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: August 5, 2024

Reviewers: Omayma Kishk, PharmD, BCPPS, Safety Evaluator
Division of Pharmacovigilance I (DPV-I)

Ivone Kim, MD, Medical Officer
DPV-I

Team Leader: Carmen Cheng, PharmD
DPV-I

Division Director: Monica Muñoz, PharmD, PhD, BCPS
DPV-I

Product Name	**Pediatric Labeling Approval Date**	**Application Type/Number**	**Applicant**
Potassium Phosphates Injection (Potassium Phosphate, Dibasic; Potassium Phosphate, Monobasic) - (phosphorus 3 mmol/mL and potassium 4.7 mEq/mL)	September 19, 2019	NDA 212121	CMP Dev, LLC
Potassium Phosphates Injection (Potassium Phosphate, Dibasic; Potassium Phosphate, Monobasic) - (phosphorus 3 mmol/mL and potassium 4.4 mEq/mL)	November 26, 2019	NDA 212832	Fresenius Kabi USA, LLC

TTT Record ID: 2024-10316

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for potassium phosphates injection injection (potassium phosphate, dibasic; potassium phosphate, monobasic) 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 United States (U.S.) serious unlabeled adverse events associated with potassium phosphates in pediatric patients.

Potassium phosphates (potassium phosphate, dibasic; potassium phosphate, monobasic) is a phosphorus replacement product. Potassium phosphates injection is indicated in intravenous fluids to correct hypophosphatemia in adults and pediatric patients when oral or enteral replacement is not possible, is insufficient, or contraindicated. It is also indicated for parenteral nutrition in adults and pediatric patients when oral or enteral nutrition is not possible, insufficient or contraindicated.

There are currently two approved concentrations of potassium phosphates injection, for intravenous use. Potassium phosphates (phosphorus 3 mmol/mL and potassium 4.7 mEq/mL) was initially approved in the U.S. on September 19, 2019, under NDA 212121. The indication for NDA 212121 is limited to use in pediatric patients 12 years of age and older due to its aluminum content. Potassium phosphates (phosphorus 3 mmol/mL and potassium 4.4 mEq/mL) was initially approved in the U.S. on November 26, 2019, under NDA 212832. NDA 212832 is approved in adult and pediatric patients including pediatric patients less than 12 years of age.

This pediatric postmarketing safety review was stimulated by the pediatric labeling at initial U.S. approval for NDA 212121 and NDA 212832 on September 19, 2019, and November 26, 2019, respectively, that included pediatric indications.

DPV searched FAERS for all U.S. serious reports with potassium phosphates in pediatric patients less than 18 years of age from April 23, 2019, through July 9, 2024, 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 potassium phosphates in pediatric patients less than 18 years of age.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for potassium phosphates injection (potassium phosphate, dibasic; potassium phosphate, monobasic) 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 United States (U.S.) serious unlabeled adverse events associated with potassium phosphates in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Potassium phosphates (potassium phosphate, dibasic; potassium phosphate, monobasic) is a phosphorus replacement product. There are currently two concentrations of potassium phosphates injection, for intravenous use on the market.

Potassium phosphates (phosphorus 3 mmol/mL and potassium 4.7 mEq/mL) was initially approved in the U.S. on September 19, 2019, under NDA 212121.[1] Due to its aluminum content, the indication for NDA 212121 is limited to use in pediatric patients 12 years of age and older.[2] NDA 212121 is currently indicated as a source of phosphorus:

- in intravenous fluids to correct hypophosphatemia in adults and pediatric patients 12 years of age and older when oral or enteral replacement is not possible, insufficient or contraindicated.
- for parenteral nutrition in adults weighing at least 45 kg and pediatric patients 12 years of age and older weighing at least 40 kg when oral or enteral nutrition is not possible, insufficient or contraindicated.

Potassium phosphates (phosphorus 3 mmol/mL and potassium 4.4 mEq/mL) was initially approved in the U.S. on November 26, 2019, under NDA 212832.[3, 4] NDA 212832 is currently indicated as a source of phosphorus:

- in intravenous fluids to correct hypophosphatemia in adults and pediatric patients when oral or enteral replacement is not possible, insufficient or contraindicated.
- for parenteral nutrition in adults and pediatric patients when oral or enteral nutrition is not possible, insufficient or contraindicated.

This pediatric postmarketing safety review was stimulated by the pediatric labeling at initial U.S. approval for NDA 212121 and NDA 212832 on September 19, 2019, and November 26, 2019, respectively, that included pediatric indications.

On September 13, 2019, DPV completed a review of all postmarketing adverse event reports through April 22, 2019, for potassium phosphates in pediatric and adult patients. DPV's evaluation identified new safety concerns with potassium phosphates and recommended additions to the WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE sections that were incorporated to the labeling at approval.[2, 4]

A pediatric safety review for potassium phosphates has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The potassium phosphates labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional potassium phosphates labeling information, please refer to the full prescribing information.

1.2.1 Potassium Phosphates (potassium phosphate, dibasic; potassium phosphate, monobasic) (phosphorous 3 mmol/mL and potassium 4.7 mEq/mL) (NDA 212121)[1]

----------**CONTRAINDICATIONS**----------

- hyperkalemia
- hyperphosphatemia (4)
- hypercalcemia or significant hypocalcemia (4)
- severe renal impairment (eGFR less than 30 mL/min/1.73m^2) and end stage renal disease (4)

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

• Serious Cardiac Adverse Reactions with Undiluted, Bolus, or Rapid Intravenous Administration: Administer only after dilution or admixing; do not exceed the recommended infusion rate. Continuous electrocardiographic (ECG) monitoring may be needed during infusion.(5.1)
• Pulmonary Embolism due to Pulmonary Vascular Precipitates: If signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation. (5.2)
• Hyperkalemia: Increased risk in patients with renal impairment, severe adrenal insufficiency, or treated with drugs that increase potassium. Patients with cardiac disease may be more susceptible. Do not exceed the maximum daily amount of potassium or the recommended infusion rate. Continuous ECG monitoring may be needed during infusion. (5.3,7.1)
• Hyperphosphatemia and Hypocalcemia: Monitor serum phosphorus and calcium concentrations during and following infusion. (5.4)
• Aluminum Toxicity: Increased risk in patients with renal impairment, including preterm infants. (5.5, 8.4).
• Hypomagnesemia: Reported in patients with hypercalcemia and diabetic ketoacidosis. Monitor serum magnesium concentrations during treatment. (5.6)
• Vein Damage and Thrombosis: Infuse concentrated or hypertonic solutions through a central catheter. (2.1, 2.3, 5.7)

----------**ADVERSE REACTIONS**----------

Adverse reactions are hyperkalemia, hyperphosphatemia, hypocalcemia and hypomagnesemia. (6)

8.4 Pediatric Use

Safety and effectiveness of POTASSIUM PHOSPHATES INJECTION have been established in:
• pediatric patients 12 years and older as a source of phosphorus in intravenous fluids to correct hypophosphatemia when oral or enteral replacement is not possible, insufficient, or contraindicated.
• pediatric patients 12 years and older weighing at least 40 kg as a source of phosphorus for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

The safety of POTASSIUM PHOSPHATES INJECTION for parenteral nutrition has not been established in pediatric patients less than 12 years of age or in adolescents weighing less than 40 kg due to the risk of aluminum toxicity [see Indications and Usage (1.2), Warnings and Precautions (5.5)].

1.2.2 Potassium Phosphates (potassium phosphate, dibasic; potassium phosphate, monobasic) (phosphorus 3 mmol/mL and potassium 4.4 mEq/mL) (NDA 212832)[3]

----------CONTRAINDICATIONS----------
• hyperkalemia (4)
• hyperphosphatemia(4)
• hypercalcemia or significant hypocalcemia (4)
• severe renal impairment (eGFR less than 30 mL/min/1.73m2) or end stage renal disease (4)

----------WARNINGS AND PRECAUTIONS ----------
• Serious Cardiac Adverse Reactions with Undiluted, Bolus, or Rapid Intravenous Administration: Administer only after dilution or admixing; do not exceed the recommended infusion rate. Continuous electrocardiographic (ECG) monitoring may be needed during infusion. (2.2, 5.1)
• Pulmonary Embolism due to Pulmonary Vascular Precipitates: If signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation.(5.2)
• Hyperkalemia: Increased risk in patients with renal impairment, severe adrenal insufficiency, or treated with drugs that increase potassium. Patients with cardiac disease may be more susceptible. Do not exceed the maximum daily amount of potassium or the recommended infusion rate. Continuous ECG monitoring may be needed during infusion. (5.3, 7.1)
• Hyperphosphatemia and Hypocalcemia: Monitor serum phosphorus and calcium concentrations during and following infusion. (5.4)
• Aluminum Toxicity: Increased risk in patients with renal impairment, including preterm infants. (5.5, 8.4).
• Hypomagnesemia: Reported in patients with hypercalcemia and diabetic ketoacidosis. Monitor serum magnesium concentrations during treatment.(5.6)
• Vein Damage and Thrombosis: Infuse concentrated or hypertonic solutions through a central catheter. (2.1, 2.3, 5.7)

----------ADVERSE REACTIONS ----------
Adverse reactions include hyperkalemia, hyperphosphatemia, hypocalcemia, and hypomagnesemia. (6)

8.4 Pediatric Use
Safety and effectiveness of Potassium Phosphates Injection have been established in pediatric patients as a source of phosphorus:
• in intravenous fluids to correct hypophosphatemia when oral or enteral replacement is not possible, insufficient, or contraindicated.
• for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Because of immature renal function, preterm infants receiving prolonged parenteral nutrition treatment with Potassium Phosphates Injection may be at higher risk of aluminum toxicity. [see Warnings and Precautions (5.6)].

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	July 10, 2024
Time period of search	April 23, 2019† - July 9, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV

Table 1. FAERS Search Strategy*	
Product terms	Product Name: Potassium Phosphate, Potassium Phosphate, Dibasic\Potassium Phosphate, Monobasic, Potassium Phosphate, Dibasic, Potassium Phosphate, Monobasic, Potassium Phosphate, Unspecified Form, Potassium Phosphates
MedDRA search terms (Version 27.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database † Data lock date of most recent postmarketing pharmacovigilance review 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 April 23, 2019 through July 9, 2024, with potassium phosphates.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From April 23, 2019 through July 9, 2024, With Potassium Phosphates			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	89 (25)	85 (21)	16 (4)
Pediatrics (0 - < 18 years)	13 (0)	12 (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. The coded outcomes are report-level outcomes, i.e., they reflect any serious outcomes for any adverse events coded to a Preferred Term in the FAERS report. Therefore, a serious outcome may not apply to all adverse events in a FAERS report. A review of the FAERS report narrative is necessary to determine adverse event-level outcomes and any association to a suspect product.			

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

There are no fatal pediatric adverse event cases for discussion.

3.1.1 Selection of U.S. Serious Non-Fatal Pediatric Cases (N=0)

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

4 DISCUSSION

DPV searched FAERS for all U.S. serious reports with potassium phosphates in pediatric patients less than 18 years of age from April 23, 2019 through July 9, 2024, 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 potassium phosphates in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Potassium phosphates, for intravenous use [Prescribing Information]. Farmville, NC: CMP Pharma Inc.; September 2019.
2. Dimick-Santos L. NDA/BLA Multidisciplinary Review and Evaluation NDA 212121 Potassium Phosphates Injection. September 2019. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212121Orig1s000MultidisciplineR.pdf.
3. Potassium phosphates, for intravenous use [Prescribing Information]. Lake Zurich, IL: Fresenius Kabi USA; November 2019.
4. Mehta R. NDA/BLA Multidisciplinary Review and Evaluation NDA 212832 Potassium Phosphates Injection. November 2019. https://www.fda.gov/media/133481/download?attachment

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.