CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

018892Orig1s037

Trade Name:	SODIUM PHOSPHATES
Generic or Proper Name:	(Disodium Hydrogen Phosphate (Dibasic Sodium Phosphate) and Monosodium Phosphate Monohydrate (Monobasic Sodium Phosphate)
Sponsor:	HOSPIRA INC.
Approval Date:	July 17, 2023
Indication:	Sodium Phosphates Injection, USP, 3 mM P/mL 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. 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. The concomitant amount of sodium (Na+ 4 mEq/mL) must be calculated into total electrolyte dose of such prepared solutions.

CENTER FOR DRUG EVALUATION AND RESEARCH

018892Orig1s037

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	
Product Quality Review(s)	**X**
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

See List of Applications

APPROVAL LETTER

Hospira Inc
Attention: Nicole Botimer
Manager, Pfizer Global Regulatory Affairs
275 North Field Drive
Bldg H1
Lake Forest, IL 60045

Dear Nicole Botimer:

Please refer to your supplemental New Drug Application(s) (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following products:

Supplemental Application	Product Information	Submit Date	FDA Received Date
NDA 018800/S-038	Bacteriostatic Sodium Chloride Injection, USP, 0.9%	February 17, 2023	February 17, 2023
NDA 018802/S-040	Bacteriostatic Water for Injection	February 17, 2023	February 17, 2023
NDA 018803/S-059	Sodium Chloride Injection, USP, 0.9%	February 17, 2023	February 17, 2023
NDA 018892/S-037	Sodium Phosphates Injection, USP, 3 mM/mL	February 17, 2023	February 17, 2023
NDA 018897/S-039	Sodium Chloride Injection, USP, 14.6%	February 17, 2023	February 17, 2023

These “Changes Being Effected in 30 days” supplemental new drug applications provide for:

Revisions to the environmental monitoring program fo (b) (4)
products at Hospira’s Rocky Mount, NC Manufacturing facilit (b) (4)

- (b) (4)

- Updating of table column headers and other minor updates in the description of the program or updates to terminology are editorial, improve clarity of the information being provided, and align with the site SOP.

APPROVAL

We have completed our review of these supplemental applications. These supplements are approved.

We remind you that you must comply with reporting requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Megan Nguyen, Regulatory Business Process Manager, at Megan.Nguyen@fda.hhs.gov or (301) 796 - 7826.

Sincerely,

{See appended electronic signature page}

David B. Lewis, Ph.D.
Branch Chief, B2
Division of Post-Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

David Lewis

Digitally signed by David Lewis
Date: 7/17/2023 03:17:39PM
GUID: 508da72000029f287fa31e664741b577
Comments: concur; recommend approval from the standpoint of CMC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

018892Orig1s037

LABELING

Caution must be exercised in the administration of parenteral fluids, especially those containing sodium ions, to patients receiving corticosteroids or corticotropin.

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 reproduction capacity. Sodium phosphate should be given to a pregnant woman only if clearly needed.

Pediatric Use: The safety and effectiveness of sodium phosphate has been established in pediatric patients (neonates, infants, children and adolescents).

Geriatric Use: An evaluation of current literature revealed no clinical experience identifying differences in response between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Sodium ions and phosphorus are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

Adverse reactions involve the possibility of phosphorus intoxication. Phosphorus intoxication results in a reduction of serum calcium and the symptoms are those of hypocalcemic tetany. See WARNINGS.

OVERDOSAGE

In the event of overdosage, discontinue infusions containing sodium phosphate immediately and institute corrective therapy to restore depressed serum calcium and to reduce elevated serum sodium levels. See WARNINGS, PRECAUTIONS and ADVERSE REACTIONS.

DOSAGE AND ADMINISTRATION

Sodium Phosphates Injection, USP, 3 mM P/mL is administered intravenously only after dilution and thorough mixing in a larger volume of fluid. The dose and rate of administration are dependent upon the individual needs of the patient. Serum sodium, phosphorus and calcium levels should be monitored as a guide to dosage. Using aseptic technique, all or part of the contents of one or more vials may be added to other intravenous fluids to provide any desired number of millimoles (mM) of phosphorus.

In patients on total parenteral nutrition, approximately 10 to 15 mM of phosphorus (equivalent to 310 to 465 mg elemental phosphorus) per liter bottle of TPN solution containing 250 g dextrose is usually adequate to maintain normal serum phosphorus, though larger amounts may be required in hypermetabolic states. The amount of sodium and phosphorus which accompanies the addition of sodium phosphate also should be kept in mind and if necessary, serum sodium levels should be monitored.

The suggested dose of phosphorus for infants receiving TPN is 1.5 to 2 mM P/kg/day.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. See PRECAUTIONS.

HOW SUPPLIED

Sodium Phosphates Injection, USP, 3 mM P/mL is supplied as per below

Unit of Sale	Concentration	Unit of Use
NDC 0409-7391-72 Tray containing 25 Vials	45 mM (3 mM P/mL) containing 60 mEq Na+ (4.0 mEq/mL)	NDC 0409-7391-82 15 mL Single-dose Plastic Vial

Each container is partially filled to provide air space needed for complete vacuum withdrawal of the contents into the I.V. container.

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

Hospira, Inc., Lake Forest, IL 60045 USA

Hospira

LAB-1094-3.0

Revised: 01/2018

SODIUM PHOSPHATES

Injection, USP

45 mM P in 15 mL

(3 mM P and 4 mEq Na^+/mL)

FOR ADDITIVE USE ONLY AFTER DILUTION IN I.V. FLUIDS

Plastic Vial

Rx only

DESCRIPTION

Sodium Phosphates Injection, USP, 3 mM P/mL (millimoles/mL), is a sterile, nonpyrogenic, concentrated solution containing a mixture of monobasic sodium phosphate and dibasic sodium phosphate in water for injection.

The solution is administered after dilution by the intravenous route as an electrolyte replenisher. *It must not be administered undiluted.*

Each mL contains 276 mg of monobasic sodium phosphate, monohydrate and 142 mg of dibasic sodium phosphate, anhydrous (equivalent to 268 mg of dibasic sodium phosphate, heptahydrate).

EN-5840

(b) (4)

One mM of phosphorus weighs 31 mg, and the product provides 93 mg (approximately 3 mM) of phosphorus/mL plus 92 mg (4 mEq) of sodium/mL. Note: 1 mM P = 1 mM PO_4. It contains no bacteriostat, antimicrobial agent or added buffer. The pH is 5.7 (5.0 to 6.0). The osmolar concentration is 7 mOsmol/mL (calc).

The solution is intended as an alternative to potassium phosphate to provide phosphorus for addition to large volume infusion fluids for intravenous use.

It is provided as a 15 mL partial-fill single-dose vial; when lesser amounts are required, the unused portion should be discarded with the entire unit.

Monobasic Sodium Phosphate, USP (monohydrate) is chemically designated $NaH_2PO_4 \cdot H_2O$, white, colorless crystals or granules freely soluble in water.

Dibasic Sodium Phosphate, USP (anhydrous) is chemically designated Na_2HPO_4, colorless or white granular salt freely soluble in water.

The semi-rigid container is fabricated from a specially formulated polyolefin. It is a copolymer of ethylene and propylene. The safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers. The container requires no vapor barrier to maintain the proper drug concentration.

CLINICAL PHARMACOLOGY

Phosphorus in the form of organic and inorganic phosphate 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 of hydrogen ion.

Phosphorus is present in plasma and other extracellular fluid, in cell membranes and intracellular fluid, as well as in collagen and bone tissues. Phosphorus in the extracellular fluid is primarily in inorganic form and plasma levels may vary somewhat with age. The ratio of disodium phosphate and monosodium phosphate in the extracellular fluid is 4 to 1 (800 to 200) at the normal pH of 7.4. This buffer ratio varies with the pH, but owing to its relatively low concentration, it contributes little to the buffering capacity of the extracellular fluid.

Phosphorus, present in large amounts in erythrocytes and other tissue cells, plays a significant intracellular role in the synthesis of high energy organic phosphates. It has been shown to be essential to maintain red cell glucose utilization, lactate production, and the concentration of both erythrocyte adenosine triphosphate (ATP) and 2,3 diphosphoglycerate (DPG), and must be deemed as important to other tissue cells. Hypophosphatemia should be avoided during periods of total parenteral nutrition, or other lengthy periods of intravenous infusions. It has been suggested that patients receiving total parenteral nutrition receive 12 to 15 mM phosphorus per 250 g of dextrose. Serum phosphorus levels should be regularly monitored and appropriate amounts of phosphorus should be added to the infusions to maintain normal serum phosphorus levels. Intravenous infusion of inorganic phosphorus may be accompanied by a decrease in the serum level and urinary excretion of calcium. The normal level of serum phosphorus is 3.0 to 4.5 mg/100 mL in adults; 4.0 to 7.0 mg/100 mL in children.

Intravenously infused phosphorus not taken up by the tissues is excreted almost entirely in the urine. Plasma phosphorus is believed to be filterable by the renal glomeruli, and the major portion of filtered phosphorus (greater than 80%) is actively reabsorbed by the tubules. Many modifying influences tend to alter the amount excreted in the urine.

Sodium is the principal cation of extracellular fluid. It comprises more than 90% of the total cations at its normal plasma concentration of approximately 142 mEq/liter. While the sodium ion can diffuse across cell membranes, intracellular sodium is maintained at a much lower concentration than extracellular sodium through the expenditure of energy by the cell (so called "sodium cation pump"). Loss of intracellular potassium ion is usually accompanied by an increase in intracellular sodium ion.

When serum sodium concentration is low, the secretion of antidiuretic hormone (ADH) by the pituitary is inhibited, thereby preventing water reabsorption by the distal renal tubules. On the other hand, adrenal secretion of aldosterone increases renal tubular reabsorption of sodium in an effort to re-establish normal serum sodium concentration.

INDICATIONS AND USAGE

Sodium Phosphates Injection, USP, 3 mM P/mL 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. 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.

The concomitant amount of sodium (Na+ 4 mEq/mL) must be calculated into total electrolyte dose of such prepared solutions.

CONTRAINDICATIONS

Sodium phosphate is contraindicated in diseases where high phosphorus or low calcium levels may be encountered, and in patients with hypernatremia.

WARNINGS

Sodium Phosphates Injection, USP, 3 mM P/mL must be diluted and thoroughly mixed before use.

To avoid phosphorus intoxication, infuse solutions containing sodium phosphate slowly. Infusing high concentrations of phosphorus may result in a reduction of serum calcium and symptoms of hypocalcemic tetany. Calcium levels should be monitored.

Solutions containing sodium ions should be used with great care, if at all, in patients with congestive heart failure, severe renal insufficiency and in clinical states in which there exists edema with sodium retention.

In patients with diminished renal function, administration of solutions containing sodium ions may result in sodium retention.

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

PRECAUTIONS

Do not administer unless solution is clear and seal is intact. Discard unused portion.

Phosphorus replacement therapy with sodium phosphate should be guided primarily by the serum phosphorus level and the limits imposed by the accompanying sodium (Na+) ion.

Use with caution in patients with renal impairment, cirrhosis, cardiac failure and other edematous or sodium-retaining states.

090177e19381315b\Final\Final On: 12-Jun-2020 08:07 (GMT)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

018892Orig1s037

PRODUCT QUALITY REVIEW(S)

CBE Microbiology Review Form

24 FEB 2023

Applicant: Hospira, Inc.

Type of Supplement: CBE-30

NDA/Supplement #:	Drug Product Name:
018800/ S-038 (lead)	Bacteriostatic Sodium Chloride Injection, USP
018802/ S-040	Bacteriostatic Water for Injection, USP
018803/ S-059	Sodium Chloride Injection, USP
018892/ S-037	Sodium Phosphates Injection, USP
018897/ S-039	Sodium Chloride Injection, USP

Receipt Date: 2/17/2023

Manufacturing Site: Hospira, Inc. Highway 301 North, Rocky Mount, NC 27801

Method of Sterilization (b) (4)

Dosage Form, Route of Administration and Strength/Potency: Sterile injectable solutions; see individual NDAs for strength information

File Name N018800S038MR01.docx

Proposed Change(s): Changes to the microbiological monitoring program for the (b) (4) manufacturing environment

Supporting/Related Documents: None

Conclusion:

☒ The supplement is recommended for approval

☐ Information requested (deficiencies to be conveyed to the applicant are listed at the end of the review)

Template: CBE Review Form.doc

Review Notes: The grouped supplement provides for changes to the microbiological monitoring program [redacted] at the Hospira Rocky Mount, NC manufacturing facility. The impacted products ar [redacted] The changes includ [redacted] g. Specifically [redacted]. The proposed monitoring program is appropriate [redacted] Changes to [redacted] are also proposed; however these are outside the scope of DMA review. No other changes to the manufacturing process, specifications, test methods, or stability protocol are proposed.

Adequate

Primary Reviewer: Jesse Wells, Ph.D.

Secondary Reviewer: Koushik Paul, Ph.D.

Jesse Wells

Digitally signed by Jesse Wells
Date: 2/24/2023 10:21:52AM
GUID: 508da70b00028ea901ac6652677f7d00

Koushik Paul

Digitally signed by Koushik Paul
Date: 2/24/2023 10:22:47AM
GUID: 5600522e0069b02f59c7bd85b6b54742

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number:** NDA-018800-SUPPL-38 (Lead), NDA 018802-SUPPL-40, NDA-018803-SUPPL-59, NDA-018897-SUPPL-39, and NDA-018892-SUPPL-37. Group ID 1948378
   sNDA Recommendation: Approval
   sNDA Managed by: OPQ

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	CBE-30	02/17/2023	02/17/2023	02/22/2023	08/17/2023	07/17/2023

   Group 1948378 includes NDA-018800-SUPPL-38 (lead), NDA 018802-SUPPL-40, NDA-018803-SUPPL-59, NDA-018897-SUPPL-39, and NDA-018892-SUPPL-37

3. **Provides For:**
   Revisions to the environmental monitoring program fo (b) (4) products at Hospira's Rocky Mount, NC Manufacturing facilit (b) (4)
   - (b) (4)
   - Updating of table column headers and other minor updates in the description of the program or updates to terminology are editorial, improve clarity of the information being provided, and align with the site SOP.

4. **Review #**: 1

5. **Clinical Review Division**: CDER/OND/OII/DHN

6. **Name and Address of Applicant**:
   Hospira, Inc.
   275 North Field Drive
   Bldg. H1
   Lake Forest, IL 60045
   USA

7. Drug Product:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Bacteriostatic 0.9% Sodium Chloride Injection, USP	Injectable	9 mg/mL	Injection (I.V., I.M., S.C.)	Rx	No

8. Chemical Name and Structure of Drug Substance:

NaCl	USAN: Sodium chloride, USP Chemical name: Sodium chloride Molecular formula: NaCl Molecular weight: 58.44 g/mol CAS No.: *7647-14-5*

9. Indication: This parenteral preparation is indicated only for diluting or dissolving drugs for intravenous, intramuscular or subcutaneous injection, according to instructions of the manufacturer of the drug to be administered.

10. Supporting/Relating Documents: Page 4-6

11. Consults:

- Request a Microbiology (DMA) Review to evaluate the proposed change.
  The submission is recommended for approval on the basis of sterility assurance by Jesse Wells, Ph.D., dated 02/24/2023.

12. Executive Summary:

This grouped Changes Being Effected in 30 Days Supplement (CBE-30) provides for Revisions to the environmental monitoring program fo (b) (4) products at Hospira's Rocky Mount, NC Manufacturing facility (b) (4) For the purpose of this drug product review, NDA-018800-SUPPL-38 is severing as the lead supplement for Group 1948378, which also includes NDA 018802-SUPPL-40, NDA-018803-SUPPL-59, NDA-018897-SUPPL-39, and NDA-018892-SUPPL-37.

The submission is recommended for approval on the basis of sterility assurance by Jesse Wells, Ph.D., dated 02/24/2023.

The grouped supplement provides for changes to the microbiological monitoring program (b) (4) (b) (4) at the Hospira Rocky Mount, NC manufacturing facility. The impacted products are (b) (4) The changes includ (b) (4) (b) (4). Specifically (b) (4) l (b) (4)

(b) (4) he proposed monitoring program is appropriat (b) (4) (b) (4) Changes to (b) (4) g are also proposed; however, these are outside the scope of DMA review. No other changes to the manufacturing process, specifications, test methods, or stability protocol are proposed. The proposed updated environmental monitoring program is adequate from the CMC standpoint.

13. Conclusions & Recommendations:
This grouped supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant:
None

15. Primary Reviewer:
Le Zhang, Ph.D., CMC reviewer, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:
David B. Lewis, Branch Chief, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

2 Pages have been Withheld in Full as CCI/TS immediately following this page.

Le Zhang

Digitally signed by Le Zhang
Date: 7/17/2023 10:56:51AM
GUID: 594abf46003a4cb7cc12cf6cfd6d8751

David Lewis

Digitally signed by David Lewis
Date: 7/17/2023 11:31:06AM
GUID: 508da72000029f287fa31e664741b577
Comments: concur; recommend approval from the standpoint of CMC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

018892Orig1s037

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

See List of Applications

CBE SUPPLEMENT - ACKNOWLEDGEMENT

Hospira Inc
Attention: Nicole Botimer
Manager, Pfizer Global Regulatory Affairs
275 North Field Drive
Bldg. H1-3S
Lake Forest, IL 60045

Dear Nicole Botimer:

We have received your supplemental new drug applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

Supplemental Application	Product Information	Submit Date	FDA Received Date
NDA 018800/S-038	Sodium Chloride Injection	February 17, 2023	February 17, 2023
NDA 018800/S-038	Bacteriostatic Sodium Chloride Injection, USP, 0.9%	February 17, 2023	February 17, 2023
NDA 018892/S-037	Sodium Phosphates Injection, USP	February 17, 2023	February 17, 2023
NDA 018802/S-040	Bacteriostatic Water for Injection, USP	February 17, 2023	February 17, 2023
NDA 018897/S-039	Sodium Chloride Injection, USP	February 17, 2023	February 17, 2023
NDA 018803/S-059	Sodium Chloride Injection, USP, 0.9%	February 17, 2023	February 17, 2023

These supplemental applications, submitted as "Changes Being Effected in 30 Days" supplements, propose the following change:

> Revisions to the environmental monitoring fo [redacted] (b) (4) products manufactured [redacted] (b) (4) at Hospira's Rocky Mount, NC Manufacturing facility.

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on April 18, 2023, in accordance with 21 CFR 314.101(a).

If the applications are filed, the user fee goal date will be August 17, 2023.

Cite the application number listed above at the top of the first page of all submissions to this application.

If you have any questions, please contact me at (301) 796 - 2497.

Sincerely,

{See appended electronic signature page}
Oluwafunmike (Funke) Ajomale, MSPH, PMP
Regulatory Business Process Manager
Division of Regulatory and Business Process Management III (DRBPMIII)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Oluwafunmike (Funke) Ajomale

Digitally signed by Oluwafunmike (Funke) Ajomale
Date: 3/01/2023 08:57:06AM
GUID: 6328e51d0031719c654b0a2822a1fb68