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 ----------

Indications and Usage, Limitations of Use (1)	7/2019
Warnings and Precautions, Acute Kidney Injury (5.4)	2/2019
Warnings and Precautions, Acute Gallbladder Disease (5.9)	2/2019
Warnings and Precautions, Macrovascular Outcomes (5.9)-removed	2/2019

---------- 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 with type 2 diabetes mellitus. (1, 14)

Limitations of Use:

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. (1)
- Should not be used to treat type 1 diabetes or diabetic ketoacidosis. (1)
- Use with prandial insulin has not been studied. (1)
- BYDUREON BCISE is an extended-release formulation of exenatide. Do not coadminister with other exenatide containing products. (1)
- Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. (1, 5.2)

---------- DOSAGE AND ADMINISTRATION ----------

- Administer 2 mg by subcutaneous injection once every seven days (weekly), at any time of day and with or without meals. (2.1)
- Administer immediately after the dose is prepared. (2.3)

---------- 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)

---------- WARNINGS AND PRECAUTIONS ----------

- Acute Pancreatitis: Including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been reported. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies if patient has history of pancreatitis. (5.2)
- Hypoglycemia: When used in combination with an insulin secretagogue (e.g., a sulfonylurea) or insulin, consider lowering dose of the secretagogue or insulin to reduce risk of hypoglycemia. (5.3)
- Acute Kidney Injury: May induce nausea and vomiting with transient hypovolemia and may worsen renal function. Postmarketing increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation has been reported. Not recommended for use in patients with eGFR below 45 mL/min/1.73 m^2. (5.4, 8.6, 12.3)
- Gastrointestinal Disease: Not recommended in patients with severe gastrointestinal disease (e.g., gastroparesis). (5.5)
- Immunogenicity: 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: Serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) have been reported. Discontinue BYDUREON BCISE and promptly seek medical advice. (5.7)
- Injection-site Reactions: Serious injection-site reactions with or without subcutaneous nodules have been reported. (5.8)
- Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated. (5.9)

---------- 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: 7/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

5.7 Hypersensitivity

There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) in patients treated with exenatide. If a hypersensitivity reaction occurs, the patient should discontinue BYDUREON BCISE and promptly seek medical advice *[see Contraindications (4) and Adverse Reactions (6.3)]*. Inform and closely monitor patients with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist for allergic reactions, because it is unknown whether such patients will be predisposed to anaphylaxis with BYDUREON BCISE.

5.8 Injection-Site Reactions

There have been postmarketing reports of serious injection-site reactions (e.g., abscess, cellulitis, and necrosis), with or without subcutaneous nodules, with the use of BYDUREON *[see Adverse Reactions (6.3)]*. Isolated cases required surgical intervention.

5.9 Acute Gallbladder Disease

Acute events of gallbladder disease have been reported in GLP-1 receptor agonist trials. In the EXSCEL trial *[see Clinical Studies (14.2)]*, 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.

6 ADVERSE REACTIONS

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

- Risk of Thyroid C-cell Tumors *[see Warnings and Precautions (5.1)]*
- Acute Pancreatitis *[see Warnings and Precautions (5.2)]*
- Hypoglycemia *[see Warnings and Precautions (5.3)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.4)]*
- Gastrointestinal Disease *[see Warnings and Precautions (5.5)]*
- Immunogenicity *[see Warnings and Precautions (5.6)]*
- Hypersensitivity *[see Warnings and Precautions (5.7)]*
- Injection-Site Reactions *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trial Experience

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

The data in this section are derived from pooled data from the controlled period of the 2 comparator-controlled trials as well as data from the extension phase of one of these trials *[see Clinical Studies (14)]*. 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%

Pediatric Patients

BYDUREON BCISE has not been studied in pediatric patients *[see Use in Specific Populations (8.4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

A 2-year carcinogenicity study was conducted with exenatide extended-release, the active component of BYDUREON 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 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus

BYDUREON BCISE has been studied as monotherapy and in combination with metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione.

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 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 (NCT01652716).

A total of 375 patients were studied: 278 (74%) were Caucasian, 61(16%) Black or African American, 25 (7%) Asian, 5 (1%) listed as other, 5 (1%) American Indian or Alaska Native, and 1 (<1%) Native

Figure G

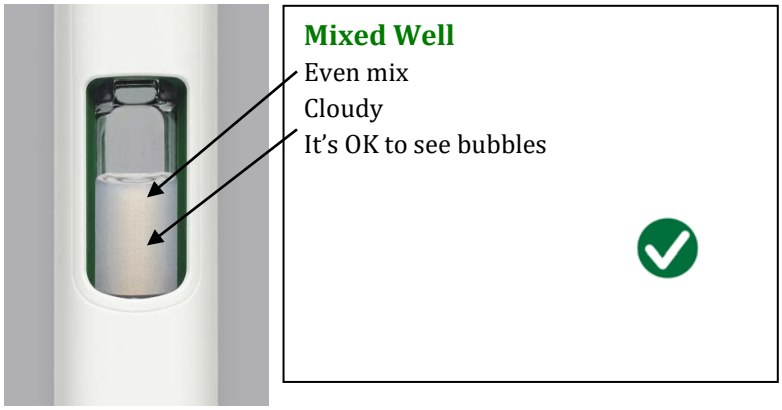


Figure H

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.

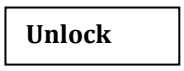
Step 3: Prepare the Autoinjector

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.

Figure I



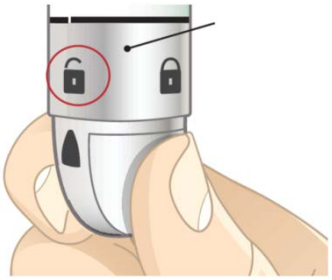


Figure J

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

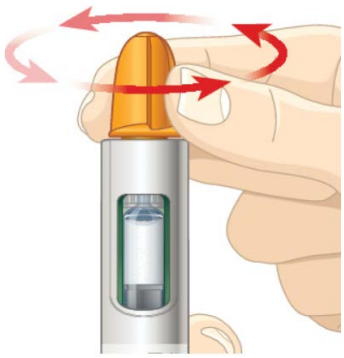


Figure L

Removed Cap

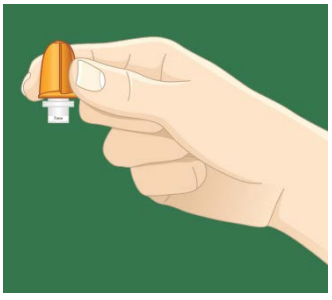
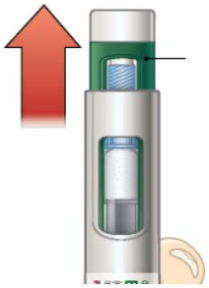


Figure M

Green shield **pops** up



Hidden Needle

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.

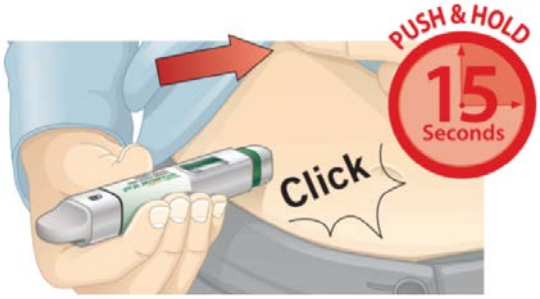


Figure O

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.

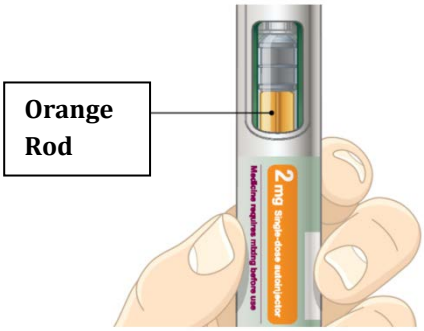


Figure P

Step 4: Inject the Dose (continued)

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?
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 1-877-700-7365.

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 won't let sharps come out
- Upright and stable during use
- Leak-resistant
- 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, 1-877-700-7365 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, 1-877-700-7365 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 1-877-700-7365.

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: 7/2019