

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212121Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 10, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 212121
Product Name and Strength:	potassium phosphates injection, USP phosphorous 45 mmol/15 mL (3mmol/mL)
Applicant/Sponsor Name:	CMP Development LLC (CMP)
FDA Received Date:	September 6, 2019
OSE RCM #:	2019-685-2
DMEPA Safety Evaluator:	Sherly Abraham, R Ph
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on September 6, 2019 for potassium phosphates injection, USP. DGIEP requested that we review the revised container label and carton labeling for potassium phosphates injection, USP (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label and the carton labeling are unacceptable from a medication error perspective. Below, we have provided recommendations in Table 1. We ask that the Division convey Table 1 in its entirety to CMP Development LLC (CMP) so that recommendations are implemented prior to approval of this NDA.

^a Abraham, S. Label and Labeling Review for potassium phosphates injection, USP (NDA 212121). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 3. RCM No.: 2019-685-1.

3 RECOMMENDATIONS FOR CMP DEVELOPMENT LLC (CMP)

We recommend the following be implemented prior to approval of this NDA:

Table 1. Identified Issues and Recommendations for CMP Development LLC (CMP) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	Negative statement “Do not freeze.” is identified.	Due to our understanding of post-marketing reports, negative statements may have the opposite of intended meaning because the word ‘not’ can be overlooked and the warning be misinterpreted as an affirmative action. ^b	Revise the identified negative sentence to read “Protect from freezing”.
Carton Labeling			
1.	The strength presentation statement is lacking prominence.	Prominence and readability of the strength presentation is required per 21 CFR 201.15(a)(6).	Increase the prominence of the strength presentation similar to the container label without decreasing the prominence of the cautionary statement “ CAUTION: MUST BE DILUTED ”.

^b Institute for Safe medication practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Safe Alert Acute Care. 2010;15(16):1-3.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
09/10/2019 03:23:55 PM

IDALIA E RYCHLIK
09/10/2019 03:30:17 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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PEDIATRIC LABELING REVIEW

From: Carolyn L. Yancey, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

Through: Hari Cheryl Sachs, MD, Pediatric Team Leader, DPMH
John J. Alexander, MD, MPH, Deputy Director, DPMH

NDA Number: 212121

Sponsor: CMP Development, LLC

Drug: Potassium Phosphates Injection

Drug Class: Phosphorus Replacement Product

**Dosage Form, Strength,
Route of Administration:** Injection, for intravenous (IV) use: 45 millimole (mmol)/ phosphorus (3 mmol phosphorus/mL) in a single dose 15 milliliter (mL) vial. Each vial also contains 71 milliequivalent (mEq) potassium (4.7 mEq potassium/mL).

Approved Indication: None

Proposed Indication: Potassium Phosphates Injection is indicated in adults and pediatric patients 12 years of age and older as:

- a source of phosphorus, for addition to large volume intravenous fluids, to prevent or correct hypophosphatemia in patients with restricted or no oral intake
- an additive for preparing specific parenteral fluid formulas when the needs of the patient cannot be met by standard electrolyte or nutrient solution

Proposed Dosing Regimen: The dose and rate of administration are dependent upon the individual needs of the patient with the adult maximum dose of 45 mmol phosphorus per day.

Consult Request: The Division of Gastroenterology and Inborn Errors Products (DGIEP) requests the DPMH Pediatric Team review of pediatric labeling for the new drug application (NDA) 212121 for Potassium Phosphates Injection, for IV use, 45 mmol phosphorus/15 mL (3 mmol

phosphorus/mL, manufactured by CMP Development, LLC (CMP). NDA 212121 is submitted via a 505(b)(2) regulatory pathway relying on the listed product, Sodium Phosphates Injection, 45 mmol (3 mmol phosphate/mL) under NDA 018892 by Hospira, Incorporated. DPMH will assist with pediatric labeling recommendations. The consult is due on August 26, 2019 (consult is dated March 19, 2019).

Background

The listed product, Sodium Phosphates Injection was FDA-approved on May 10, 1983 under NDA 018892 Sodium Phosphates Injection, 45 mM (3 mM phosphorus/mL) which also contains 4 mEq/mL sodium by Hospira, Incorporated. Sodium phosphates is a sterile, nonpyrogenic, concentrated solution containing a mixture of monobasic sodium phosphate and dibasic sodium phosphate in water for injection provided as a 15 mL partial fill single-dose vial.¹ Sodium Phosphates Injection is indicated for all ages, including neonates as “a source of phosphorus, for addition to large volume IV fluids, to prevent or correct hypophosphatemia in patients with restricted or no oral intake. It is also useful as an additive for preparing specific parenteral fluid formulas when the needs of the patient cannot be met by standard electrolyte or nutrient solutions.”² The solution with sodium phosphates is intended as an alternative to potassium phosphate to provide phosphorus for addition to large volume infusion fluids for intravenous use. Approved labeling for sodium phosphates includes dosing for all ages, including neonates. Use of sodium phosphates includes caution in patients with renal impairment, cirrhosis, cardiac failure and other edematous or sodium-retaining conditions.³

NDA 212121 is submitted, as an alternative to sodium phosphates injection, as a source of phosphorus in patients who are at risk for administration of sodium/sodium restricted, i.e., patients with renal impairment, cirrhosis, cardiac failure and other edematous or sodium-retaining conditions. The dose of phosphorus and rate of administration needs to be individualized based on careful monitoring of serum potassium, phosphorus, calcium, and magnesium. Each mL contains 175 milligrams (mg) of monobasic potassium phosphate, (b) (4), and 300 mg of dibasic potassium phosphate, (b) (4). One mmol of phosphorus weighs 31 mg, and the product provides 93 mg (approximately 3 mmol) of phosphorus/mL and 4.7 mEq of potassium/mL.⁴ The maximal adult phosphorus dosage is 45 millimoles of phosphorus per 24 hours.

Phosphorus in the form of organic and inorganic phosphate has a variety of biochemical functions in the body and is involved in many metabolic and enzyme reactions in almost all organs and tissues. Phosphorus exerts a modifying influence on the steady state of calcium levels, a buffering effect on acid-base equilibrium, and a key role in renal excretion of hydrogen ions. Potassium is the major cation of intracellular fluid and is essential for conduction of nerve impulses in heart, brain, and skeletal muscle; contraction of cardiac, skeletal and smooth muscles; as well as maintenance of normal renal function, acid-base balance, carbohydrate metabolism, and gastric secretion. In adult and pediatric patients who are phosphorus depleted and are hypophosphatemic, the mechanism of action of IV potassium phosphate is to replete phosphorus.⁵

The labeling under this review is for Potassium Phosphates Injection (cited above) submitted on March 19, 2019 by CMP. The applicant seeks to revise the target patient population for parenteral nutrition to include adults and to limit pediatric patients to adolescents, 12 years and older weighing at least 40 kg because this formulation contains an unsafe level of aluminum for patients less than 12 years of age or for adolescent

¹ NDA 018892 Sodium Phosphates Injection by Hospira (approved on May 10, 1983), see section on Description and on Clinical Pharmacology

² NDA 018892 Sodium Phosphates Injection by Hospira, see section on Indications and Usage (PLR labeling).

³ NDA 01889 Sodium Phosphates Injection by Hospira, see section on Precautions.

⁴ NDA 212121 Potassium Phosphates Injection by CMP proposed labeling see Section 11 Description (per DGIEP dated August 26, 2019).

⁵ NDA 212121 Potassium Phosphates Injection proposed labeling (Section 12.3 Mechanism of Action (per DGIEP dated August 26, 2019).

patients weighing less than 40 kg.

Reviewer Comment:

This proposed formulation has relatively high levels of aluminum and therefore, will not be recommended for parenteral nutrition in pediatric patients less than 12 years of age weighing less than 40 kg or adolescent patients weighing less than 40 kg. Potentially toxic levels of aluminum may occur with prolonged parenteral administration if kidney function is impaired. Preterm infants are particularly at risk for aluminum toxicity because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which also contain aluminum. Patients with impaired kidney function, including preterm neonates who receive greater than 4 to 5 mcg/kg/day of parenteral aluminum can accumulate aluminum to levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.⁶ Safety risks of aluminum toxicity are addressed in the proposed substantially complete labeling for Potassium Phosphates Injection [see Indications and Usage (1), Warnings and Precautions (5.6), and Pediatric Use (8.4)].

Pediatric Research Equity Act Requirements

Under PREA, (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. CMP's drug product, Potassium Phosphates Injection is a new active ingredient.

Agreed initial Pediatric Study Plan

An Agreed iPSP (dated December 14, 2018 under investigational new drug (IND) 122149 includes:

- plans to request deferral of required pediatric studies in patients from neonates to less than 12 years of age until the time an age appropriate formulation with an acceptable level of aluminum becomes available and
- plans to perform a pediatric assessment based on adult-to-pediatric extrapolation with literature findings to support the proposed indications (cited earlier in this review) for adolescents, 12 years to less than 18 years of age.

There are currently no planned pediatric pharmacokinetic (PK) studies or pediatric efficacy and safety studies. ^{(b) (4)}

Reviewer Comments: This iPSP was discussed at PeRC on December 12, 2018 and the committee concurred with the general plan. DPMH defers to CMC on the approach to resolve the existing level of aluminum that is only acceptable in patients 12 years and older weighing at least 40 kg for parenteral nutrition. ^{(b) (4)}

NDA 212121 Potassium Phosphates Injection Pediatric Assessment

The applicant proposes to rely on published literature for extrapolation from adult data based on extensive clinical experience with the dosing regimen for sodium phosphates injection as well as potassium phosphates injection (though the later product is marketed and unapproved). There are no adequate and well-controlled

⁶ See 21 Code of Federal Regulations (CFR): <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=201.323>

clinical studies in pediatric patients. Phosphorus dosing and total parenteral nutrition (TPN) requirements in adolescents (as well as younger pediatric patients down to neonates) is described in clinical practice guidelines for parenteral nutrition formulation recommendations⁷ as well as a single daily bolus dosing recommendation.^{8,9} The applicant used published literature to recommend pediatric once daily dosing based on laboratory reference ranges for serum phosphate and serum potassium. Conditions such as drug-drug interactions as well as diabetic ketoacidosis (DKA) with a higher risk of hyperkalemia are considered among the literature submitted in the pediatric assessment. DPMH agrees with the applicant's approach to dosing potassium phosphates injection considering the safety risks driven by hyperkalemia and hyperphosphatemia which underscore the need for electrocardiographic (ECG) monitoring as well as careful monitoring of serum phosphorus, potassium and calcium levels during treatment.

The DGIEP clinical review team concludes that the proposed formulation relying on the approved unmarketed product (Sodium Phosphates Injection under NDA 018892 by Hospira) will be acceptable for parenteral nutrition in patients 12 years and older weighing at least 40 kg and acceptable as a source of phosphorus in intravenous fluids in patients 12 years and older based on the approval of sodium phosphates in pediatric patients, extensive clinical experience and the published literature submitted in the pediatric assessment. Dosing in adolescents will be weight-based relying on reference laboratory ranges for phosphorus. The maximum dose of 40 mmol phosphorus is consistent with published guidelines in adolescent patients and limited for use in parenteral nutrition to adolescents weighing at least 40 kg due to the aluminum content. DPMH agrees with DGIEP/Clinical Pharmacology and Chemistry and Manufacturing Controls (CMC) with limiting the indication and usage of CMP's Potassium Phosphates Injection formulation in parenteral nutrition to patients 12 years and older weighing at least 40 kg based on the aluminum content which is unacceptable for younger patients less than 12 years of age or adolescents weighing less than 40 kg.

Reviewer Comments: DPMH agrees that efficacy can be extrapolated from adults to adolescents and supports a weight-based dosing regimen for adolescents that will be adjusted based on phosphate and other relevant electrolytes, namely potassium and calcium. DPMH defers to DGIEP Clinical/Clinical Pharmacology to revise Section 2.4 Recommended Dosage and Monitoring to add a dosing regimen for parenteral nutrition in pediatric patients 12 years to less than 18 years of age weighing at least 40 kg and to inform prescribers on the maximal dosage of 40 mmol phosphorus per day for adolescents.

PREA Post Marketing Requirement

DGIEP proposes a PREA PMR to develop an age-appropriate formulation with an acceptable aluminum content for use in parenteral nutrition in pediatric patients less than 12 years of age and adolescents as well as younger patients weighing less than 40 kg.

DPMH Pediatric Labeling Recommendations

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population compared with the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric population. The proposed indication for CMP's Potassium Phosphates

⁷ The Harriett Lane Handbook, A Manual for Pediatric House Officers (2^{1st} Edition), Chapter 21 Nutrition and Growth, Initiation and

⁸ Advancement of Parenteral Nutrition, American Society for Parenteral and Enteral Nutrition (ASPEN). Safe practices for parenteral nutrition. JPEN 2004; 28(6):S39-S70.

⁹ Lexicomp Pediatric & Neonatal Dosage Handbook – An Extensive Resource for Clinicians Treating Pediatric and Neonatal Patients. 2017 Wolters Kluwer Clinical Drug Information.

Injection is in adults and pediatric patients 12 years of age and older weighing at least 40 kg for parenteral nutrition and in adults and pediatric patients 12 years and older as a source of phosphorus, the two indications as cited earlier in this review.

As stated previously, the applicant proposes to restrict the proposed indication in parenteral nutrition to adults and adolescents 12 years and older weighing at least 40 kg because the aluminum concentration is not acceptable (too high) in younger/lighter weight pediatric patients. Proposed labeling, submitted in non-PLLR format, includes revisions to update Section 2 Dosage and Administration on important preparation and administration instructions, recommended rate of infusion and the need for ECG monitoring during potassium infusions. Labeling cautions not to infuse potassium phosphates with calcium containing IV fluids and consider mmol of phosphorus and mEq of potassium in the calculation of the dose and rate of administration due to the risk of hyperkalemia, Warnings and Precautions (5.3) and hyperphosphatemia and hypocalcemia (5.4). Safety risk information on aluminum toxicity appears in (5.5) as well as in (8.4) Pediatric Use reporting that the safety of potassium phosphates injection has not been established for parenteral nutrition in pediatric patients less than 12 years of age or in adolescents weighing less than 40 kg due to the risk of aluminum toxicity. This safety risk information in Section 8.4 is cross-referenced with Indications and Usage (1), and Warnings and Precautions (5.3) and (5.5). There is no juvenile animal data reported in Section 8.4. See reviewer comments later in this review.

DPMH defers to DGIEP/Clinical Pharmacology and Clinical Review Team on revisions to Indications and Usage, Dosing and Administration, and Warnings and Precautions based on the well-known safety risks associated with potassium phosphates injection. The Division of Pharmacovigilance (DPV) review¹⁰ includes events of hyperkalemia, hyperphosphatemia, hypocalcemia, and aluminum toxicity as well as adverse reactions cited in labeling Section 6 Adverse Reactions. DGIEP substantially complete proposed Potassium Phosphates Injection, for IV use, labeling is dated September 9, 2019. DPMH's recommended information to be added to the labeling is underlined. Information to be deleted has a ~~strike through~~. Comments and rationale for DPMH's recommendations to the labeling are in *italics*.

1 INDICATIONS AND USAGE

1.1 In Intravenous Fluids to Prevent or Correct Hypophosphatemia

(b) (4)



1.2 For Parenteral Nutrition

(b) (4)



Reviewer Comments: DPMH recommends separating the indications into subsections (1.1 and 1.2) to more

¹⁰ NDA 212121 Potassium Phosphates Injection, Pharmacovigilance Review by Michelle Hines, PharmD, BCPS (dated August 13, 2019)

clearly inform prescribers that pediatric patients 12 years and older are included in the target population for use of this potassium phosphates formulation as a source of phosphorus to correct hypophosphatemia. However, pediatric patients 12 years and older weighing at least 40 kg are included in the indication for parental nutrition. DPMH recommends no longer considering adding a Limitations of Use statement as safety risk information on aluminum toxicity is adequately addressed in Warnings and Precautions (5.5). DPMH agrees with DGIEP's changes to the indication statement, noting the indication may be restricted to only one indication statement, namely "to prevent or correct hypophosphatemia in patients with restricted or no oral intake".

2.4 Dosage and Monitoring for Administration in Parenteral Nutrition

POTASSIUM PHOSPHATES Injection provides phosphorus 3 mmol/mL (potassium 4.7 mEq/mL).

Individualize the dosage based upon the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral phosphorus and potassium intake. The amount of phosphorus that can be added to parenteral nutrition may be limited by the amount of calcium that is also added to the solution (b) (4) .

Daily Dosage

In adults and pediatric patients 12 years of age weighing at least 40 kg, the generally recommended dosage is phosphorus 20 to 45 mmol/day (potassium 31 to 71 mEq/day) in parenteral nutrition.

In patients with moderate renal impairment (eGFR > 30 mL/min/1.73 m² to < 60 mL/min/1.73 m²) start at the low end of the dosage range.

The maximum dose of POTASSIUM PHOSPHATES Injection is phosphorus 45 mmol per day (potassium 70.5 mEq/day) based upon the aluminum content of the products [see Warnings and Precautions (5.65), Use in Specific Populations (8.4)].

Monitoring

Monitor serum phosphorus, potassium, calcium and magnesium (b) (4) concentrations and adjust the dosage accordingly.

Reviewer Comments: As of this review, these are preliminary revisions from DGIEP Clinical Pharmacology to the applicant's proposed labeling. However, DPMH acknowledges that there will be extensive revisions to Section 2.4 Recommended Dosage and Monitoring. DPMH recommends that the maximum dosage for parenteral nutrition should be clearly specified and defers to DGIEP Clinical Pharmacology on the maximum threshold value which is limited by the aluminum content as well as the potassium. DPMH also recommends describing dosages in mg/kg and informing prescribers that the maximal dosage for this formulation in pediatric patients 12 years and older weighing at least 40 kg is limited by the aluminum content. DPMH recommends to spell-out the terms, phosphorus and potassium, rather than using abbreviations and to employ units of phosphorus as millimole (mmol). DPMH recommends including a minimum patient weight of at least 40 kg based on 40 mmol of Phosphorus/day as the maximal dose for adolescent patients 12 years and older.

8 USE IN SPECIAL POPULATIONS

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 to correct hypophosphatemia. 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 possible, insufficient, or contraindicated.

Safety and effectiveness of POTASSIUM PHOSPHATES Injection have been established in pediatric patients 12 years and older weighing at least 40 g as a source of phosphorus for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated

(b) (4)



Reviewer Comments: DPMH recommends to first state the two different target pediatric populations in which the product will be indicated and then inform prescribers that the safety of POTASSIUM PHOSPHATES Injection has not been established in pediatric patients less than 12 years of age or weighing less than 40 kg for the parenteral nutrition indication due to the risk of aluminum toxicity. DPMH recommends cross referencing this risk to Section (1) Indications and Usage (1.2) as well as Warnings and Precautions (5.3) and (5.5).

DPMH Actions and Labeling Recommendations

DPMH reviewed the applicant's proposed labeling for POTASSIUM PHOSPAHTES Injection, for intravenous use and participated in meetings with the DGIEP Clinical Team from May 2, 2019 to September 5, 2019. The most recent proposed labeling revisions per DGIEP are dated September 9, 2019. DPMH labeling recommendations were provided in meeting discussions for DGIEP consideration. DPMH input will be reflected in the final labeling and the action letter from DGIEP. Final labeling will be negotiated with the applicant and may differ from comments and recommendations in this DPMH labeling review. See the **Appendix** for a summary of the information in the Unireview, Section 10 Pediatrics.

Appendix

Summary in Unireview

Under the Pediatric Research Equity Act (PREA) (21 U. S. C. 335), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. This NDA 212121 for Potassium Phosphates Injection, USP previously a marketed unapproved drug product, is a new active ingredient (new salt) and therefore, triggers PREA. Currently, there is no approved and marketed formulation of potassium phosphates injection in pediatric patients of any age group. There is an approved NDA 018892 for Sodium Phosphates Injection by Hospira, LLC. indicated in all pediatric age groups. NDA 212121, under this review, relies on the listed product by Hospira for safety and efficacy. The parenteral phosphorus product under NDA 212121 will be approved for parenteral nutrition in adults and pediatric patients 12 years to less than 18 years of age weighing at least 40 kg due to the elevated aluminum content which is too high for younger (less than 12 years of age) and lighter patients (less than 40 kg). The maximum proposed amount of phosphates (1 mmol/kg/day, maximum 40 mmol/day) would yield more than 5 mcg/kg/day of aluminum for an adolescent less than 40 kg. In addition, (b) (4)

The parenteral product under NDA 212121 will also be approved as a source of phosphorus to correct hypophosphatemia in adult and pediatric patients 12 years and older.

There is an Agreed Initial Pediatric Study Plan (iPSP), dated December 14, 2018 under IND 122149, that details a plan for a pediatric assessment based on adult-to-pediatric extrapolation of efficacy using published literature findings to support the two proposed indications (e.g., as a source of phosphorus for correcting or preventing hypophosphatemia and/or as an additive to parenteral fluid formulas). The iPSP also outlines plans to request a deferral for the assessment in patients from birth to less than 12 years of age, including the appropriate dose regimen for this age group for use in parenteral nutrition, until the time at which an age-appropriate formulation with an acceptable level of aluminum becomes available. The applicant proposes to rely on published literature for extrapolation from adult data based on extensive clinical experience with the dosing regimen for sodium and potassium phosphates injection (though the latter product is marketed and unapproved). There are no adequate and well-controlled clinical studies in pediatric patients. Phosphorus dosing to correct hypophosphatemia and for use in total parenteral nutrition (TPN) requirements in adolescents (as well as younger pediatric patients down to neonates) are described in clinical practice guidelines for parenteral nutrition formulation recommendations. There are currently no planned pediatric pharmacokinetic (PK) studies or pediatric efficacy and safety studies. (b) (4)

Therefore, a new PREA postmarketing requirement (PMR) is proposed for the applicant to develop an age-appropriate formulation with an acceptable aluminum content for pediatric patients less than 12 years of age and for lower-weight adolescents for use in parenteral nutrition. The safety risks of hyperkalemia, hyperphosphatemia, and hypocalcemia and the dosing in adolescent patients are similar to adults. The maximum dosing for use in parenteral nutrition in pediatric patients less than 12 years of age or adolescents weighing less than 40 kg, however is limited by the amount of aluminum in the formulation.

Section 8.4 (Pediatric Use) will reflect that safety and effectiveness of POTASSIUM PHOSPHATES Injection have been established in pediatric patients 12 years and older as a source of phosphorus to correct hypophosphatemia and that safety and effectiveness of POTASSIUM PHOSPHATES have been established for parenteral nutrition in pediatric patients 12 years and older weighing at least 40 kg, also noting in Section 8.4 that the safety of Potassium Phosphates Injection, USP has not been established for lower weight adolescent patients less than 40 kg or younger pediatric patients less than 12 years of age for parenteral nutrition. A separate Division of Pediatric and Maternal Health (DPMH) Labeling Review is in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS) dated September 9, 2019.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CAROLYN L YANCEY

09/09/2019 04:23:33 PM

NDA 212121 Potassium Phosphates Injection DPMH Labeling Review

HARI C SACHS

09/09/2019 04:57:06 PM

I agree with these recommendations.

JOHN J ALEXANDER

09/09/2019 06:03:12 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 3, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 212121
Product Name and Strength:	potassium phosphates injection, USP 45 mmol phosphorous/15 mL (3 mmol phosphorous/mL)
Applicant/Sponsor Name:	CMP Development LLC (CMP)
FDA Received Date:	August 21, 2019
OSE RCM #:	2019-685-1
DMEPA Safety Evaluator:	Sherly Abraham, R Ph
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and new carton labeling for single count vial received on August 21, 2019 for potassium phosphates injection, USP. DGIEP requested that we review the revised container label and new carton labeling for potassium phosphates injection, USP (Appendix A) to determine if it is acceptable from a medication error perspective. (b) (4)

[REDACTED] The container revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label and the new carton labeling are unacceptable from a medication error perspective. Below, we have provided recommendations in Table 1. We ask that the

^a Abraham, S. Label and Labeling Review for potassium phosphates injection, USP (NDA 212121). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 15. RCM No.: 2019-685.

Division convey Table 1 in its entirety to CMP Development LLC (CMP) so that recommendations are implemented prior to approval of this NDA.

3 RECOMMENDATIONS FOR CMP DEVELOPMENT LLC (CMP)

We recommend the following be implemented prior to approval of this NDA:

Table 1. Identified Issues and Recommendations for CMP Development LLC (CMP) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	(b) (4)		
2.			
3.			
2.	The statement “ Must be refrigerated ” is omitted from the storage statement.	Lack of prominence of refrigeration information may result in the risk of the storage information being overlooked.	Revise and bold (carton labeling) the storage statement to read “ Must be refrigerated, store at 2°C to 8°C (36°F to 46°F). ”.
3.	Negative statement “Contains no more than 15,000 mcg/L of aluminum.” is identified.	Due to our understanding of post-marketing reports, negative statements may have the opposite of intended meaning because the word ‘not’ can be overlooked and the warning be misinterpreted as an affirmative action. ^c	Revise the identified negative sentence to read “Contains 15,000 mcg/L or less of aluminum”.

^b Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Safe Alert Acute Care. 2014;19(23):1-4.

^c Institute for Safe medication practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Safe Alert Acute Care. 2010;15(16):1-3.

Table 1. Identified Issues and Recommendations for CMP Development LLC (CMP) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	(b) (4)		
Carton Labeling			
1.	The strength presentation statement is lacking prominence.	Prominence and readability of the strength presentation is required per 21 CFR 201.15(a)(6).	Increase the prominence of the strength presentation similar to the container label.
2.	It is difficult to decipher which face of the carton is the principal display panel (PDP).	All three sides (PDP and the two side panels) of the carton labeling appear very similar. This similarity may lead the reader to overlook important information such as the warning/cautionary statements and the route of administration (ROA) statement on the PDP.	Ensure all sides of the carton labeling mirror the primary display panel. Utilize the back panel for all auxiliary information typically found on the side and back panel, including the storage statement.
3.	As currently displayed, the net quantity statement is as prominent as the product strength statement.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is prominent.	Decrease the prominence of the net quantity statement.
4.	The “Rx Only” statement is prominent and clutters	As currently presented, the “Rx only” statement takes	Relocate the “Rx Only” statement to the corner of

Table 1. Identified Issues and Recommendations for CMP Development LLC (CMP) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	the important warning/cautionary statement (CAUTION: MUST BE DILUTED)	away readers attention from more important warning/cautionary statement " CAUTION: MUST BE DILUTED ".	the PDP similar to the container label.

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/s/

SHERLY ABRAHAM
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09/03/2019 02:27:34 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 15, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 212121
Product Name and Strength:	potassium phosphates injection, USP 45 mM phosphorous/15 mL (3 mM phosphorous/mL)
Total Product strength:	45 mM phosphorous/15 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	CMP Development LLC
FDA Received Date:	March 19, 2019 and June 7, 2019
OSE RCM #:	2019-685
DMEPA Safety Evaluator:	Sherly Abraham, R Ph
Postmarketing Reviewer:	Ashleigh Lowery, PharmD, BCCCP
DMEPA Team Leader (Acting):	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the review process for potassium phosphates, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the proposed potassium phosphates prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
FDA Adverse Event Reporting System (FAERS)*	C
Other	D-N/A
Labels and Labeling	E

N/A=not applicable for this review

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container label, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Postmarketing Medication Error Cases			
1.	18 FAERS Medication Error Cases associated with potassium phosphates injection or sodium phosphate injection that are described in appendix C2.	We note that a 15 mL vial of potassium phosphate injection contains 71 mEq of potassium and is at risk for serious adverse events and death if administered undiluted.	As currently presented, the dilution warning in the prescribing information (PI) is expressed as a negative statement, "Not for direct injection". Although no root cause could be attributed to the medication error cases reviewed, post-marketing

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		DMEPA considered the risk of medication errors and the following current mitigations: a) Potassium phosphates is included on the Institute of Safe Medication Practices (ISMP) high alert list.^a b) ISMP has published safety strategies for Potassium phosphates injection. Their recommendations include development of standard protocols, 'order sets' (preprinted or electronic) and removal of potassium phosphates injection storage from patient care areas.^b d) The Joint Commission has advised that concentrated electrolytes are not to be kept in patient care areas where access is not urgently needed.^c As per Joint Commission guidelines, when an organization determines that concentrated	reports have shown negative statements may have the opposite of the intended meaning because the word 'not' may be overlooked and the warning may be misinterpreted as an affirmative action. In order to potentially further mitigate the risk for medication preparation and administration errors, we provide alternative language in the Prescribing Information section of Table 2, recommendation 5 below. Moreover, we note that the proposed container label and carton labeling prominently state the "Must be Diluted" statement, however to ensure proper administration of drug product, we provided additional recommendations to the Applicant in the Container label section of Table 3, recommendation 2 and Carton labeling section of Table 3, recommendation 2 below.

^aISMP's List of High-Alert Medications in Acute Care Settings [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2014 [cited 2019 JUL 08]. Available from: <https://www.ismp.org/recommendations/high-alert-medications-acute-list>

^b <https://www.ismp-canada.org/download/safetyBulletins/ISMPCSB2006-02PotassiumPhosphates.pdf>.

^chttps://www.jointcommission.org/standards_information/jcfaqdetails.aspx?StandardsFAQId=1534

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		electrolytes will be stored outside of the pharmacy, appropriate safeguards must be developed to prevent inadvertent administration of these medications without proper dilution.^d e) Both the carton labeling and container labels have prominent warning statements (CAUTION: Must dilute) on the Principal Display Panel (PDP). Additionally, the rate of infusion is prominently stated in the Dosage and administration section of the FPI.	
Prescribing Information – General Issues			
2.	The strength presentation (45 mM) is missing the word “Phosphorus” in some sections.	Inconsistencies in strength presentation can lead to confusion and dosing errors.	Revise the strength presentation to read 45 mM phosphorous/15 mL (3 mM phosphorous/mL)
3.	As currently presented, the strength quantity statement is expressed without the total volume.	Expressing the strength presentation without total volume could lead to dosing errors.	Revise the strength presentation to include total quantity per total volume. For example, 45 mM phosphorous/15 mL (3 mM phosphorous/mL) 71 mEq potassium/15 mL

^dhttps://www.jointcommission.org/standards_information/jcfaqdetails.aspx?StandardsFAQId=1534.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			(4.7 mEq potassium/mL)
4.	(b) (4)	The usage of symbols and abbreviations can cause misinterpretation and confusion. ^e	Replace the symbols and abbreviations with their intended meaning.
5.		Due to our understanding of post-marketing reports, negative statements may have the opposite of intended meaning because the word 'not' can be overlooked and the warning be misinterpreted as an affirmative action. ^f	Revise the negative statement 'Not for direct injection' to read 'Intravenous infusion after dilution and admixing only'.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, important dosage and administration information is burdensome to read and difficult for the reader to decipher.	Presenting important dosage and administration information to the reader in a text heavy format with decreased readability may lead to misinterpretation and medication preparation and administration errors.	To increase readability, consider the use of additional subsections within Section 2: Dosage and Administration. For example, consider organizing information into the following subsections: 2.1 Important Administration Information, 2.2 Preparation and Administration Instructions, 2.3 Preparation Instructions for Admixing Parental Nutrition.
2.	(b) (4)	Per USP guidelines, the correct terminology utilized for Normal Saline	We recommend using the terminology "0.9% Sodium Chloride Injection, USP" instead of Normal Saline.

^eISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 Sep 16]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

^f Institute for Safe medication practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Safe Alert Acute Care. 2010;15(16):1-3.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		should be: 0.9% Sodium Chloride Injection, USP.	
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	(b) (4)	(b) (4)	(b) (4)

Table 3. Identified Issues and Recommendations for CMP Development LLC (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	(b) (4)	Strength presentation is inconsistent with the Prescribing Information.	Align the strength statement with the PI; revise the strength presentation to read 45 mM phosphorous/15 mL (3 mM phosphorous/mL)
2.	As currently presented, the strength quantity statement omits the total volume metric unit of measure (i.e. mL).	Ensuring the product strength is expressed as total quantity per total volume followed by the concentration per milliliter (mL) mitigates the potential for medication dosing errors.	Revise the strength presentation to express total quantity per total volume, ensure the strength statements prominently displayed. For example: 45 mM phosphorous/15 mL (3 mM phosphorous/mL) 71 mEq potassium/15 mL (4.7 mEq potassium/mL)
3.	(b) (4)	In order to minimize the risk of the entire contents of the vial being given as a	Revise the statement “Single-Dose” to read “Single-Dose

Table 3. Identified Issues and Recommendations for CMP Development LLC (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)	single dose, appropriate package type terms and instruction should be utilized.	Vial – Discard Unused Portion”.
4.	The machine readable product identifier required under the Drug Supply Chain Security Act (DSCSA) is missing on the label.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. ¹ The Act requires manufacturers and re-packagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling.
5.	(b) (4)	(b) (4)	(b) (4)

Table 3. Identified Issues and Recommendations for CMP Development LLC (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			(b) (4)
6.	Usage of confusing symbols and abbreviations (e.g., “mM”, “P” and “K”)	The usage of symbols and abbreviations can cause misinterpretation and confusion.	Replace the symbols and abbreviations with their intended meaning.
Container Label			
1.	As currently displayed, the manufacturer name(“CMP”) is more prominent in size than the most important information (i.e., established name, strength, route of administration).	This takes readers’ attention away from other important information such as established name, strength, route of administration and cautionary statements.	Decrease the prominence of the manufacturer name on the Principal Display Panel (PDP).
2.	(b) (4)	Omitting product dilution and administration warnings and inclusion of abbreviations in the ROA statement can create confusion and lead to prescribing or administration errors.	Revise the route of administration statement from (b) (4) to “For intravenous infusion after dilution and admixing only”.
3.	The net quantity statement is more prominent than the product strength statement.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity	Decrease the prominence of net quantity statement. Consider font/formatting options such as black, unbolded font and relocating statement to a less prominent position on the Primary

Table 3. Identified Issues and Recommendations for CMP Development LLC (entire table to be conveyed to Applicant)

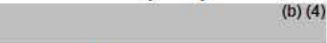
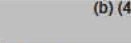
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		statement is more prominent.	Display Panel (such as to the bottom of the label).
4.	It is unclear if the linear barcode on the container label is scannable when placed around the curvature of the vial.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature.	Verify that the linear barcode on the container label is scannable when placed around the curvature of the vial.
5.	Inconsistent terminology used for recommended dosage statement.	21 CFR 201.55	To ensure consistency with the Prescribing Information, revise the statement, "Usual dosage: See prescribing information" to read "Recommended Dosage: See prescribing information."
Carton Labeling			
1.	As currently depicted,  (b) (4) competes in prominence with the established name of the product and strength statement.	21 CFR 201.10 (a), 21 CFR 202.1(a)(1)	Remove or relocate the graphic and decrease the prominence of  (b) (4) to ensure that it does not compete in prominence with more important product information on the PDP.
2.	ROA is missing from the PDP.	As per 21 CFR 201.100(b)(3), ROA is required to be on the PDP in a non-abbreviated statement.	Add the following ROA statement to the PDP: "For intravenous infusion after dilution and admixing only".
3.	The storage statement "Store at 2°C to 8°C (36°F to 46°F)" is on the PDP.	PDP is reserved for the most important information. The storage information should be on the side panel.	Relocate the storage statement from PDP to side panel.

Table 3. Identified Issues and Recommendations for CMP Development LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	The admixed product storage information is missing.	To minimize the risk of administering expired products.	If space permits, storage information for admixed product should be included on the carton labeling.
5.	(b) (4)	(b) (4)	(b) (4)
6.	The “Rx only” statement is missing from the PDP.	The “Rx only” statement is required on the drug label by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.	Add the “Rx only” statement to PDP of carton labeling.
7.	The “Usual Dose” statement is missing from the side panel.	The “Usual Dose” statement is required as per 21 CFR 201.55	Include a usual dose statement to the side panel of the carton labeling. “Recommended Dosage: See prescribing information.”
8.	As currently presented, there is more than one linear barcode on labeling.	The drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes may be confusing to healthcare providers.	We recommend removing duplicate/unnecessary barcodes from labeling.
9.	The lot number statement is missing.	The lot number statement is required as per 21 CFR 201.10(i)(1).	Submit the lot number statement.

4 CONCLUSION

Our evaluation of the proposed potassium phosphates prescribing information (PI), container label, and carton labeling identified areas of vulnerability that may lead to medication errors.

Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to CMP Development LLC so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for potassium phosphates that CMP Development LLC submitted on March 19, 2019 and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and potassium phosphates		
Product Name	sodium phosphate	potassium phosphates
Initial Approval Date	May 10, 1983	N/A
Active Ingredient	sodium phosphate	potassium phosphates
Indication	Sodium phosphate is indicated as a source of phosphorous, for addition to large volume intravenous fluids, to prevent or correct hypophosphatemia in patients with restricted or no oral intake. It is also useful as an additive for preparing specific parenteral fluid formulas when the needs of the patient cannot be met by standard electrolyte or nutrient solutions.	potassium phosphates is indicated: - as a source of phosphorus, for addition to large volume intravenous fluids, to prevent or correct hypophosphatemia in patients with restricted or no oral intake. - as an additive for preparing specific parenteral fluid formulas when the needs of the patient cannot be met by standard electrolyte or nutrient solutions
Route of Administration	Intravenous	
Dosage Form	Injection	
Strength	45 mmol Phosphorus/15 mL (3 mmol Phosphorous/mL)	
Dose and Frequency	In patients on total parenteral nutrition, approximately 12 mM to 15 mM of phosphorous (equivalent to 372 to 465 elemental phosphorus) per liter bottle of TPN solution containing 250 gram dextrose is usually adequate to maintain normal serum phosphorous though larger amounts maybe required in hypermetabolic states.	<u>Adults</u> : The maximum dosage is 45 mM phosphate per day. Dosage may be determined based per kg body weight or a fixed dose regimen. The following recommended dosages are suitable for most patients: 0.16 mmol P/kg to 0.64 mmol P/kg (or 10 mmol P to 45 mmol P) infused over 3 to 6 hours (≤ 7 mmol P/hr). However, based on clinical requirements, some patients

	The suggested dose of phosphorous for infants receiving TPN is 1.5 to 2 mM P/kg/day.	may require higher or lower dosages. <u>Pediatric Patients 12 to <18 years of age</u>: The dose and rate of administration are dependent on the individual needs of the patient. The maximum dose in adolescent patients (12 to <18 years of age) is 40 mM phosphate per day or (b) (4). Dosage may be determined based per kg body weight or a fixed dose regimen. Recommended dosages are: 0.16 mmol P/kg to 0.64 mmol P/kg (b) (4). However, based on clinical requirements, some patients may require higher or lower dosages
How Supplied	Tray containing 25 vials and each single-dose vial is 15 mL.	15 mL single-dose glass vial
Storage	Store at 20°C to 25°C (68°F to 77°F)	Store at 2° - 8°C (36°F to 46°F).

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 12, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, potassium phosphate. Our search identified no previous reviews.

APPENDIX C. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

C.1 Methods

On June 19, 2019, we searched FAERS using the criteria in the table below and identified 108 case reports. We individually reviewed the cases, and limited our analysis to cases that described medication errors associated with potassium phosphate injection or sodium phosphate injection. We used the NCC MERP Taxonomy of Medication Errors to code the type of error and factors contributing to the errors when sufficient information was provided by the reporter.⁸ We excluded 88 reports that were associated with oral or rectal dosage forms (e.g., Visicol, Neutra-Phos, sodium phosphate enema), 1 report involving sodium chloride and sodium acetate (not potassium phosphate or sodium phosphate), and 1 report that described the use of a potassium phosphate product a week prior to receiving a recall notice for the product.

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	Initial marketing to 01Jun2019
Product Name:	---
Product Active Ingredient (PAI):	POTASSIUM PHOSPHATE,POTASSIUM PHOSPHATE, DIBASIC,POTASSIUM PHOSPHATE, DIBASIC\POTASSIUM PHOSPHATE, MONOBASIC,POTASSIUM PHOSPHATE, DIBASIC\POTASSIUM PHOSPHATE, MONOBASIC\SODIUM PHOSPHATE, DIBASIC\SODIUM PHOSPHATE, MONOBASIC,POTASSIUM PHOSPHATE, DIBASIC\SILICON DIOXIDE\MILK THISTLE\SODIUM SULFATE\STRYCHNOS NUX-VOMICA SEED,POTASSIUM PHOSPHATE, DIBASIC\SODIUM,POTASSIUM PHOSPHATE, DIBASIC\SODIUM CHLORIDE\SODIUM PHOSPHATE, DIBASIC, ANHYDROUS,POTASSIUM PHOSPHATE, DIBASIC\SODIUM CHLORIDE\TRIBASIC CALCIUM PHOSPHATE,POTASSIUM PHOSPHATE, DIBASIC\SODIUM PHOSPHATE, DIBASIC, ANHYDROUS\SODIUM SULFATE,POTASSIUM PHOSPHATE, DIBASIC\SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE\TRIBASIC CALCIUM PHOSPHATE,POTASSIUM PHOSPHATE, MONOBASIC,POTASSIUM PHOSPHATE, MONOBASIC\SODIUM BICARBONATE,POTASSIUM PHOSPHATE, MONOBASIC\SODIUM PHOSPHATE, DIBASIC, ANHYDROUS,POTASSIUM PHOSPHATE, MONOBASIC\SODIUM PHOSPHATE, DIBASIC, ANHYDROUS\SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE,POTASSIUM PHOSPHATE, MONOBASIC\SODIUM PHOSPHATE, DIBASIC\SODIUM PHOSPHATE, MONOBASIC,POTASSIUM PHOSPHATE, MONOBASIC\SODIUM PHOSPHATE, MONOBASIC, ANHYDROUS,POTASSIUM PHOSPHATE, UNSPECIFIED FORM,POTASSIUM PHOSPHATE\SODIUM,POTASSIUM PHOSPHATE\SODIUM

⁸ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Available from: <https://www.nccmerp.org/sites/default/files/taxonomy2001-07-31.pdf>

Criteria Used to Search FAERS	
	PHOSPHATE,SODIUM PHOSPHATE,SODIUM PHOSPHATE DIHYDRATE\SODIUM PHOSPHATE, MONOBASIC,SODIUM PHOSPHATE P-32,SODIUM PHOSPHATE, DIBASIC,SODIUM PHOSPHATE, DIBASIC, ANHYDROUS,SODIUM PHOSPHATE, DIBASIC, ANHYDROUS\SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE\SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE,SODIUM PHOSPHATE, DIBASIC, ANHYDROUS\SODIUM PHOSPHATE, MONOBASIC,SODIUM PHOSPHATE, DIBASIC, ANHYDROUS\SODIUM PHOSPHATE, MONOBASIC, ANHYDROUS,SODIUM PHOSPHATE, DIBASIC, ANHYDROUS\SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE,SODIUM PHOSPHATE, DIBASIC, DIHYDRATE,SODIUM PHOSPHATE, DIBASIC, DIHYDRATE\SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE,SODIUM PHOSPHATE, DIBASIC, DODECAHYDRATE\SODIUM PHOSPHATE, MONOBASIC,SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE\SODIUM PHOSPHATE, MONOBASIC,SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE\SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE,SODIUM PHOSPHATE, DIBASIC, MONOHYDRATE,SODIUM PHOSPHATE, DIBASIC\SODIUM PHOSPHATE, DIBASIC, DODECAHYDRATE,SODIUM PHOSPHATE, DIBASIC\SODIUM PHOSPHATE, MONOBASIC,SODIUM PHOSPHATE, DIBASIC\SODIUM PHOSPHATE, MONOBASIC, ANHYDROUS,SODIUM PHOSPHATE, MONOBASIC,SODIUM PHOSPHATE, MONOBASIC, ANHYDROUS,SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE,SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM,SODIUM PHOSPHATE, TRIBASIC, DODECAHYDRATE,SODIUM PHOSPHATE\SODIUM PHOSPHATE, DIBASIC,SODIUM PHOSPHATE\SODIUM PHOSPHATE, DIBASIC, ANHYDROUS,SODIUM PHOSPHATE\SODIUM PHOSPHATE, MONOBASIC,SODIUM PHOSPHATE\SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM
Product Role	Primary Suspect
Event:	SMQ <i>Medication errors</i> (Narrow)
Country (Derived):	USA

C.2 Results

Using the methods described in Appendix C.1, we identified 18 medication error case reports.

As shown in Table 6 below, most of the cases (n=17/18) were associated with potassium phosphate, and involved wrong drug errors (n=8/18) followed by preparation errors (n=5/18), wrong dose errors (n=4/18), and wrong dose and wrong drug error (n=1/18). Eleven patients were impacted by the error, including ten cases that reported a serious outcome (death: 7, and “arrested”, “cardiac arrest” or “required resuscitation”: 3). The ten cases describing a serious outcome were associated with preparation errors (e.g., not diluted or incorrectly diluted prior to administration, wrong concentration compounded), wrong dose error secondary to miscalculation or transcribing a verbal order, and wrong drug error (e.g., solution compounded with calcium gluconate instead of the intended potassium phosphate).

Table 6 summarizes the reported characteristics for the 18 case reports. Section C.3 provides a line listing of the 18 case reports.

Table 6. Summary of Reported Characteristics for US FAERS Medication Error Cases Associated with Potassium Phosphate Injection or Sodium Phosphate Injection, marketing to 01Jun2019, n=18	
Reported Characteristic	# of Cases Reporting
Product Name	
Potassium Phosphate	17
Sodium Phosphate	1
Type of Error (categorized by originating error)	
Wrong drug	8
- Product compounded with Calcium Gluconate instead of intended Potassium Phosphate, root cause not provided (1) - Administered Potassium Phosphate instead of intended Heparin Flush, one report stated cause as "potassium phosphate is not clearly labeled" (2) - Potassium Phosphate vials look alike with Sodium Phosphate vials (2) - Potassium Phosphate vials look alike with Sodium Acetate vials (2) - Potassium Phosphate vials look alike with Sodium Bicarbonate vials (1)	
Preparation error	5
- Potassium phosphate administered undiluted (2) - Potassium phosphate diluted 15 mL in 15 mL of NS; administered at 1 mL/min (1) - Potassium phosphate-calcium precipitate not noticed prior to administration (1) - Sodium phosphate solution incorrectly prepared and delivered 501 mmol dose instead of intended 25 mmol (1)	
Wrong dose (all involving Potassium Phosphate)	4
"Order entered as 7.3 mEq = 7.3 mM K Phos which it does not" - Dose ordered in milligrams of phosphate, and an error occurred when the dose was converted to mEq - Verbal order for "K Phos 40 mEq in 1/ 2 NS 200 cc over 3 hours" was transcribed as "K Phos 400 mEq in 1/ 2 NS 200 cc over 3 hours" - Verbal order for "15 mmol" misunderstood as "50 mmol"	
Wrong drug/Wrong dose (illegible handwritten order)	1
Root Causes/Contributing Factors (cases may described more than 1 root cause/contributing factor)	17
Concentrated potassium phosphate dispensed in syringe or available on patient care units	
Unclear order (includes illegible, verbal, text orders)	

Table 6. Summary of Reported Characteristics for US FAERS Medication Error Cases Associated with Potassium Phosphate Injection or Sodium Phosphate Injection, marketing to 01Jun2019, n=18	
• Knowledge deficit (didn't realize the product needed to be diluted, unfamiliar with "dialysis circuit")	
• "Followed old procedure" when compounding sodium phosphate solution	
• Unit of measure confusion (between mg and mmol and or mEq)	
• Labeling confusion (e.g., not clearly labeled)	
• Look alike labels and or container closures	
• Precipitate not noticed	
• IV solution improperly labeled by pharmacy	
• Root cause or contributing factors not reported (1)	
Serious Outcomes	10
Death (7) Patient "arrested" in emergency department, experienced "cardiac arrest" in dialysis unit), or "required resuscitation" (3)	

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^h along with postmarket medication error data, we reviewed the following potassium phosphates labels and labeling submitted by CMP Development LLC.

- Container label received on March 19, 2019
- Carton labeling received on March 19, 2019
- Prescribing Information (Image not shown) received on June 7, 2019
<\\cdsesub1\evsprod\nda212121\0007\m1\us\1-14-labeling\1-14-1-draft-labeling\1-14-3-1-draft-pi-clean.docx>

F.2 Label and Labeling Images

Container label(s)

(b) (4)



1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

^h Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Division of Pediatric and Maternal Health Memorandum

Date: June 10, 2019 **Date Consulted:** March 22, 2019

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Lynne Yao, MD, Director
Division of Pediatric and Maternal Health (DPMH)

To: Thao Vu, Regulatory Project Manager (RPM)
Division of Gastroenterology and Inborn Error Products (DGEIP)

Drug: Potassium Phosphates Injection

NDA: 212121

Proposed Indication: A source of phosphorus, for addition to large volume intravenous fluids, to prevent or correct hypophosphatemia in patients with restricted or no oral intake.

An additive for preparing specific parental fluid formulas when the needs of the patient cannot be met by standard electrolyte or nutrient solutions.

Applicant: CMP Development LLC

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- NDA 212121 submitted on March 19, 2019

Consult Question: DGEIP requests review of PLLR labeling for this new NDA

INTRODUCTION

On March 19, 2019, the applicant, CMP Development LLC, submitted an original new drug application (NDA) for Potassium Phosphates Injection via the 505(b)(2) regulatory pathway. On March 22, 2019, the Division of Gastroenterology and Inborn Error Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections.

BACKGROUND

Regulatory History

- The proposed indications for Potassium Phosphates Injection in adult and pediatric patients 12 years of age and older include:
 - a source of phosphorus, for addition to large volume intravenous fluids, to prevent or correct hypophosphatemia in patients with restricted or no oral intake.
 - an additive for preparing specific parental fluid formulas when the needs of the patient cannot be met by standard electrolyte or nutrient solutions.
- Potassium Phosphate has been approved for use in a number of large volume parental and irrigation solution products, but none of these products are approved for the treatment of hypophosphatemia.
- The applicant is relying on the Agency's previous finding of safety and efficacy for the listed drug, Sodium Phosphates Injection (NDA 018892), approved in 1983 as well as published literature. Potassium Phosphates Injection provides the same phosphorus concentration and will be administered at the same dosage level, for the same duration, and for the same indication as the listed drug.

Potassium Phosphates Injection Drug Characteristics¹

- *Mechanism of action (MOA):* In adult and pediatric patients who are hypophosphatemic, the MOA of intravenous potassium phosphate is to replete phosphorous. Phosphorus has a variety of important biochemical functions in the body and is involved in many significant metabolic and enzyme reactions in almost all organs and tissues. It exerts a modifying influence on the steady state of calcium levels, a buffering effect on acid-base equilibrium, and a primary role in the renal excretion on hydrogen ion. Potassium is the major cation of intracellular fluid and is essential for the conduction of nerve impulses in heart, brain, and skeletal muscles; contraction of cardiac, skeletal and smooth muscles; maintenance of normal renal function, acid-base balance, carbohydrate metabolism, and gastric secretion.
- *Dosage forms and strengths:* Single-dose vial which contains 3 mM of phosphorus/mL and 4.7 mEq of potassium/mL
- *Dosage and administration:* The dosage and rate of administration are dependent on the individual needs of the patient. Monitor for serum phosphorus, potassium, and calcium.
- *Adverse reactions:* Hyperphosphatemia, hyperkalemia, and aluminum toxicity

Reviewer's Comment

The proposed labeling includes Warnings and Precautions for hyperkalemia and aluminum toxicity particularly in patients with renal impairment (including preterm infants because

¹ Potassium Phosphates Injection (NDA 212121) proposed prescribing information

preterm infants have physiologically low GFR). Pregnant women do not appear to be at increased risk for these adverse reactions because normal pregnancy is characterized by a physiologic increase in the glomerular filtration rate (GFR) which results in a decrease in the serum creatinine concentration.²

Current State of the Labeling³

Sodium Phosphates Injection (NDA 018892), the listed drug relied upon, currently approved labeling is not in the Physicians Labeling Rule (PLR) format or the PLLR format.

- *Pregnancy:* Animal reproduction studies have not been conducted with sodium phosphate. It is also not known whether sodium phosphate can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Sodium phosphate should be given to a pregnant woman only if clearly needed.
- No information is included regarding use in lactation or effects on fertility.

Practice Guidelines for Parenteral Nutrition in Pregnancy⁴

Few pregnant women will require use of parental nutrition; however, the American College of Obstetrics and Gynecology (ACOG) supports the use of parental nutrition when both anti-emetic medications and enteral feedings via naso-gastric tube have failed to maintain the pregnant women's weight in patients with hyperemesis gravidarum.

Reviewer's Comment

DPMH previously reviewed the published literature related to the effects of malnutrition in pregnancy.⁵ DPMH concluded severe malnutrition in pregnancy is associated with adverse maternal and fetal outcomes including preterm delivery, low birth weight, intrauterine growth restriction, congenital malformations, and perinatal mortality.

Phosphorous is essential for metabolic functions and is tightly regulated by bone and kidney. The recommended dietary allowance (RDA) of phosphorus is 700 mg per day in adult women, pregnant women, and lactating women.⁶ No studies have examined the effect of dietary phosphorus on mineral economy in pregnancy or on the health outcomes for the mother or child.

REVIEW

PREGNANCY

Nonclinical Experience

Animal reproduction studies have not been conducted with Potassium Phosphates Injection.

Applicant's Review of Published Literature

The applicant did not perform a published literature search related to potassium phosphate and pregnancy.

² Maternal physiology. In: Williams Obstetrics, 24th ed, Cunningham FG, Leveno KJ, Bloom SL, et al (Eds), McGraw-Hill Education, 2014. p63.

³ Sodium Phosphates Injection currently approved labeling.

⁴ ACOG Practice Bulletin Clinical Management Guidelines for Ob/Gyns, No. 189. Nausea and Vomiting of Pregnancy, January 2018.

⁵ DPMH Review of Travasol (amino acids) Injection by Jane Liedtka, MD, dated August 19, 2016.

⁶ Picciano MF: Pregnancy and lactation: physiological adjustments, nutritional requirements and the role of dietary supplements. J Nutr 2003; 133:1997S-2002S.

DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, Micromedex⁷, TERIS⁸, Reprotox⁹, and Briggs¹⁰ to find relevant articles not cited by the applicant. Search terms included: “potassium phosphate” AND “pregnancy,” “pregnant women,” “birth defects,” “congenital malformations,” “stillbirth,” “spontaneous abortion,” or “miscarriage.”

- No relevant publications were identified in **PubMed** or **Embase**.
- **Micromedex** states “Pregnancy Category C. There are no adequate and well-controlled studies of potassium phosphate use in pregnant women.”
- **Reprotox** states “Potassium phosphate includes three potassium salts with one, two, or three potassium atoms per molecule of phosphoric acid. These agents have been used as buffers, food additives, and in fertilizers. A solution of mono and dibasic potassium phosphate is available as a supplement to intravenous fluids for prevention or correction of hypophosphatemia. We have not located published studies on possible reproductive or lactation effects of these agents. Monopotassium phosphate was found not to be embryotoxic or teratogenic in mice or rats when administered to the dam at up to 320 mg/kg and 282 mg/kg, respectively.”¹¹
- No reference to potassium phosphate was found in **Briggs** or **TERIS**.

LACTATION

Nonclinical Experience

Animal lactation studies have not been performed with Potassium Phosphates Injection.

Applicant's Review of Published Literature

The applicant did not perform a published literature search related to potassium phosphate and lactation.

DPMH's Review of Published Literature

This Reviewer performed a search in *Medications and Mother's Milk*¹², LactMed¹³, Micromedex⁷, Reprotox⁹, Briggs¹⁰, PubMed, and Embase using the terms “potassium phosphate” AND “lactation” OR “breastfeeding.”

⁷Truven Health Analytics information, <http://www.micromedexsolutions.com>, Accessed 5/30/19.

⁸TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 5/30/19.

⁹Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 2/13/19

¹⁰ Briggs GG, et al. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*, 9th Ed. 2011.

¹¹ Food and Drug Research Labs: Teratologic evaluation of FDA 73-65, monopotassium phosphate, in mice and rats. NTIS Report PB-245 521, 1975. <https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB245521.xhtml>.

¹² Hale, Thomas (2017) *Medications and Mother's Milk*. Amarillo, Texas. Hale Publishing.

¹³ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 5/30/19

- No relevant publications were identified in **PubMed** or **Embase**.
- **Micromedex** states “infant risk cannot be ruled out. It is not known whether potassium phosphate is excreted into human breast milk, and the potential for adverse effects in the nursing infant from exposure to the drug are unknown.”
- **Reprotox** states “potassium phosphate has been used in human milk fortifiers for preterm infants.”¹⁴
- No reference to potassium phosphate was found in *Medications in Mother’s Milk*, **LactMed**, or **Briggs**.

Reviewer’s Comment

Phosphate is a normal constituent of breastmilk.¹⁵ Breastmilk generally provides infants approximately 130 mg of inorganic phosphorus daily.¹⁶ There have been few studies on the effect of the maternal diet on the metabolism or breastmilk concentrations of phosphorus.¹⁷ However, limited evidence suggests that dietary intakes of phosphorus has little influence on breastmilk composition.¹⁸

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Animal studies have not been conducted with potassium phosphate to establish the effects on fertility and reproductive performance.

Applicant’s Review of Published Literature

The applicant did not perform a published literature search related to the effects of potassium sulfate on male and female fertility.

DPMH’s Review of Published Literature

This Reviewer performed a search in PubMed, Embase, and Reprotox⁹ using the terms “potassium phosphate” AND “fertility,” “contraception,” “oral contraceptives,” OR “infertility.”

- No relevant publications were identified.

¹⁴ Lauwers J, et al. 2010. Counseling the Nursing Mother. Sudbury, MA: Jones and Bartleett Learning, pg. 204.

¹⁵ Kent JC, et al. Calcium, phosphate and citrate in human milk at initiation of lactation. J Dairy Res. 1992;59:161-7.

¹⁶ Allen JC, et al. Studies in human lactation: milk composition and daily secretion rates of macronutrients in the first year of lactation. Am J Clin Nutr. 1991;54:69-80.

¹⁷ Prentice, A. Micronutrients and the bone mineral content of the mother, fetus, and newborn. The Journal of Nutrition, Volume 133, Issue 5, May 2003, Pages 1693S-1699S.

¹⁸ Bates C. J. & Prentice A. (1996) Vitamins, minerals and essential trace elements. In: Drugs and Human Lactation, 2nd Edition, (Bennett P. ed.), pp. 533–607. Elsevier, Amsterdam.

DISCUSSION and CONCLUSIONS

Pregnancy

Phosphorus is an essential mineral needed for numerous metabolic functions. Although animal reproduction studies have not been conducted with Potassium Phosphates Injection, both Potassium Phosphate and the listed drug relied upon (Sodium Phosphate) have been used in humans for decades. Potassium Phosphate Injection is not expected to be harmful during pregnancy as there are no published reports of adverse pregnancy outcomes due to phosphate supplementation in pregnant women.

DPMH recommends subsection 8.1 of labeling state administration of the approved recommended dose of Potassium Phosphates Injection in parental nutrition is not expected to cause major birth defects, miscarriage, or adverse maternal or fetal outcomes. DPMH also recommends adding a Clinical Consideration for prescribers to consider parental nutrition with potassium phosphate if a pregnant woman's nutritional requirements cannot be fulfilled by oral or enteral intake.

Lactation

DPMH recommends subsection 8.2 of labeling state that phosphorus is present in human milk. Administration of the approved recommended dose of Potassium Phosphates Injection in parental nutrition is not expected to cause harm to a breastfed infant. There is no information on the effects of potassium phosphate on milk production. DPMH recommends including the following risk/benefit statement, "the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Potassium Phosphates Injection and any potential adverse effects on the breastfed infant from Potassium Phosphates Injection or from the underlying maternal condition."

Females and Males of Reproduction Potential

DPMH recommends subsection 8.3 of labeling be omitted. There are no available human or animal data to evaluate the effects of potassium phosphate on fertility. Pregnancy testing and contraception subheadings are not recommended because there are no data to suggest potassium phosphate is associated with embryo-fetal toxicity.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR. The recommendations below are pending input from the Nonclinical Review Team. DPMH discussed our labeling recommendations with the Division at the June 12, 2019 labeling meeting. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Potassium Phosphates Injection Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Administration of the approved recommended dose of Potassium Phosphates Injection in parental nutrition is not expected to cause major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with Potassium Phosphates Injection.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo-Fetal Risk

Phosphorus is an essential mineral in pregnancy. Parental nutrition with potassium phosphate should be considered if a pregnant woman's nutritional requirements cannot be fulfilled by oral or enteral intake.

8.2 Lactation

Risk Summary

Phosphorus is present in human milk. Administration of the approved recommended dose of Potassium Phosphates Injection in parenteral nutrition is not expected to cause harm to a breastfed infant. There is no information on the effects of potassium phosphate on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Potassium Phosphates Injection and any potential adverse effects on the breastfed infant from Potassium Phosphates Injection or from the underlying maternal condition.

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/s/

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