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:	February 23, 2024
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Product Name:	Riomet ER (metformin hydrochloride for extended-release oral suspension)
Pediatric Labeling Approval Date:	August 29, 2019
Application Type/Number:	NDA 212595
Applicant:	Sun Pharmaceutical Industries, Ltd.
TTT Record ID:	2023-7529

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Riomet ER (metformin hydrochloride for extended-release oral suspension) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Riomet ER in pediatric patients.

Riomet ER is a biguanide originally approved in the U.S. on August 29, 2019, as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus. In 2020, the applicant for Riomet ER withdrew the application for NDA 212595. Riomet ER is no longer marketed in the United States.

This pediatric postmarketing safety review was prompted by the pediatric labeling at initial approval of Riomet ER, which included a pediatric indication. DPV has not previously presented Riomet ER for the Pediatric Advisory Committee (PAC). On February 14, 2005, the Office of Drug Safety (ODS) presented a postmarketing pharmacovigilance review for another metformin product, Glucovance (glyburide and metformin hydrochloride) tablets. ODS's evaluation identified no new safety concerns. The PAC agreed with ODS's recommendation to continue routine pharmacovigilance for Glucovance.

DPV searched FAERS for all serious reports with Riomet ER in pediatric patients less than 17 years of age through December 13, 2023, and did not identify any reports.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Riomet ER in pediatric patients less than 17 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Riomet ER (metformin hydrochloride for extended-release oral suspension) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Riomet ER in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Riomet ER is a biguanide originally approved in the U.S. on August 29, 2019. It is currently indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus.[1] In 2022, the applicant for Riomet ER withdrew the application for NDA 212595. Riomet ER is no longer marketed in the United States.[2]

This pediatric postmarketing safety review was prompted by the pediatric labeling at initial approval of Riomet ER which included a pediatric indication. DPV has not previously completed a pediatric postmarketing pharmacovigilance review for Riomet ER for the Pediatric Advisory Committee (PAC). On February 14, 2005, the Office of Drug Safety (ODS)[a] presented a postmarketing pharmacovigilance review for another metformin product, Glucovance (glyburide and metformin hydrochloride) tablets. ODS's evaluation identified no new safety concerns. The PAC agreed with ODS's recommendation to continue routine pharmacovigilance for Glucovance.[3]

1.2 RELEVANT LABELED SAFETY INFORMATION

The Riomet ER labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Riomet ER labeling information, please refer to the full prescribing information.[1]

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning

- **Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally > 5 mcg/mL. (5.1)**
- **Risk factors include renal impairment, concomitant use of certain drugs, age ≥ 65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5.1)**
- **If lactic acidosis is suspected, discontinue RIOMET ER and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

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

- Severe renal impairment (eGFR below 30 mL/min/1.73 m2) (4, 5.1)

[a] The Office of Drug Safety later became the Office of Surveillance and Epidemiology

- Hypersensitivity to metformin (4)
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. (4)

----------WARNINGS AND PRECAUTIONS----------
- Lactic acidosis: See boxed warning. (5.1)
- Vitamin B12 deficiency: Metformin may lower vitamin B12 levels. Measure
- hematological parameters annually and vitamin B12 at 2 to 3 year intervals and manage any abnormalities. (5.2)
- Hypoglycemia with Concomitant Use with Insulin and Insulin
- Secretagogues: Increased risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue. Lower dose of insulin or insulin secretagogue may be required (5.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions (> 5.0%) are diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache. (6.1)

8.4 Pediatric Use
The safety and effectiveness of RIOMET ER as an adjunct to diet and exercise to improve glycemic control in pediatric patients 10 years of age and older with type 2 diabetes mellitus have been established. Use of RIOMET ER for this indication is supported by evidence from adequate and well-controlled studies of metformin HCl immediate-release tablet in adults with additional data from a controlled clinical study using metformin HCl immediate-release tablets in pediatric patients 10 to 16 years old with type 2 diabetes mellitus [see Clinical Studies (14.1)].

Safety and effectiveness of RIOMET ER have not been established in pediatric patients less than 10 years old.

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	December 14, 2023
Time period of search	All dates through December 13, 2023
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product name: Riomet ER NDA: 212595
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, NDA=New Drug Application	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 1 presents the number of adult and pediatric FAERS reports through December 13, 2023, with Riomet ER.

Table X. Total Adult and Pediatric FAERS Reports* Received by FDA Through December 13, 2023, With Riomet ER			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	0 (0)	0 (0)	0 (0)
Pediatrics (0 - < 17 years)	1 (1)	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 Serious Pediatric Cases in FAERS

Our FAERS search retrieved no serious pediatric reports through December 13, 2023.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

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

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

4 DISCUSSION

DPV searched FAERS for all serious reports with Riomet ER in pediatric patients less than 17 years of age through December 13, 2023, and did not identify any reports.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Riomet ER in pediatric patients less than 17 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Riomet ER (metformin hydrochloride for extended-release oral suspension). [Prescribing information]. Cranbury, NJ; Sun Pharmaceutical Industries, Ltd: August, 2019.
2. Riomet ER (metformin hydrochloride for extended-release oral suspension). NDA 212595. Available at: Drugs@FDA: FDA-Approved Drugs
3. Swann J. ODS Postmarketing Safety Review. Glucovance (glyburide/metformin) NDA 021178. January 7, 2005. Available at: https://wayback.archive-it.org/7993/20170405100905/https://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4089b1_04_01_glyburide.pdf

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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