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:	November 9, 2023
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Product Name:	Gvoke (glucagon) injection
Pediatric Labeling Approval Date:	September 10, 2019
Application Type/Number:	NDA 212097
Applicant:	Xeris Pharmaceuticals, Inc.
TTT Record ID:	2023-5967

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Gvoke (glucagon) injection in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with Gvoke in pediatric patients.

Gvoke (glucagon) injection, for subcutaneous use is available as an autoinjector, pre-filled syringe, and a kit containing a vial and syringe. It is an antihypoglycemic agent initially approved in the U.S. on September 10, 2019. Gvoke is currently indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and above.

This pediatric postmarketing safety review was stimulated by pediatric labeling upon Gvoke approval that included use in pediatric patients with diabetes ages 2 years and above.

DPV did not identify any U.S. serious FAERS reports with Gvoke in the pediatric population (0 - <18 years of age) from September 10, 2019, through August 10, 2023.

DPV did not identify any new pediatric safety concerns for Gvoke at this time and will continue to monitor all adverse events associated with the use of Gvoke.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Gvoke (glucagon) injection in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with Gvoke in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1]

Gvoke (glucagon) injection for subcutaneous use is available as an autoinjector, pre-filled syringe, and a kit containing a vial and syringe. It is an antihypoglycemic agent initially approved in the U.S. on September 10, 2019. Gvoke is currently indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and above.

This pediatric postmarketing safety review was stimulated by pediatric labeling upon Gvoke approval that included use in pediatric patients with diabetes ages 2 years and above.

DPV has not previously presented an evaluation of postmarketing adverse event reports for Gvoke in pediatric patients to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION[2]

The Gvoke labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* and *Pediatric Patients with Type 1 Diabetes Mellitus* subsections. For additional Gvoke labeling information, please refer to the full prescribing information.

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

- Pheochromocytoma
- Insulinoma
- Known hypersensitivity to glucagon or to any of the excipients

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

- Substantial Increase in Blood Pressure in Patients Pheochromocytoma: Contraindicated in patients with pheochromocytoma because GVOKE may stimulate the release of catecholamines from the tumor.
- Hypoglycemia in Patients with Insulinoma: In patients with insulinoma, administration may produce an initial increase in blood glucose; however, GVOKE may stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. If a patient develops symptoms of hypoglycemia after a dose of GVOKE, give glucose orally or intravenously.

- Hypersensitivity and Allergic Reactions: Allergic reactions have been reported and include generalized rash, and in some cases anaphylactic shock with breathing difficulties, and hypotension.
- Lack of Efficacy in Patients with Decreased Hepatic Glycogen: GVOKE is effective in treating hypoglycemia only if sufficient hepatic glycogen is present. Patients in states of starvation, with adrenal insufficiency or chronic hypoglycemia may not have adequate levels of hepatic glycogen for GVOKE to be effective. Patients with these conditions should be treated with glucose.
- Necrolytic Migratory Erythema (NME) a skin rash, has been reported postmarketing following continuous glucagon infusion and resolved with discontinuation of the glucagon. Should NME occur, consider whether the benefits of continuous glucagon infusion outweigh the risks.

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

- Most common adverse reactions (incidence 2% or greater) reported were:
- Adults—nausea, vomiting, injection site edema raised 1 mm or greater, and headache
- Pediatric Patients—nausea, hypoglycemia, vomiting, headache, abdominal pain, hyperglycemia, injection site discomfort and reaction, and urticaria

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

8.4 Pediatric Use

The safety and effectiveness of GVOKE for the treatment of severe hypoglycemia in patients with diabetes have been established in pediatric patients ages 2 years and above. Use of GVOKE for this indication is supported by evidence from a study in 31 pediatric patients ages 2 and older with type 1 diabetes mellitus.

The safety and effectiveness of GVOKE have not been established in pediatric patients younger than 2 years of age.

----------CLINICAL STUDIES----------

14.2 Pediatric Patients with Type 1 Diabetes Mellitus

GVOKE was evaluated in a study in 31 pediatric patients with type 1 diabetes mellitus. Patients were administered insulin to induce a plasma glucose of less than 80 mg/dL. Patients ages 2 to under 6 years and 6 to under 12 years of age then received a 0.5 mg dose of GVOKE. Patients ages 12 and older received a 0.5 mg or 1 mg dose of GVOKE.

All evaluable pediatric patients (30/30) achieved a target glucose increase of at least 25 mg/dL. Following administration, plasma glucose levels over time showed similar glucose responses for patients in each age group.

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	August 11, 2023
Time period of search	September 10, 2019† - August 10, 2023
Search type	RxLogix Post-Market Cases Quick Query
Product terms	Product Name: Gvoke, Gvoke Kit, Gvoke Kit Vial
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † U.S. approval date for Gvoke. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from September 10, 2019, through August 10, 2023, with Gvoke.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From September 10, 2019 -August 10, 2023 for Gvoke			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	10 (10)	2 (2)	1 (1)
Pediatrics (0 - < 18 years)	0 (0)	0 (0)	0 (0)
* May include duplicates and transplacental exposures, and have not been assessed for causality † 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.			

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

Our FAERS search retrieved no U.S. serious pediatric reports from September 10, 2019 through August 10, 2023.

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

Our FAERS search retrieved no U.S. fatal pediatric adverse event cases associated with Gvoke.

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

Our FAERS search retrieved no U.S. serious pediatric reports associated with Gvoke.

4 DISCUSSION

DPV searched FAERS for all reports with Gvoke in pediatric patients (ages 0- <18) received by the FDA from September 10, 2019, through August 11, 2023 and identified no cases.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths associated with Gvoke in pediatric patients.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Gvoke at this time.

6 REFERENCES

1. Drug Approval Package: Gvoke Injection. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212097Orig1s000TOC.cfm Accessed: August 14, 2023

2. Gvoke (glucagon) [package insert]. Chicago, IL. Xeris Pharmaceuticals, Inc. Revised August 2021.

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.

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/s/

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