Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date: April 14, 2025

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Product Name	Application	Applicant	Pediatric Labeling Date
Bydureon BCise (exenatide)	NDA 209210	AstraZeneca AB	7/22/2021
Bydureon (exenatide)	NDA 022200	AstraZeneca AB	7/22/2021
Byetta (exenatide)	NDA 021773	AstraZeneca AB	11/4/2021

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Bydureon (exenatide) suspension, extended release; Bydureon BCise (exenatide) suspension, extended release; and Byetta (exenatide) injectable in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with exenatide in pediatric patients.

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). Three exenatide products are approved in the U.S. and are described below:

> Byetta (exenatide) injection was first approved in the U.S. on April 28, 2005, and it is currently indicated as adjunctive therapy to improve glycemic control in adult patients with T2DM. On August 16, 2024, the applicant notified FDA of its plan to permanently discontinue marketing of Byetta.
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> Bydureon (exenatide) extended-release for injectable suspension was first approved in the U.S. on January 27, 2012. It is currently indicated as an adjunct to diet and exercise to improve glycemic control in patients aged 10 years and older with T2DM in multiple clinical settings. Of note, the Applicant for Bydureon discontinued marketing with permanent withdrawal from sale of all strengths of Bydureon as of March 2021.
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> Bydureon BCise (exenatide) extended-release injectable suspension was first approved in the U.S. on October 20, 2017. It is currently indicated as an adjunct to diet and exercise to improve glycemic control in patients aged 10 years and older with T2DM. On August 16, 2024, the applicant for Bydureon BCise notified FDA of its plan to permanently discontinue marketing of Bydureon BCise.

DPV reviewed all U.S. serious FAERS reports with exenatide in pediatric patients less than 18 years of age from April 24, 2005 – January 29, 2025, and identified 11 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with exenatide in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for exenatide at this time and will continue routine pharmacovigilance monitoring for exenatide.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Bydureon (exenatide) suspension, extended release; Bydureon BCise (exenatide) suspension, extended release; and Byetta (exenatide) injectable in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with exenatide in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). Three exenatide products are approved in the U.S. and are described below.[a]

Byetta (exenatide) injection was first approved in the U.S. on April 28, 2005, and it is currently indicated as adjunctive therapy to improve glycemic control in adult patients with T2DM.[1,2,b] On November 4, 2021, the labeling for Byetta was updated to include information on a clinical study that failed to demonstrate safety and effectiveness of Byetta in pediatric patients.[3] On August 16, 2024, the applicant for Byetta notified FDA of its plan to permanently discontinue marketing of all strengths of Byetta.[4,5]

Bydureon (exenatide) extended-release for injectable suspension was first approved in the U.S. on January 27, 2012, and it was initially indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM in multiple clinical settings.[6,c] On July 22, 2021, FDA expanded the Bydureon indication to include use as an adjunct to diet and exercise to improve glycemic control in patients aged 10 years and older with T2DM.[7] Of note, the Applicant for Bydureon discontinued marketing with permanent withdrawal from sale of all strengths of Bydureon as of March 2021.[8]

Bydureon BCise (exenatide) extended-release injectable suspension was first approved in the U.S. on October 20, 2017, and it was initially indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.[9,b] On July 22, 2021, FDA expanded the Bydureon BCise indication to include use as an adjunct to diet and exercise to improve glycemic control in patients aged 10 years and older with T2DM.[10] On August 16, 2024, the applicant for Bydureon

[a] Three exenatide products are approved under New Drug Applications. Exenatide is also available under an Abbreviated New Drug Application.

[b] Byetta is not a substitute for insulin and should not be used in patients with type 1 diabetes mellitus (T1DM) or for the treatment of diabetic ketoacidosis. Concurrent use of Byetta with insulin has not been studied and cannot be recommended. Byetta has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with history of pancreatitis.

[c] Bydureon and Bydureon BCise are not recommend as first-line therapy for patients who have inadequate glycemic control on diet and exercise. Bydureon and Bydureon BCise are extended-release formulations of exenatide and should not be used with other exenatide-containing products. Bydureon has not been studied in patients with a history of pancreatitis and providers should consider antidiabetic therapies in patients with a history of pancreatitis.

BCise notified FDA of its plan to permanently discontinue marketing of Bydureon BCise.[11,12]

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling on July 22, 2021, for Bydureon and Bydureon BCise, and the pediatric labeling on November 4, 2021, for Byetta. DPV has not previously performed a pediatric postmarketing pharmacovigilance review for exenatide for the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Byetta and Bydureon BCise[d] labeling contain the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsections. For additional Byetta, Bydureon, or Bydureon BCise labeling information, please refer to the full prescribing information.[2,13,14]

Byetta[2]

----------CONTRAINDICATIONS ----------

- History of severe hypersensitivity to exenatide or any of the excipients in BYETTA. (4)
- History of drug-induced immune-mediated thrombocytopenia from exenatide products. (4)

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

- Never share a BYETTA pen between patients, even if the needle is changed. (5.1)
- Acute Pancreatitis: Postmarketing reports with exenatide, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue BYETTA promptly. BYETTA should not be restarted. Consider other antidiabetic therapies in patients with a history of pancreatitis. (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: Postmarketing reports with exenatide, sometimes requiring hemodialysis and kidney transplantation. BYETTA should not be used in patients with severe renal impairment or end-stage renal disease and should be used with caution in patients with renal transplantation. Caution should be applied when initiating BYETTA or escalating the dose of BYETTA in patients with moderate renal failure. (5.4, 8.6, 12.3)
- Severe Gastrointestinal Disease: Use of BYETTA is 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 BYETTA and promptly seek medical advice. (5.7)
- Drug-induced Immune-mediated Thrombocytopenia: Serious bleeding which may be fatal has been reported. Discontinue BYETTA promptly and avoid re-exposure to exenatide. (5.8)
- Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated. (5.9)
- 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. (5.10)

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

- Most common (≥5%) and occurring more frequently than placebo in clinical trials: nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia, constipation, asthenia. Nausea usually decreases over time. (5.3, 6)

[d] Bydureon and Bydureon BCise have near identical information in the Highlights section of the product labeling. For additional Bydureon labeling information, please refer to full prescribing information.

- Postmarketing reports with exenatide of increased international normalized ratio (INR) with concomitant use of warfarin, sometimes with bleeding. (6.2, 7.3)

8.4 Pediatric Use
The safety and effectiveness of BYETTA have not been established in pediatric patients.

Effectiveness of BYETTA was not demonstrated in a randomized, double-blind, placebo-controlled study conducted in 120 pediatric patients (78 received BYETTA and 42 received placebo) aged 10 to 17 years with type 2 diabetes mellitus.

Bydureon BCise[13]

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)**

----------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: 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 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: 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 m2. (5.4, 8.6, 12.3)
- Gastrointestinal Disease: Not recommended in patients with severe gastrointestinal disease (e.g., 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)

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.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	January 30, 2025
Time period of search	April 24, 2005† - January 29, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: Exenatide
MedDRA search terms (Version 27.1)	All Preferred Terms
Other search terms‡	Case Seriousness: Serious Country Derived: USA
* See Appendix A for a description of the FAERS database. † Byetta injection U.S. approval date ‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; USA=United States of America	

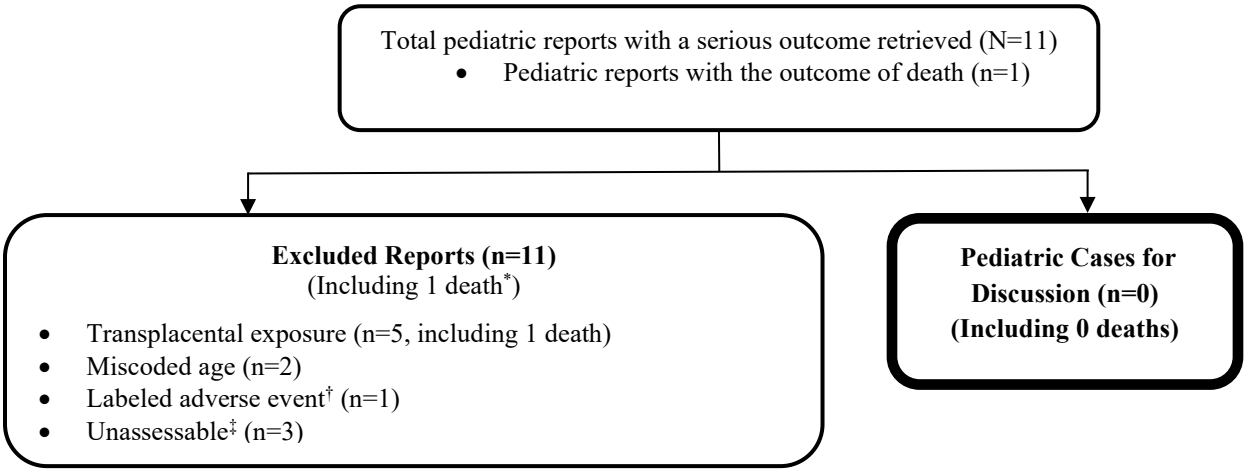
3 RESULTS

3.1 FAERS

3.1.1 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 11 U.S. serious pediatric reports for patients less than 18 years old from April 24, 2005 – January 29, 2025. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 11 reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of U.S. Serious Pediatric Cases With Exenatide



* One excluded U.S. FAERS report described a fatal outcome. The report described a neonate with a complicated prenatal course including prenatal exposure to exenatide and multiple other medications who was born prematurely and had congenital anomalies consistent with VACTERL syndrome. The case reports the patient died but did not provide any clinical context or history to determine cause of death.
† Labeled adverse event does not represent increased severity.
‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.3 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with exenatide in pediatric patients less than 18 years of age from April 24, 2005 – January 29, 2025, and identified 11 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with exenatide in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for exenatide at this time and will continue routine pharmacovigilance monitoring for exenatide.

6 REFERENCES

1. Byetta (exenatide) injection. [Prescribing information]. San Diego, CA; Amylin Pharmaceuticals, Inc.: April 2005.
2. Byetta (exenatide) injection. [Prescribing information]. Wilmington, DE; AstraZeneca Pharmaceuticals LP: November 2024.
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5. NDA 021773. FDA Drug shortages. Available at: https://dps.fda.gov/drugshortages/discontinuations/exenatide-synthetic-injection.
6. Bydureon (exenatide extended-release for injectable suspension). [Prescribing information]. San Diego, CA; Amylin Pharmaceuticals, Inc.: January 2012.
7. Bydureon (exenatide extended-release) for injectable suspension. [Prescribing information]. Wilmington, DE; AstraZeneca Pharmaceuticals LP: July 2021.
8. NDA 022200. Correspondence: Discontinuation of Marketing Drug Product Letter. September 21, 2020.
9. Bydureon BCise (exenatide extended-release) injectable suspension. [Prescribing information]. Wilmington, DE; AstraZeneca Pharmaceuticals LP: October 2017.
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11. NDA 209210. Correspondence: Discontinuation of Marketing Drug Product Letter. August 16, 2024.
12. NDA 209210. FDA Drug shortages. Available at: https://dps.fda.gov/drugshortages/discontinuations/exenatide-synthetic-injectable-suspension-extended-release.
13. Bydureon BCise (exenatide) extended-release injectable suspension. [Prescribing information]. Wilmington, DE; AstraZeneca Pharmaceuticals LP: November 2024.
14. Bydureon (exenatide) for extended-release injectable suspension. [Prescribing information]. Wilmington, DE; AstraZeneca Pharmaceuticals LP: November 2024.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a

product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.