the mean trough concentrations of levonorgestrel after repeated daily dosing of the oral contraceptive for both regimens. However, the mean trough concentration of ethinyl estradiol was increased by 20% when the OC was administered 30 minutes after BYETTA administration injection as compared to when the OC was given alone. The effect of BYETTA on OC pharmacokinetics is confounded by the possible food effect on OC in this study *[see Drug Interactions (7)]*.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of BYDUREON BCISE or of other exenatide products.

Immunogenicity of BYDUREON BCISE in Adult Patients

Anti-exenatide antibodies were measured at prespecified intervals in the two controlled studies of BYDUREON BCISE in adults with type 2 diabetes mellitus (Trials 1 and 2) *[see Clinical Studies (14.2)]*. During the 28-week treatment period in these trials, 125/393 (32%) of the BYDUREON BCISE-treated

patients with evaluable anti-exenatide antibody measurements developed high titer antibodies (high titer was defined as ≥625). BYDUREON BCISE-treated patients that had higher titer antibodies had a lower glycemic response compared to BYDUREON BCISE-treated patients who did not have anti-exenatide antibodies during the treatment period *[see Warnings and Precautions (5.6)]*. The percentage of BYDUREON BCISE-treated patients with positive antibody titers peaked at approximately Weeks 8-16 of dosing.

Amongst BYDUREON BCISE-treated patients evaluable for anti-exenatide antibodies (N=393), injection site reactions were more commonly observed in those with high titer anti-exenatide antibodies (≥625) compared to those with low titer anti-exenatide antibodies (<625) or those who did not develop anti-exenatide antibodies [*see Adverse Reactions (6.1)]*. There is insufficient data to assess whether the observed anti-exenatide antibodies in adult patients had an effect on the severity of injection site reactions, or on the incidence or severity of hypersensitivity reactions.

A total of 118 adult patients with high titer anti-exenatide antibodies in BYDUREON BCISE trials were tested for the presence of cross-reactive antibodies to GLP-1 and/or glucagon and one patient (0.8%) developed cross-reactive antibodies to GLP-1 and/or glucagon.

Immunogenicity of BYDUREON in Pediatric Patients

In a 52-week BYDUREON trial (24-week controlled and 28-week extended treatment period) for the improvement of glycemic control in pediatric patients with type 2 diabetes mellitus (Trial 9) *[see Clinical Studies (14.6)]*, 37/58 (64%) of BYDUREON-treated patients had high titer anti-exenatide antibodies (high titer was defined as ≥625) at any time during the study. In this trial, 60% of these patients had a peak high-titers at approximately Week 12. BYDUREON-treated pediatric patients that had high titer anti-exenatide antibodies appeared to have had a lower glycemic response compared to BYDUREON-treated pediatric patients who did not have anti-exenatide antibodies during this trial [*see Warnings and Precautions (5.6)]*.

There is insufficient data to assess whether the observed anti-exenatide antibodies in pediatric patients had an effect on the incidence or severity of hypersensitivity reactions or injection site reactions.

The potential for development of antibodies cross-reactive with endogenous GLP-1 and glucagon has not been evaluated in BYDUREON-treated pediatric patients.

Anti-Drug Antibody Effects on Pharmacokinetics in Adult and Pediatric Patients

The percentage of exenatide-treated adult and pediatric patients (age ≥11 years) with high anti-exenatide antibody titers (≥625) that had steady state exenatide plasma concentrations below limit of quantitation was higher than in those with low anti-exenatide antibody titers (<625).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

A 2-year carcinogenicity study was conducted with exenatide extended-release, the active component of BYDUREON BCISE, in male and female rats at doses of 0.3, 1.0, and 3.0 mg/kg (2-, 10-, and 27-times human systemic exposure at the maximum recommended human dose (MRHD) of 2 mg/week. BYDUREON BCISE based on plasma exenatide AUC, respectively) administered by subcutaneous injection every other week. In this study there was an increased incidence of C-cell adenomas and C-cell carcinomas at all doses. An increase in benign fibromas was seen in the skin subcutis at injection sites of males given 3 mg/kg. No treatment-related injection-site fibrosarcomas were observed at any dose. The human relevance of these findings is currently unknown.

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

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

In mouse fertility studies with exenatide, the active ingredient in BYDUREON BCISE, at twice-daily subcutaneous doses of 6, 68, or 760 mcg/kg/day, males were treated for 4 weeks prior to and throughout mating, and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 760 mcg/kg/day, a systemic exposure 163-times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

BYDUREON BCISE has been studied in adult patients with type 2 diabetes mellitus as monotherapy and in combination with metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione *[see Clinical Studies (14.2)]*.

The effectiveness of BYDUREON BCISE as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus was also supported by adequate and well-controlled studies of BYDUREON, another extended-release exenatide product, in adult and pediatric patients aged 10 years and older with type 2 diabetes mellitus *[see Clinical Studies (14.3, 14.4, 14.6)]*.

Cardiovascular (CV) outcomes were studied in the EXSCEL trial that enrolled adult patients with type 2 diabetes mellitus and multiple risk factors for CV disease or established CV disease *[see Clinical Studies (14.5)]*.

14.2 BYDUREON BCISE Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus

BYDUREON BCISE versus BYETTA, Both as Monotherapy or as Add-on to Metformin, a Sulfonylurea, a Thiazolidinedione, or Combination of Oral Agents

A 28-week, randomized, open-label comparator-controlled trial was conducted to compare the safety and efficacy of BYDUREON BCISE to BYETTA in adult patients with type 2 diabetes and inadequate glycemic control with diet and exercise alone or with oral antidiabetic therapy, including metformin, a sulfonylurea, a thiazolidinedione, or a combination of any two of these therapies (Trial 1 -

NCT01652716). Patients were randomly assigned to receive BYDUREON BCISE 2 mg given subcutaneously once every 7 days (weekly) (n=229) or BYETTA (10 mcg twice daily) (n=146), in addition to existing oral antidiabetic agents. Patients assigned to BYETTA initiated treatment with 5 mcg twice daily then increased the dosage to 10 mcg twice daily after 4 weeks.

A total of 375 adult patients were studied: 278 (74%) were White, 61 (16%) were Black or African American, 25 (7%) were of Asian ethnicity, 5 (1%) were listed as other, 5 (1%) were American Indian or Alaska Native, and 1 (<1%) was Native Hawaiian or Other Pacific Islander. 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 HbA_{1c} was 8.5%.

The primary endpoint was change in HbA_{1c} from baseline to Week 28.

Efficacy Results:

The results for the primary endpoint at Week 28 are summarized in Table 4. Treatment with BYDUREON BCISE 2 mg once weekly (QW) resulted in a statistically significantly greater reduction in HbA_{1c} compared to BYETTA 10 mcg twice daily. The mean reduction in HbA_{1c} was non-inferior compared with BYETTA 10 mcg twice daily at the pre-specified non-inferiority margin +0.4% in this study. BYDUREON BCISE 2 mg QW was statistically superior to BYETTA 10 mcg twice daily (ANCOVA p-value=0.0032).

The proportions of subjects achieving HbA_{1c} <7.0% at Week 28 were 40% in BYDUREON BCISE group compared to 38% in BYETTA group. Subjects with missing values at Week 28 counted as non-responders. The mean changes from baseline to Week 28 for fasting plasma glucose were -36 mg/dL and -27 mg/dL for BYDUREON BCISE and BYETTA, respectively, and for body weight were -1.4 kg and -1.9 kg for BYDUREON BCISE and BYETTA, respectively.

Table 4: 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 in Adult Patients with Type 2 Diabetes Mellitus (Trial 1)

	BYDUREON BCISE 2 mg QW	**BYETTA 10 mcg twice daily***
Intent-to-Treat Population (N)	229	146
HbA_{1c} (%)		
Mean Baseline	8.5	8.5
Mean Change at Week 28	-1.39	-1.03
Difference from BYETTA* [95% CI]	-0.36† (-0.66, -0.14)	

N = number of patients in each treatment group, CI = unadjusted confidence interval, QW = once weekly.

* Least squares means were obtained using an Analysis of Covariance (ANCOVA) model with treatment, baseline HbA_{1c}, baseline HbA_{1c} stratum (<9% or ≥9%), diabetes management method at screening (diet/exercise alone, SU use, or non-SU use), and renal function (normal, mild, or moderate renal impairment) in the population included subjects discontinued treatment before 28 weeks regardless of initiation of rescue medicine.

† p-value <0.01

BYDUREON BCISE versus Sitagliptin and Placebo, All as Add-on to Metformin Therapy

A 28-week open-label (oral medication blinded), comparator- and placebo-controlled trial was conducted to compare the safety and efficacy of BYDUREON BCISE to sitagliptin and placebo in adult patients with type 2 diabetes whose glycemic control was inadequate with metformin therapy (Trial 2 - NCT01652729). Patients were randomly assigned to receive BYDUREON BCISE 2 mg given subcutaneously once every 7 days (weekly) (n=181), sitagliptin 100 mg/day (n=122) or placebo (n=61), in addition to their existing metformin therapy.

A total of 364 adult patients were studied, 296 (81%) were White, 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 HbA_{1c} was 8.5%.

The primary endpoint was change in HbA_{1c} from baseline to Week 28.

Efficacy Results:

Results for the primary endpoint at 28 weeks are summarized in Table 5. In this study, treatment with BYDUREON BCISE 2 mg once weekly resulted in a statistically significant mean reduction in HbA_{1c} compared to placebo. BYDUREON BCISE 2 mg was statistically superior to placebo (ANCOVA p-value=0.02).
The proportions of subjects who achieved an HbA_{1c} <7.0% at Week 28 were 41%, 31%, and 26% in BYDUREON BCISE, Sitagliptin and Placebo groups, respectively. Subjects with missing values at Week 28 counted as non-responders. The mean changes from baseline to Week 28 for fasting plasma glucose were -24 mg/dL, -19 mg/dL and -1 mg/dL for BYDUREON BCISE, Sitagliptin and Placebo, respectively, and for body weight were -1.4 kg, -1.2 kg, and 0.4 kg for BYDUREON BCISE, Sitagliptin and Placebo, respectively.

Table 5: Results of 28-Week Trial of BYDUREON BCISE versus Sitagliptin and Placebo, All as Add-On to Metformin Therapy in Adult Patients with Type 2 Diabetes Mellitus (Trial 2)

	BYDUREON BCISE 2 mg QW	**Sitagliptin 100 mg/day**	**Placebo once daily**
Intent-to-Treat Population (N)	181	122	61
HbA_{1c} (%)			
Mean Baseline	8.4	8.5	8.5
Mean Change at Week 28	-1.07	-0.79	-0.59
Difference from sitagliptin*,† [95% CI]	-0.28 (-0.62, 0.02)		
Difference from placebo* [95% CI]	-0.49 (-0.91, -0.07)‡		

N = number of patients in each treatment group, CI = unadjusted confidence interval, QW = once weekly.
* Least squares means were obtained using an Analysis of Covariance (ANCOVA) model with treatment, baseline HbA_{1c} and baseline HbA_{1c} stratum (<9% or ≥9%) in the population included subjects discontinued treatment before 28 weeks regardless of initiation of rescue medicine.
† Sitagliptin 100 mg/day did not show the superiority to placebo in this study.
‡ p-value <0.05

14.3 BYDUREON Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus - Monotherapy

BYDUREON, another exenatide extended-release product, has been studied as monotherapy in adult patients with type 2 diabetes mellitus.

BYDUREON Monotherapy versus Metformin, Sitagliptin, and Pioglitazone

A 26-week, randomized, comparator-controlled trial was conducted to compare the safety and efficacy of BYDUREON to metformin, sitagliptin, and pioglitazone in patients with type 2 diabetes whose glycemic control was inadequate with diet and exercise (Trial 3 - NCT00676338). Patients were randomly assigned to receive BYDUREON 2 mg given subcutaneously once every seven days (weekly), titrated metformin from 1000 to 2500 mg/day, sitagliptin 100 mg/day or titrated pioglitazone from 30 to 45 mg/day, all dosed according to approved labeling.

A total of 820 patients were studied: 552 (67%) were White, 102 (12%) were East Asian, 71 (9%) were West Asian, 65 (8%) were Hispanic or Latino, 25 (3.0%) were Black or African American, 4 (0.5%) were of Native American ethnicity, and 1 was classified otherwise. The mean baseline HbA_{1c} was 8.5%.

The primary endpoint was change in HbA_{1c} from baseline to Week 26 (or the last value at time of early discontinuation).

Efficacy Results:

Treatment with BYDUREON 2 mg once weekly (QW) resulted in mean HbA_{1c} reduction that was statistically significantly greater compared to sitagliptin 100 mg/day. The mean reduction in HbA_{1c} was non-inferior compared with metformin 1000-2500 mg/day (mean dose 2077 mg/day at study endpoint). Non-inferiority of BYDUREON 2 mg QW to pioglitazone 30-45 mg/day (mean dose 40 mg/day at study endpoint) in reducing HbA_{1c} after 26 weeks of treatment was not demonstrated (the mean change from baseline in HbA_{1c} after 26 weeks was -1.6% with BYDUREON and -1.7% with pioglitazone). The non-inferiority margin was set at +0.3% in this study. The results for the primary endpoint at 26 weeks are summarized in Table 6.

The proportion of patients with a Week 26 value achieving HbA_{1c} of less than 7% at Week 26 were 56%, 52%, 40%, and 55% for BYDUREON, metformin, sitagliptin, and pioglitazone, respectively. Patients who did achieve HbA_{1c} goal <7% and discontinued before Week 26 were not included as responders. The mean changes from baseline to Week 26 for fasting serum glucose
were -41 mg/dL, -36 mg/dL, -20 mg/dL and -46 mg/dL, and for body weight
were -2.0 kg, -2.0 kg, -0.8 kg and +1.5 kg for BYDUREON, metformin, sitagliptin, and pioglitazone, respectively.

Table 6: Results of 26-Week Trial of BYDUREON Monotherapy versus Metformin, Sitagliptin, and Pioglitazone in Patients with Type 2 Diabetes Mellitus (Trial 3)

	BYDUREON 2 mg QW	Metformin 1000-2500 (mean dose 2077) mg/day	Sitagliptin 100 mg/day	Pioglitazone 30-45 (mean dose 40) mg/day
Intent-to-Treat Population (N)	248	246	163	163
HbA_{1c} (%)				
Mean Baseline	8.4	8.6	8.4	8.5
Mean Change at Week 26*	−1.6	−1.5	−1.2	−1.7
Difference from metformin* [Bonferroni-adjusted 98.3% CI]	−0.05 [−0.26, 0.17]			
Difference from sitagliptin* [Bonferroni-adjusted 98.3% CI]	−0.39† [−0.63, −0.16]			
Difference from pioglitazone* [Bonferroni-adjusted 98.3% CI]	0.16 [−0.08, 0.41]			

N = number of patients in each treatment group; mean change is least squares mean change; QW = once weekly.
The primary efficacy analysis was adjusted for multiple comparisons and a two-sided 98.3% confidence interval was utilized to assess difference between treatments.
HbA_{1c} change data at 26 weeks were available from 86%, 87%, 85%, and 82% of the randomized subjects in the BYDUREON, metformin, sitagliptin, and pioglitazone groups, respectively.
* Least squares means were obtained using a mixed model repeated measure analysis with treatment, pooled country, visit, baseline HbA_{1c} value, and treatment by visit interaction as fixed effects, and subject as a random effect.
† $p<0.001$, treatment vs comparator.

14.4 BYDUREON Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus - Combination Therapy

BYDUREON, another exenatide extended-release product, has been studied in combination with metformin, sulfonylurea, thiazolidinedione, sodium-glucose cotransporter-2 (SGLT2) inhibitor and basal insulin in adult patients with type 2 diabetes mellitus.

BYDUREON versus Sitagliptin and Pioglitazone, All as Add-on to Metformin Therapy

A 26-week double-blind comparator-controlled trial was conducted to compare the safety and efficacy of BYDUREON to sitagliptin and pioglitazone in patients with type 2 diabetes whose glycemic control was inadequate with metformin therapy (Trial 4 - NCT00637273). Patients were randomly assigned to receive BYDUREON 2 mg given subcutaneously once every 7 days (weekly), sitagliptin 100 mg/day or pioglitazone 45 mg/day, in addition to their existing metformin therapy.

A total of 491 patients were studied 168 (34.2%) were White, 143 (29.1%) were Hispanic or Latino, 119 (24.2%) were Asian, 52 (10.6%) were Black or African American, 3 (0.6%) were of Native American ethnicity, and 6 (1.2%) were classified otherwise. The mean baseline HbA_{1c} was 8.5%.

The primary endpoint was change in HbA_{1c} from baseline to Week 26 (or the last value at time of early discontinuation).

Efficacy Results:

In this study, treatment with BYDUREON 2 mg QW resulted in a statistically significant mean HbA_{1c} reduction compared to sitagliptin 100 mg/day. There was a numerically greater reduction in HbA_{1c} with BYDUREON compared to pioglitazone, but there was not sufficient evidence to conclude superiority of BYDUREON 2 mg QW to pioglitazone 45 mg/day in reducing HbA_{1c} after 26 Weeks of treatment. Results for the primary endpoint at 26 Weeks are summarized in Table 7.

The proportion of patients with a Week 26 value achieving HbA_{1c} of less than 7% at Week 26 were 46%, 30%, and 39% for BYDUREON, sitagliptin, and pioglitazone, respectively. Patients who did achieve an HbA_{1c} goal <7% and discontinued before Week 26 were not included as responders. The mean changes from baseline to Week 26 for fasting serum glucose were -32 mg/dL, -16 mg/dL and -27 mg/dL, and for body weight were -2.3 kg, -0.8 kg and +2.8 kg for BYDUREON, sitagliptin, and pioglitazone, respectively.

Table 7: Results of 26-Week Trial of BYDUREON versus Sitagliptin and Pioglitazone, All as Add-On to Metformin Therapy in Patients with Type 2 Diabetes Mellitus (Trial 4)

	BYDUREON 2 mg QW	**Sitagliptin 100 mg/day**	**Pioglitazone 45 mg/day**
Intent-to-Treat Population (N)	160	166	165
HbA_{1c} (%)			
Mean Baseline	8.6	8.5	8.5
Mean Change at Week 26*	−1.5	−0.9	−1.2
Difference from sitagliptin* [95% CI]	−0.63 [−0.89, −0.37]		
Difference from pioglitazone* [95% CI]	−0.32 [−0.57, −0.06]		

N = number of patients in each treatment group; mean change is least squares mean change; QW = once weekly.
* Least squares means were obtained using an ANCOVA model with treatment, baseline HbA_{1c} stratum, and country as fixed effects. Missing Week 26 data (28%, 18%, and 24% for the BYDUREON, sitagliptin, and pioglitazone groups, respectively) were imputed by the LOCF technique.

BYDUREON versus Insulin Glargine, Both as Add-on to Metformin or Metformin + Sulfonylurea Therapy

A 26-week open-label comparator-controlled trial was conducted to compare the safety and efficacy of BYDUREON to titrated insulin glargine in patients with type 2 diabetes whose glycemic control was inadequate with metformin or metformin plus sulfonylurea therapy (Trial 5 - NCT00641056). Patients were randomly assigned to receive BYDUREON 2 mg given subcutaneously once every 7 days (weekly) or insulin glargine once daily in addition to their existing oral antidiabetic therapy. Insulin glargine was dosed to a target fasting glucose concentration of 72 to 100 mg/dL.

The mean dose of insulin glargine was 10 units/day at baseline and 31 units/day at endpoint. At Week 26, 21% of insulin glargine-treated patients were at fasting glucose goal.

A total of 456 patients were studied: 379 (83.1%) were White, 47 (10.3%) were Hispanic or Latino, 25 (5.5%) were East Asian, 3 (0.7%) were Black or African American, and 2 (0.4%) were of West Asian

ethnicity. Background therapy was either metformin (70%) or metformin plus sulfonylurea (30%). The mean baseline HbA_{1c} was 8.3%.

The primary endpoint was change in HbA_{1c} from baseline to Week 26 (or the last value at time of early discontinuation).

Efficacy Results:

Treatment with BYDUREON once weekly resulted in a mean reduction in HbA_{1c} from baseline at 26 weeks of -1.5%. The mean reduction in HbA_{1c} seen in insulin glargine arm at 26 weeks was -1.3%. The difference in observed effect size between BYDUREON and glargine in this trial excluded the pre-specified non-inferiority margin of +0.3%.

The proportion of patients with a Week 26 value achieving HbA_{1c} of less than 7% at Week 26 were 57% and 48% for BYDUREON and insulin glargine, respectively. Patients who did achieve an HbA_{1c} goal <7% and discontinued before Week 26 were not included as responders. The mean changes from baseline to Week 26 for fasting serum glucose in this study were -38 mg/dL and -50 mg/dL, and for body weight were -2.6 kg and +1.4 kg for BYDUREON and insulin glargine, respectively.

BYDUREON versus Liraglutide, Both as Add-on to Metformin, a Sulfonylurea, Metformin + Sulfonylurea, or Metformin + Pioglitazone Therapy

A 26-week open-label comparator-controlled trial was conducted to compare the safety and efficacy of BYDUREON to liraglutide in patients with type 2 diabetes whose glycemic control was inadequate with metformin, a sulfonylurea, metformin plus sulfonylurea, or metformin plus pioglitazone therapy (Trial 6 - NCT01029886). Patients were randomly assigned to receive BYDUREON 2 mg given subcutaneously once every 7 days (weekly) or liraglutide uptitrated from 0.6 mg/day to 1.2 mg/day, then 1.8 mg/day in addition to their existing oral antidiabetic therapy. Each titration was to be completed after at least one week, but could be delayed if the patient had severe nausea or vomiting as established by the investigator. Patients not tolerating the 1.8 mg/day dose of liraglutide by Week 4 were discontinued from the study.

A total of 911 patients were studied: 753 (82.7%) were White, 111 (12.2%) were Asian, 32 (3.5%) were American Indian or Alaska Native, 8 (0.9%) were of Black or African American ethnicity, 6 (0.7%) were multiple races, and 1 (0.1%) was Pacific Islander. Background therapy was either a single oral antidiabetic agent (35%) or a combination of oral antidiabetic agents (65%). The mean baseline HbA_{1c} was 8.4%.

The primary endpoint was change in HbA_{1c} from baseline to Week 26 (or the last value at time of early discontinuation).

Efficacy Results:

Treatment with BYDUREON once weekly resulted in a mean reduction in HbA_{1c} from baseline at 26 weeks of -1.3%. The mean reduction in HbA_{1c} seen in the liraglutide arm at 26 weeks was -1.5%. The HbA_{1c} reduction with BYDUREON did not meet predefined non-inferiority criteria compared to liraglutide 1.8 mg/day. The non-inferiority margin was set at +0.25% in this study. Results for the primary endpoint at 26 weeks are summarized in Table 8.

The proportion of patients with a Week 26 value achieving HbA_{1c} of less than 7% at Week 26 were 48% and 56% for BYDUREON and liraglutide, respectively. Patients who did achieve an HbA_{1c} goal <7% and discontinued before Week 26 were not included as responders. The mean changes from baseline to Week 26 for fasting serum glucose were -32 mg/dL and -38 mg/dL, and for body weight were -2.7 kg and -3.6 kg for BYDUREON and liraglutide, respectively.

Table 8: Results of 26-Week Trial of BYDUREON versus Liraglutide, Both as Add-On to Metformin, a Sulfonylurea, Metformin + Sulfonylurea, or Metformin + Pioglitazone Therapy in Patients with Type 2 Diabetes Mellitus (Trial 6)

	BYDUREON 2 mg QW	**Liraglutide 1.8 mg/day**
Intent-to-Treat Population (N)	461	450
HbA_{1c} (%)		
Mean Baseline	8.5	8.4
Mean Change at Week 26*	−1.3	−1.5
Difference from liraglutide* [95% CI]	0.2 [0.08, 0.33]	

N = number of patients in each treatment group; mean change is least squares mean change; QW = once weekly. HbA_{1c} change data at 26 weeks were available from 85% and 86% of the randomized subjects in the BYDUREON and liraglutide groups, respectively.
* Least squares means were obtained using a mixed model repeated measure analysis with treatment, country, OAD stratum, baseline HbA_{1c} stratum, visit, baseline HbA_{1c} and treatment by visit interaction as fixed effects, and subject as a random effect.

BYDUREON in Combination with Dapagliflozin versus BYDUREON Alone and Dapagliflozin Alone, All as Add-On to Metformin

A 28-week double-blind comparator-controlled trial was conducted to compare the efficacy of BYDUREON and dapagliflozin (an SGLT2 inhibitor) to BYDUREON alone and dapagliflozin alone in patients with type 2 diabetes with inadequate glycemic control with metformin therapy (Trial 7 - NCT02229396). All patients entered a 1-week placebo lead–in period. Patients with HbA_{1c} ≥8.0% and ≤12% and on metformin at a dose of at least 1,500 mg per day were randomly assigned to receive either BYDUREON 2 mg given subcutaneously once every 7 days (weekly) plus dapagliflozin 10 mg once daily, BYDUREON 2 mg given subcutaneously once weekly, or dapagliflozin 10 mg once daily.

A total of 694 patients were studied; 580 (83.6%) were White, 96 (13.8%) were Black or African American, 5 (0.7%) were of Asian ethnicity, 2 (0.3%) were American Indian or Alaska Native, and 11 (1.6%) were classified otherwise. The mean baseline HbA_{1c} was 9.3%.

The primary endpoint was change in HbA_{1c} from baseline to Week 28.

Efficacy Results:

At Week 28, BYDUREON in combination with dapagliflozin provided statistically significantly greater reductions in HbA_{1c} (-1.77%) compared to BYDUREON alone (-1.42%, p=0.012) and dapagliflozin alone (-1.32%, p=0.001). BYDUREON in combination with dapagliflozin provided statistically significantly greater reductions in FPG (-57.35 mg/dL) compared to BYDUREON alone (-40.53, p <0.001) and dapagliflozin alone (-44.72 mg/dL, p=0.006).

BYDUREON versus Placebo, Both as Add-On to Basal Insulin or Basal Insulin + Metformin Therapy

A 28-week, double-blind, placebo-controlled trial was conducted to compare the safety and efficacy of BYDUREON to placebo when added to basal insulin glargine, with or without metformin, in patients with type 2 diabetes with inadequate glycemic control (Trial 8 - NCT02229383). Patients on sulfonylurea therapy discontinued sulfonylurea. Patients on metformin continued the same dose of metformin. All patients initially entered an 8-week insulin dose-titration phase. Insulin glargine was to be titrated every 3 days with an aim of achieving a target fasting plasma glucose concentration of 72 to 99 mg/dL. Following the titration period, patients with HbA_{1c} ≥7.0% and ≤10.5% were then randomly assigned to receive either BYDUREON 2 mg given subcutaneously once every 7 days (weekly) or placebo once every 7 days (weekly).

A total of 460 patients were studied: 400 (87.0%) were White, 47 (10.2%) were Black or African American, 6 (1.3%) were Asian, 1 (0.2%) was American Indian or Alaska Native, 1 (0.2%) was Pacific Islander, and 5 (1.1%) were classified otherwise.

The primary endpoint was the change in HbA_{1c} from baseline to Week 28.

Efficacy Results:

Compared to placebo, treatment with BYDUREON resulted in a statistically significant reduction in mean HbA_{1c} from baseline to Week 28 (Table 9).

The mean change in fasting plasma glucose from baseline to Week 28 was -12.50 mg/dL for BYDUREON and -2.26 mg/dL for placebo. The mean change from baseline to Week 28 in body weight was -0.92 kg for BYDUREON and +0.38 kg for placebo.

Table 9: Results of 28-Week Trial of BYDUREON versus Placebo, Both as Add-On to Insulin Glargine or Insulin Glargine + Metformin (Trial 8)

	BYDUREON 2 mg QW	**Placebo QW**
Intent-to-Treat Population (N)	231	229
Mean HbA_{1c} (%)		
Mean Baseline	8.53	8.53
Mean Change at Week 28*	-0.88 (0.070)	-0.24 (0.069)
Difference from Placebo [95% CI]	-0.64† [-0.83, -0.45]	
Percentage Achieving HbA_{1c} <7.0% at Week 28 (%)‡	32.5†	7.0

N = number of patients in each treatment group, CI = confidence interval, QW = once weekly.
Note: mean change is least squares mean change.
*Adjusted LS means and treatment group difference(s) in the change from baseline values at Week 28 using a multiple imputation method that models a "wash-out" for patients having missing data who discontinued treatment. ANCOVA was used with treatment, region, baseline HbA_{1c} stratum (<9.0% or ≥9.0%), and baseline SU-use stratum (yes vs. no) as fixed factors, and baseline value as a covariate.

† p-value <0.001 (adjusted for multiplicity).

‡Categories are derived from continuous measurements. All patients with missing endpoint data are imputed as non-responders. Treatment comparison is based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline

HbA_{1c} (<9.0% or ≥9.0%), and baseline SU-use stratum (yes vs. no). P-values are from the general association statistics.

Analyses include measurements post rescue therapy and post premature discontinuation of study medication.

14.5 EXSCEL Cardiovascular Outcomes Trial in Adult Patients with Type 2 Diabetes

EXSCEL was a multinational, placebo-controlled, double-blind, randomized, parallel group pragmatic study that evaluated cardiovascular (CV) outcomes during treatment with BYDUREON (exenatide) for extended-release injectable suspension in adult patients with type 2 diabetes and any level of CV risk when added to the current usual care (NCT01144338).

A total of 14,752 adult patients were randomized 1:1 to either BYDUREON 2 mg given subcutaneously once weekly or placebo and followed as in routine clinical practice for a median of 38.7 months with a median treatment duration of 27.8 months.

Ninety six percent of the patients in both treatment groups completed the study in accordance with the protocol, and the vital status was known at the end of the study for 98.9% and 98.8% of the patients in the BYDUREON and placebo group, respectively. The mean age at study entry was 62 years (21 to 92 years with 8.5% of the patients ≥75 years). Approximately 62.0% of the patients were male, 75.8% were White, 9.8% were Asian, 6.0% were Black or African American, and 20.5% were of Hispanic or Latino ethnicity. The mean BMI was 32.7 kg/m^2 and the mean duration of diabetes was 13.1 years. Approximately 49.3% had mild renal impairment (estimated glomerular filtration rate [eGFR] ≥60 to ≤89 mL/min/1.73 m^2) and 21.6% had moderate renal impairment (eGFR ≥30 to ≤59 mL/min/1.73 m^2).

The mean HbA_{1c} was 8.1%. At baseline, 1.5% of patients were not treated with either oral antidiabetic medications or insulin, 42.3% were treated with one oral antidiabetic medication and 42.4% were treated with two or more oral antidiabetic medications. Usage of oral antidiabetic medications included metformin (76.6%), sulfonylurea (36.6%), dipeptidyl peptidase-4 (DPP-4) inhibitors (14.9%), thiazolidinediones (3.9%), and SGLT2 inhibitors (0.9%). Overall insulin usage was 46.3% (13.8% with insulin alone and 32.6% with insulin and one or more oral antidiabetic medications).

Overall, at baseline, 26.9% of patients did not have established cardiovascular (CV) disease, while 73.1% had established CV disease. The concomitant use of CV medications (e.g., ACE inhibitors, angiotensin receptor blockers, diuretics, beta blockers, calcium channel blockers, antithrombotic and anticoagulants, and lipid-lowering agents) was similar in the BYDUREON and placebo groups. At baseline, the mean systolic blood pressure was 135.5 mmHg, the mean diastolic blood pressure was 78.1 mmHg, the mean LDL was 95.0 mg/dL, and the mean HDL was 44.0 mg/dL.

The primary endpoint in EXSCEL was the time to first confirmed Major Adverse Cardiac Event (MACE) from randomization. MACE was defined as occurrence of either a cardiovascular (CV)-related death, or a nonfatal myocardial infarction (MI) or a nonfatal stroke. All-cause mortality, CV-related death, and fatal or nonfatal MI or stroke, hospitalization for acute coronary syndrome, and hospitalization for heart failure were also assessed as secondary endpoints.

A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE and superiority on MACE if non-inferiority was demonstrated. Type-1 error was controlled across multiple tests using a hierarchical testing strategy.

MACE Results:

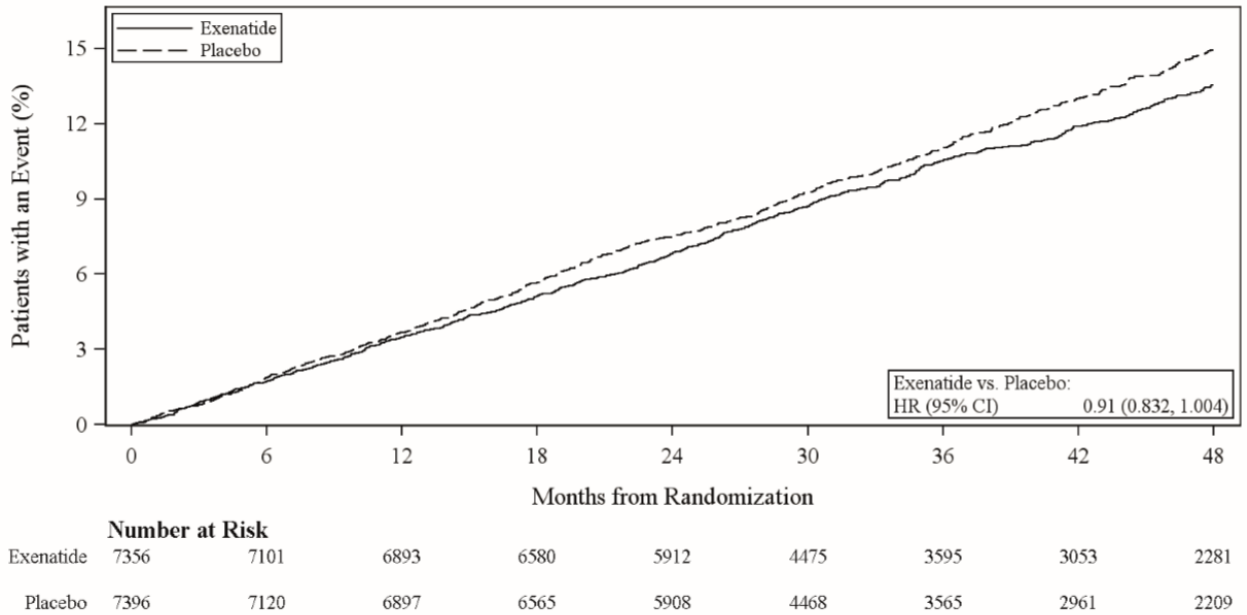
BYDUREON did not increase the risk of MACE in adult patients with type 2 diabetes mellitus (HR: 0.91; 95% CI: 0.832, 1.004; P<0.001 for non-inferiority; P=0.06 for superiority). See results in Table 10 and Figure 2. The incidence of MACE in patients with and without established CV disease was 13.4% in the BYDUREON group versus 14.6% in the placebo group and 6.0% (BYDUREON) versus 5.9% (placebo), respectively. Five hundred and seven (507) patients (6.9%) died in the BYDUREON group versus 584 (7.9%) in the placebo group.

Table 10: Analysis of Primary Composite Endpoint MACE and Its Components in Adult Patients with Type 2 Diabetes (EXSCEL)

	BYDUREON N=7356	**Placebo N=7396**	**HR* (95% CI)**
MACE Composite of CV death, nonfatal MI or nonfatal stroke (time to first confirmed event)	839 (11.4%)	905 (12.2%)	0.91 (0.832, 1.004)
Cardiovascular Death	340 (4.6%)	383 (5.2%)	0.88 (0.76, 1.02)
Nonfatal Myocardial Infarction	466 (6.3%)	480 (6.5%)	0.96 (0.85, 1.09)
Nonfatal Stroke	169 (2.3%)	193 (2.6%)	0.86 (0.70, 1.06)

N=number of patients in each treatment group, HR=hazard ratio, CI=confidence interval, CV=cardiovascular, MI=myocardial infarction.
* HR (active/placebo) and CI are based on Cox proportional hazards regression model, stratified by established CV disease, with treatment group only as explanatory variable.

Figure 2: Time to First Adjudicated MACE in Adult Patients with Type 2 Diabetes (EXSCEL)



HR=hazard ratio, CI=confidence interval.

14.6 Glycemic Control Trial in Pediatric Patients 10 Years of Age and Older with Type 2 Diabetes Mellitus

The efficacy and safety of BYDUREON 2 mg given subcutaneously once weekly or placebo was evaluated in a 24-week randomized, double-blind, placebo-controlled, parallel-group study (Trial 9 - NCT01554618) in 82 patients aged 10 to 17 years with type 2 diabetes treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agents and/or insulin. This study included a 28-week open-label long-term extension in which patients in both treatment groups received BYDUREON 2 mg given subcutaneously once weekly after the 24-week controlled period.

In this trial, 88% of patients completed the assessment period. The mean age at study entry was 15.1 years (13% were 11 to 12 years old, 59% were 13 to 16 years old and 28% were older than 16 years). Approximately 42% of the patients were male, 43% were White, 4% were Asian, 31% were Black or African American, 6% were American Indian or Alaska Native, and 44% were Hispanic or Latino. The mean body weight was 100.6 kg (67% were in ≥97 weight percentile group, 26% in ≥85 to <97 and 6% in ≥3 to <85), mean BMI was 36.4 kg/m^2 and the mean duration of diabetes was 2.3 years.

At baseline, mean HbA_{1c} was 8.17%, 12.2% of patients were not treated with either oral antidiabetic medications or insulin, 40.2% were treated with one oral antidiabetic medication and 1.2% were treated with two oral antidiabetic medications. 79.3% of patients were receiving metformin and 1.2% were receiving sulfonylurea. Overall insulin usage was 46.3% (8.5% with insulin alone and 37.8% with insulin and one other oral antidiabetic medication).

The primary endpoint of the study was the change in HbA_{1c} from baseline to Week 24.

Efficacy Results:

BYDUREON was superior to placebo in reducing HbA_{1c} (Table 11).

The mean changes from baseline to Week 24 for body weight were -0.17 kg with (SE 0.7) and +0.88 kg (SE 1.0) for BYDUREON and placebo, respectively.

Table 11: Results of 24-Week Trial of BYDUREON versus Placebo, Both alone or in Combination with Oral Antidiabetic Agents and/or Insulin in Pediatric Patients 10 Years of Age and Older with Type 2 Diabetes Mellitus (Trial 9)

	BYDUREON 2 mg QW	**Placebo QW**
Intent-to-Treat Population (N)	58	24
HbA_{1c} (%)		
Mean Baseline	8.13	8.28
Mean Change at Week 24 (SE)*	-0.25 (0.21)	0.45 (0.29)
Difference from Placebo (95% CI)	-0.71† (-1.42, 0)	
HbA_{1c}<7%		
Percentage achieved goal at Week 24	31.0	8.3

Table 11: Results of 24-Week Trial of BYDUREON versus Placebo, Both alone or in Combination with Oral Antidiabetic Agents and/or Insulin in Pediatric Patients 10 Years of Age and Older with Type 2 Diabetes Mellitus (Trial 9)

	BYDUREON 2 mg QW	Placebo QW
Fasting Plasma Glucose (mg/dL)		
Mean Baseline	165.2	170.5
Mean Change at Week 24 (SE)‡	-1.3 (8.1)	16.2 (11.9)

* Adjusted LS means and treatment group difference(s) in the change from baseline values at Week 24 using a multiple imputation method that models a "wash-out" for patients having missing data who discontinued treatment. ANCOVA was used with treatment, region as fixed factors, and baseline HbA_{1c} value as a covariate. SE – standard error.
† $p<0.05$
‡ Adjusted LS means in the change from baseline values at Week 24 using a multiple imputation method that models a "wash-out" for patients having missing data who discontinued treatment. ANCOVA was used with treatment, region, as fixed factors, and baseline FPG value as a covariate.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

- BYDUREON BCISE contains 2 mg of exenatide in 0.85 mL vehicle, in a pre-filled, single-dose autoinjector. Redispersion by mixing provides a white to off-white, opaque, extended-release injectable suspension, available in cartons that contain four single-dose autoinjectors (NDC 0310-6540-04).

Storage and Handling

- BYDUREON BCISE must be stored FLAT.
- Store the autoinjector in the original package. Protect from light. Do not use past the expiration date.
- Store BYDUREON BCISE in the refrigerator at 36°F to 46°F (2°C to 8°C).
- BYDUREON BCISE can be kept at room temperature not to exceed 86°F (30°C) for no more than a total of 4 weeks, if needed.
- Discard BYDUREON BCISE after use in a puncture-resistant container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Thyroid C-cell Tumors

Inform patients that exenatide extended-release causes benign and malignant thyroid C-cell tumors in rats and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) to their physician *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Acute Pancreatitis

Inform patients of the potential risk for acute pancreatitis and its symptoms: severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting. Instruct patients to discontinue BYDUREON BCISE promptly and contact their physician if pancreatitis is suspected *[see Warnings and Precautions (5.2)]*.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Inform patients that the risk of hypoglycemia is increased when BYDUREON BCISE is used in combination with an agent that induces hypoglycemia, such as a sulfonylurea or insulin. Educate patients on the signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.3)]*.

Acute Kidney Injury Due to Volume Depletion

Inform patients of the potential risk of acute kidney injury due to dehydration associated with gastrointestinal adverse reactions. Advise patients to take precautions to avoid fluid depletion. Inform patients of the signs and symptoms of acute kidney injury and instruct them to promptly report any of these signs or symptoms or persistent (or extended) nausea, vomiting, and diarrhea to their healthcare provider.*[see Warnings and Precautions (5.4)]*.

Severe Gastrointestinal Adverse Reactions

Inform patients of the potential risk of severe gastrointestinal adverse reactions. Instruct patients to contact their healthcare provider if they have severe or persistent gastrointestinal symptoms *[see Warnings and Precautions (5.5)]*.

Hypersensitivity Reactions

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

Drug-Induced Thrombocytopenia

Inform patients that drug-induced immune-mediated thrombocytopenia has been reported during use of exenatide. Inform patients that if symptoms of thrombocytopenia occur, e.g., bleeding, stop taking BYDUREON BCISE and seek medical advice promptly *[see Warnings and Precautions (5.8)]*.

Serious Injection-Site Reactions

Inform patients that there have been postmarketing reports of serious injection-site reactions with or without subcutaneous nodules, with the use of BYDUREON. Isolated cases of injection-site reactions required surgical intervention. Advise patients to seek medical advice if symptomatic nodules occur, or for any signs or symptoms of abscess, cellulitis, or necrosis *[see Warnings and Precautions (5.9)]*.

Acute Gallbladder Disease

Inform patients of the potential risk for cholelithiasis or cholecystitis. Instruct patients to contact their physician if cholelithiasis or cholecystitis is suspected for appropriate clinical follow-up *[see Warnings and Precautions (5.10)]*.

Pulmonary Aspiration During General Anesthesia or Deep Sedation

Inform patients that BYDUREON BCISE may cause their stomach to empty more slowly which may lead to complications with anesthesia or deep sedation during planned surgeries or procedures. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking BYDUREON BCISE *[see Warnings and Precautions (5.11)]*.

Instructions

Train patients on how to use BYDUREON BCISE properly prior to administration. Instruct patients and caregivers on proper mixing and injection technique to ensure the product is adequately mixed and a full dose is delivered. Instruct caregivers to assist pediatric patients with mixing and administration. Refer patients and caregivers to the accompanying Instructions for Use for complete administration instructions with illustrations.

Inform patients formerly on BYETTA who start BYDUREON BCISE that they may experience transient elevations in blood glucose concentrations, which generally improve within the first 4 weeks after initiation of therapy *[see Dosage and Administration (2.1)]*.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

By:
Resilience US, Inc.
West Chester, OH 45071
and
Vetter Pharma-Fertigung GmbH & Co. KG
88214 Ravensburg
Germany

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MEDICATION GUIDE
BYDUREON BCISE® (by-DUR-ee-on B-cise)
(exenatide) extended-release injectable suspension
for subcutaneous use

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

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

- **Possible thyroid tumors, including cancer**. Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rats, BYDUREON and medicines that work like BYDUREON caused thyroid tumors, including thyroid cancer. It is not known if BYDUREON BCISE will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.
- Do not use BYDUREON BCISE if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

What is BYDUREON BCISE?

- BYDUREON BCISE is an injectable prescription medicine that is used along with diet and exercise to improve blood sugar (glucose) in adults and children who are 10 years of age and older with type 2 diabetes mellitus.
- BYDUREON BCISE is not recommended for people who take exenatide or other medicines called glucagon-like peptide-1 (GLP-1) receptor agonists.
- It is not known if BYDUREON BCISE is safe and effective for use in children younger than 10 years of age.

Do not use BYDUREON BCISE if:

- you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- you have had a severe allergic reaction to exenatide or any of the ingredients in BYDUREON BCISE. See the end of this Medication Guide for a complete list of ingredients in BYDUREON BCISE. See "**What are the possible side effects of BYDUREON BCISE?**" for symptoms of a serious allergic reaction. you have a history of low blood platelet count from using exenatide medicines (drug-induced thrombocytopenia).

Before using BYDUREON BCISE, tell your healthcare provider about all of your medical conditions, including if you:

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

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. BYDUREON BCISE may affect the way some medicines work and some medicines may affect the way BYDUREON BCISE works.
Before using BYDUREON BCISE, talk to your healthcare provider about low blood sugar and how to manage it. Tell your healthcare provider if you are taking other medicines to treat diabetes, including insulin or sulfonylureas.
Especially tell your healthcare provider if you take warfarin.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use BYDUREON BCISE?

- Read the **Instructions for Use** that comes with BYDUREON BCISE.
- Use BYDUREON BCISE exactly as your healthcare provider tells you to.
- **Your healthcare provider should show you how to use BYDUREON BCISE before you use it for the first time.**
- Inject BYDUREON BCISE right away after you prepare your dose.
- Caregivers should help children with mixing and injecting BYDUREON BCISE.
- Inject BYDUREON BCISE under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm. **Do not** inject BYDUREON BCISE into a muscle (intramuscularly) or vein (intravenously).
- **Use BYDUREON BCISE 1 time each week on the same day each week at any time of the day.**
- BYDUREON BCISE may be taken with or without food.
- If you miss a dose of BYDUREON BCISE, take the missed dose as soon as possible if there are at least 3 days (72 hours) until your next scheduled dose. If there are less than 3 days remaining, skip the missed dose and take your next dose on the regularly scheduled day. **Do not** take 2 doses of BYDUREON BCISE within 3 days of each other.
- You may change the day of the week as long as your last dose was given 3 or more days before.
- If you use a different long acting exenatide medicine and your healthcare provider switches your medicine to BYDUREON BCISE, you should start using BYDUREON BCISE at your next scheduled dose.
- **Do not** mix insulin and BYDUREON BCISE together in the same injection.
- You may give an injection of BYDUREON BCISE and insulin in the same body area (such as, your stomach area), but not right next to each other.
- Change (rotate) your injection site with each weekly injection. **Do not** use the same site for each injection.
- **Do not share your BYDUREON BCISE pen with other people, even if the needle has been changed.** You may give other people a serious infection or get a serious infection from them.
- If you take too much BYDUREON BCISE, call your healthcare provider or Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of BYDUREON BCISE?

BYDUREON BCISE may cause serious side effects, including:

- **See "What is the most important information I should know about BYDUREON BCISE?"**
- **inflammation of your pancreas (pancreatitis).** Stop using BYDUREON BCISE and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- **low blood sugar (hypoglycemia).** Your risk for getting low blood sugar may be higher if you use BYDUREON BCISE with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin. **Signs and symptoms of low blood sugar may include:**
  - dizziness or light-headedness
  - blurred vision
  - anxiety, irritability, or mood changes
  - sweating
  - slurred speech
  - hunger
  - confusion or drowsiness
  - shakiness
  - weakness
  - headache
  - fast heartbeat
  - feeling jittery
- **dehydration leading to kidney problems.** Diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems. It is important for you to drink fluids to help reduce your chance of dehydration. Tell your healthcare provider right away if you have nausea, vomiting, or diarrhea that does not go away.
- **severe stomach problems.** Stomach problems, sometimes severe, have been reported in people who use BYDUREON BCISE. Tell your healthcare provider if you have stomach problems that are severe or will not go away**.**
- **serious allergic reactions.** Stop using BYDUREON BCISE and get medical help right away if you have any symptoms of a serious allergic reaction, including
  - swelling of your face, lips, tongue or throat
  - fainting or feeling dizzy
  - problems breathing or swallowing
  - very rapid heartbeat
  - severe rash or itching
- **low blood platelet count (drug-induced thrombocytopenia).** BYDUREON BCISE may cause the number of platelets in your blood to be reduced. When your platelet count is too low, your body cannot form blood clots. You could have serious bleeding that could lead to death. **Stop using BYDUREON BCISE and call your healthcare provider right away if you have unusual bleeding**

or bruising. Your blood platelet count may continue to be low for about 10 weeks after stopping BYDUREON BCISE.

- **serious injection-site reactions.** Serious injection-site reactions, with or without bumps (nodules), have happened in some people who use BYDUREON BCISE. Some of these injection-site reactions have required surgery. Call your healthcare provider if you have any symptoms of an injection-site reaction, including severe pain, swelling, blisters, an open wound, a dark scab.
- **gallbladder problems.** Gallbladder problems have happened in some people who take BYDUREON BCISE. Tell your healthcare provider right away if you get symptoms of gallbladder problems which may include:
  - pain in your upper stomach (abdomen)
  - fever
  - yellowing of skin or eyes (jaundice)
  - clay-colored stools
- **food or liquid getting into the lungs during surgery or other procedures that use anesthesia or deep sleepiness (deep sedation).** BYDUREON BCISE may increase the chance of food getting into your lungs during surgery or other procedures. Tell all your healthcare providers that you are taking BYDUREON BCISE before you are scheduled to have surgery or other procedures.

The most common side effects of BYDUREON BCISE may include a bump (nodule) at the injection site and nausea.

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

These are not all the possible side effects of BYDUREON BCISE.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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

General information about the safe and effective use of BYDUREON BCISE.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BYDUREON BCISE for a condition for which it was not prescribed. Do not give your BYDUREON BCISE to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about BYDUREON BCISE that is written for health professionals.

What are the ingredients in BYDUREON BCISE?

Contents of the powder:

Active ingredient: exenatide.

Inactive ingredients: polylactide-co-glycolide and sucrose.

Contents of liquid (diluent):

Inactive Ingredients: medium chain triglycerides.

BYDUREON, BCISE and BYETTA are trademarks of the AstraZeneca group of companies. All other marks are the marks of their respective owners.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
By:
Resilience US, Inc.
West Chester, OH 45071 and
Vetter Pharma-Fertigung GmbH & Co. KG
88214 Ravensburg
Germany

For more information about BYDUREON BCISE, go to www.BYDUREONBCISE.com or call 1-800-236-9933.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 05/2025

INSTRUCTIONS FOR USE

BYDUREON BCISE® (by-DUR-ee-on B-cise)
(exenatide) extended-release injectable suspension
for subcutaneous use
once-weekly

Read the Instructions for Use before you start using BYDUREON BCISE.
Before using BYDUREON BCISE, talk to your healthcare provider about how to use it the right way.
Caregivers should help children with mixing and injecting BYDUREON BCISE.

Before You Begin

The autoinjector:
- Is a single use, fixed dose autoinjector that automatically injects your medicine.
- Is injected 1 time per week under the skin.
- 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 36°F to 46°F (2°C to 8°C).
- 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

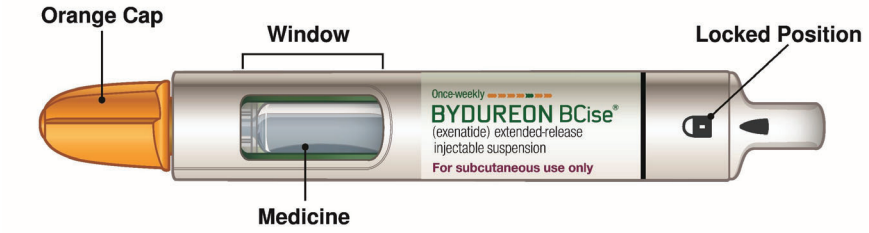

Figure A

Reference ID: 5598578

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 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. If the expiration date has passed, throw it away and get a new autoinjector.

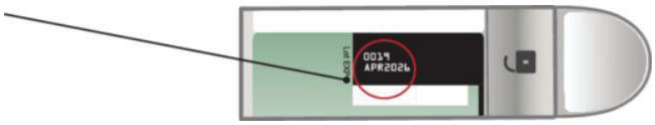

Figure C

C. Wash your hands.

D. Choose your injection site.
You can inject into 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.

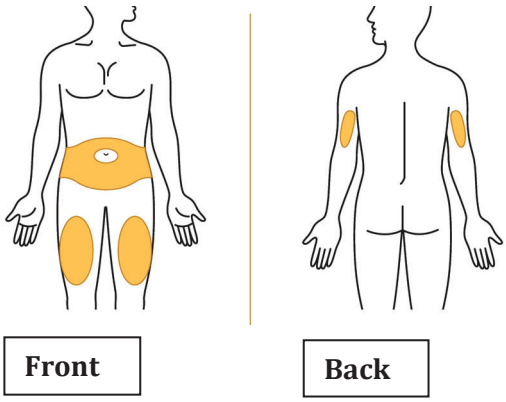

Figure D

Reference ID: 5598578

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.

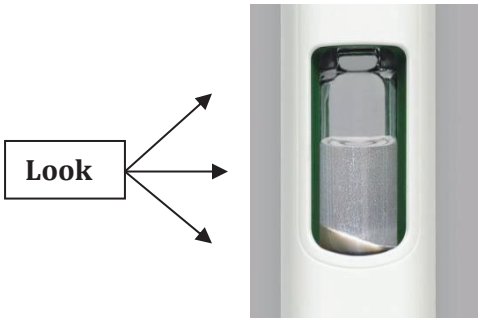

Figure E

B. Shake the 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.**
- The autoinjector may need to be shaken longer than 15 seconds if the autoinjector has not been correctly stored flat.

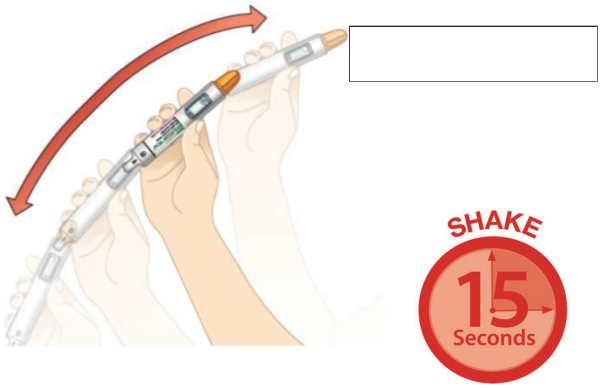

Figure F

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.

Reference ID: 5598578

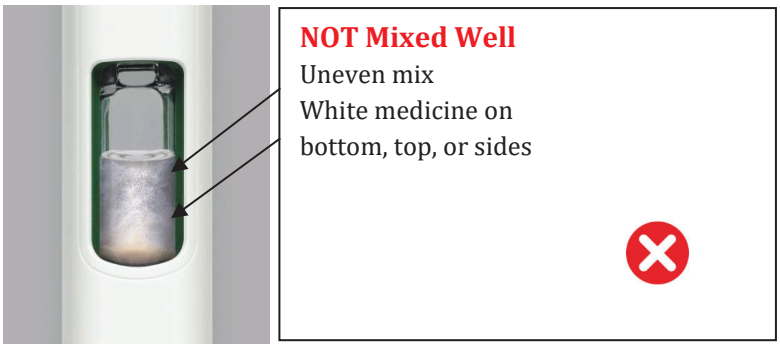

Figure G

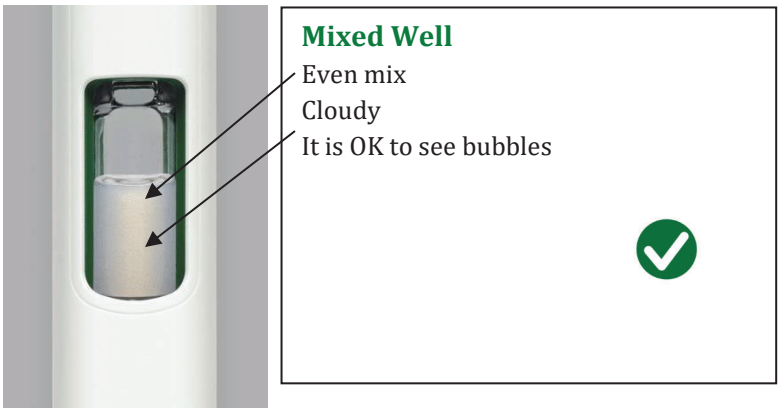

Figure H

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 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.

Reference ID: 5598578

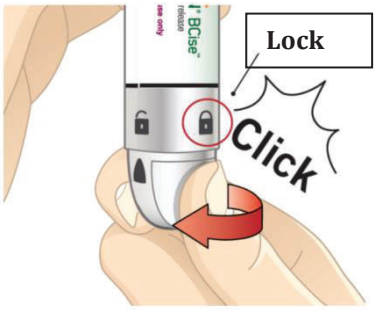

Figure I

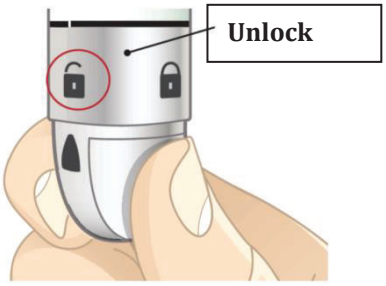

Figure J

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** and **firmly** unscrew in a counterclockwise direction.

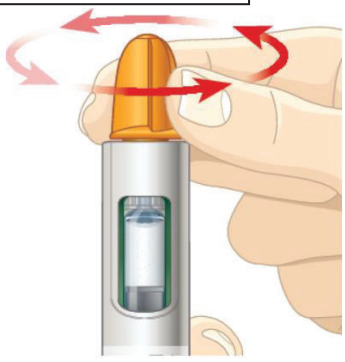

Figure K **Figure L**

Removed Cap

Green shield **pops** up

Reference ID: 5598578

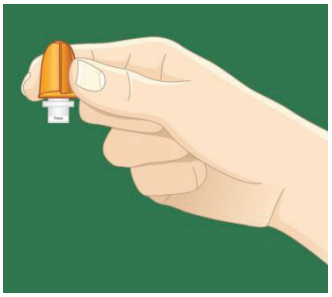

Figure M

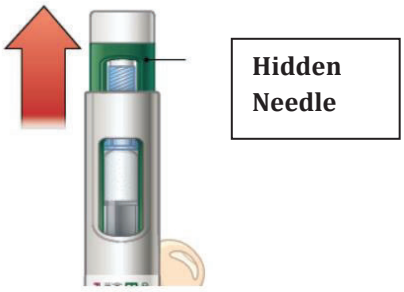

Figure N

Step 4: Inject the Dose

A. Inject and hold:

- Push the 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.

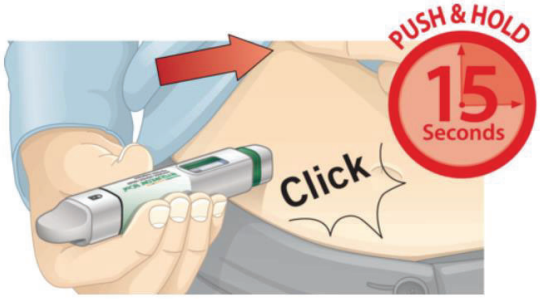

Figure O

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 and Answers for what to do if you do not see the orange rod in the window after injection.

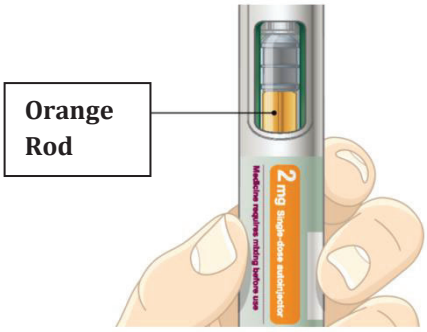

Figure P

Step 4: Inject the Dose (continued)

Reference ID: 5598578

C. Disposal.
Put your used autoinjector in a FDA-cleared sharps disposal container right away after use.
Do not throw away (dispose of) loose needles and syringes into your household trash. If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- Made of heavy-duty plastic
- Can be closed with a tight-fitting, puncture-resistant lid that will not let sharps come out
- Upright and stable during use
- Leak-resistant, and
- Properly labeled to warn of hazardous waste inside the container

Figure Q

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to FDA's website at: http://www.fda.gov/safesharpsdisposal.

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container. See "Common Questions and Answers" for additional disposal information.

Please keep these instructions to use for your next dose.

Common Questions and Answers

1. Where is the needle?
The needle is attached to the 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 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?

Reference ID: 5598578

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.

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 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 Customer Service at 1-800-236-9933.

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 do not have an FDA-cleared sharps disposal container?
Do not throw away (dispose of) the autoinjector in your household trash. If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- Made of heavy-duty plastic
- Can be closed with a tight-fitting, puncture-resistant lid, that will not let sharps come out
- Upright and stable during use
- Leak-resistant, and
- Properly labeled to warn of hazardous waste inside the container

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and autoinjectors.

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

8. What if I cannot unlock the autoinjector?
Review the Instructions for Use Step 3 to make sure you are following the right instructions, then contact Customer Service, 1-800-236-9933 for help as needed. Do not try to unlock with excessive force or tools.

9. What if I cannot remove the orange cap from the autoinjector?
Review the Instructions for Use Step 3 to make sure you are following the right instructions. You should also check that the knob is fully in the unlocked position, then contact Customer Service, 1-800-236-9933 for help as needed. Do not use tools or try to force the cap off.

10. For other questions about BYDUREON BCISE:
Visit www.BydureonBCise.com.
Call Customer Service at 1-800-236-9933.

How to Store BYDUREON BCISE Autoinjector

- Store the autoinjector flat in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Each autoinjector can be kept at room temperature not to exceed 86°F (30°C) for no more than a total of 4 weeks, if needed.
- Store in the packaging provided to protect from light until you are ready to prepare and use your dose.
- Do not use the autoinjector past the expiration date. The expiration date is labeled EXP.
- Keep the autoinjector clean and away from spills.

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: 03/2024

Reference ID: 5598578