FRESENIUS KABI

IMPORTANT CORRECTION OF DRUG INFORMATION

Subject: Change to osmolarity concentration on Sodium Phosphates Injections USP Labeling

August 31, 2017

Product Name	Strength	NDC Number	Product Code
Sodium Phosphates Injection, USP	**Phosphorus 15mmol/5 mL (3 mmol/mL)** **Sodium 20mEq/5mL (4 mEq/mL)**	**63323-170-05**	**17005PX**
Sodium Phosphates Injection, USP	**Phosphorus 45mmol/15 mL (3 mmol/mL)** **Sodium 60mEq/15mL (4 mEq/mL)**	**63323-170-15**	**17015PX**

Dear Customer/Health Care Professional:

Fresenius Kabi USA, LLC ("Fresenius Kabi"), will change the labels of its Sodium Phosphates Injection, USP (primary (vial) label, package insert and tray label) to reflect the calculated osmolarity value at the pH of the product, an osmolarity value of **7** mOsmol/mL, to come into line with recent changes to other marketed Sodium Phosphates Injection, USP products. The Fresenius Kabi Sodium, Phosphates Injection, USP is currently labeled with the theoretically calculated osmolarity concentration of 12 mOsmol/mL as illustrated in the photograph below.

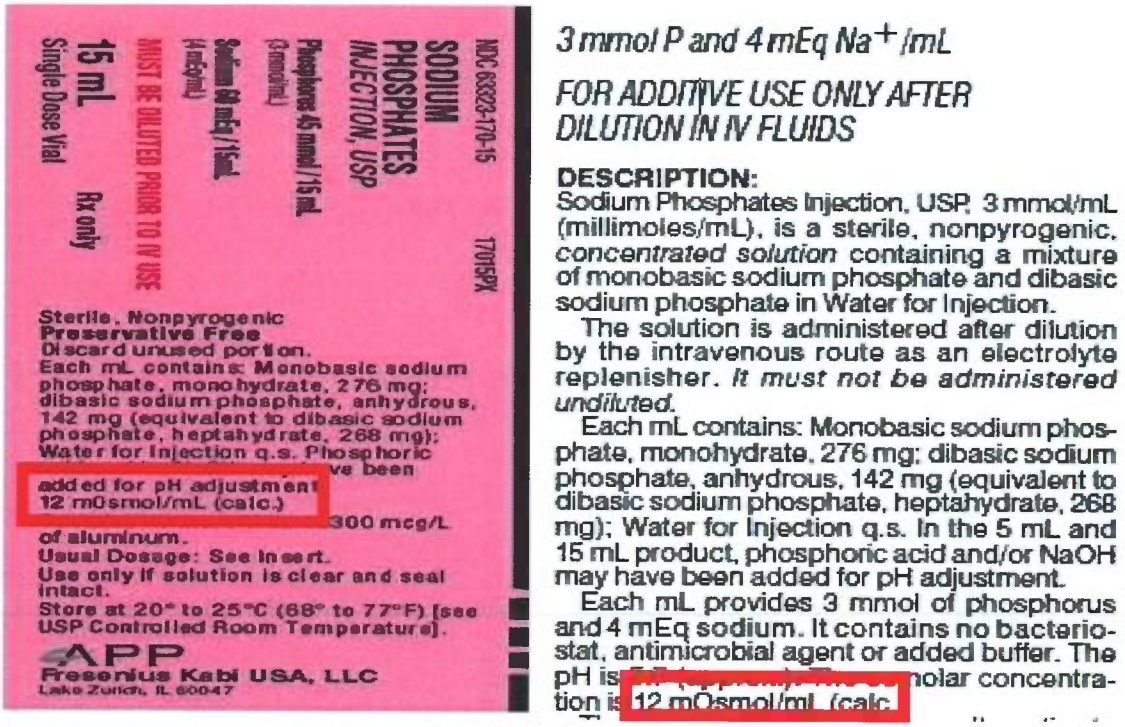

Figure 1: Photograph of the Primary (Vial) Label and Package Insert

Please note that all other information is correct and there are no known or reported quality issues with the product. The product strength is accurately stated in the label as 3 mmol of phosphorus and 4 mEq sodium per ml. There are no changes to the formulation or solution in the vial. Fresenius Kabi conducted a Health Hazard Evaluation, which concluded the health hazard is assessed as low and should have minimal impact on patient safety.

The impacted product lots within expiry were distributed from August 2015 through September 2017. See Appendix A.

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Recommendation to Health Care Professionals and Wholesalers

It is not necessary to return the product, however it is important that this information be provided to all appropriate staff. If you have further distributed this product, please communicate this information to your customers immediately. Please respond to this notification even if you do not have affected product remaining in your inventory. To respond, complete the attached response form and return it as directed.

Reporting Adverse Events

Fresenius Kabi strongly encourage you to report all serious and unexpected adverse reactions or quality problems experienced with the use of this product to Fresenius Kabi at the number(s) listed below.

Serious and unexpected adverse reactions or quality problems experienced with the use of this product may also be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail, or by fax.

- **Complete and submit the report Online**: www.fda.gov/medwatch/report.htm
- **Regular Mail or Fax**: Download form www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

Fresenius Kabi CONTACT NUMBERS: Please use the following contact numbers. Hours of operation: Monday through Friday 8:00 am to 5:00 pm CST.

Number	Department	Reason to Call
866-716-2459	Quality Assurance Department	Information on DHCP Letter
800-551-7176	Vigilance or Medical Affairs Dept.	Clinical/Technical Information/ADE/Complaints

We apologize for any inconvenience this may cause you.

Sincerely,

Melanie Power-Burns
Vice President Quality Assurance

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Appendix A

Impacted Lots of NDC 63323-170-05 and NDC 63323-170-15 within Expiry

Product Code	Batch	Expiry
17005PX	6010361	08/17
	6010362	08/17
	6011449	03/18
	6011837	06/18
	6011838	06/18
	6012163	06/18
	6012164	06/18
	6014107	05/19
	6014108	05/19
	6014644	07/19
	6014645	07/19
17015PX	6010363	08/17
	6011447	03/18
	6011448	03/18
	6011835	04/18
	6011836	04/18
	6012166	06/18
	6012167	06/18
	6012168	06/18
	6014184	05/19
	6014185	05/19
	6014646	07/19
	6014647	07/19

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Appendix B

45780G/Revised: August 2017

SODIUM PHOSPHATES

INJECTION, USP

3 mmol P and 4 mEq Na^+/mL

FOR ADDITIVE USE ONLY AFTER DILUTION IN IV FLUIDS

DESCRIPTION:

Sodium Phosphates Injection, USP, 3 mmol/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: Monobasic sodium phosphate, monohydrate, 276 mg; dibasic sodium phosphate, anhydrous, 142 mg (equivalent to dibasic sodium phosphate, heptahydrate, 268 mg); Water for Injection q.s. In the 5 mL and 15 mL product, phosphoric acid and/or NaOH may have been added for pH adjustment.

Each mL provides 3 mmol of phosphorus and 4 mEq sodium. It contains no bacteriostat, antimicrobial agent or added buffer. The pH is 5.7 (approx.). The osmolar concentration is 7 mOsmol/mL (calc.)

The solution is intended as an alternative to potassium phosphate to provide phosphate ion (PO_4^{3-}) for addition to large volume infusion fluids for intravenous use.

Sodium Phosphates, USP, monohydrate monobasic is chemically designated $NaH_2PO_4 \cdot H_2O$. Occurs as white, odorless crystals or granules freely soluble in water.

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

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. Phosphate 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 (80% to 20%) 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.

Phosphate, 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 (TPN), or other lengthy periods of intravenous infusions. It has been suggested that patients receiving TPN receive 20 mEq phosphate (13 mmol phosphate)/1000 kcal from dextrose. Serum phosphate levels should be regularly monitored and appropriate amounts of phosphate should be added to the infusions to maintain normal serum phosphate levels. Intravenous infusion of inorganic

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phosphate may be accompanied by a decrease in the serum level and urinary excretion of calcium. The normal level of serum inorganic phosphate is 3 to 4.5 mg/100 mL in adults; 4 to 7 mg/100 mL in children.

Intravenously infused phosphate not taken up by the tissues is excreted almost entirely in the urine. Plasma phosphate is believed to be filterable by the renal glomeruli, and the major portion of filtered phosphate (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/L. 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 is indicated as a source of phosphate, 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 (4 mEq/mL) must be calculated into total electrolyte dose of such prepared solutions.

CONTRAINDICATIONS:

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

WARNINGS:

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.

Sodium Phosphates Injection must be diluted and thoroughly mixed before use.

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

Solutions containing sodium ion 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.

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PRECAUTIONS:

General

Use with caution in patients with renal impairment, cirrhosis, cardiac failure or in conjunction with other edematous medications. It should not be used with sodium-retaining medications.

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

Laboratory Tests

Phosphate replacement therapy with sodium phosphate should be guided primarily by serum inorganic phosphate levels and the limits imposed by the accompanying sodium (Na^+) ion. Frequent monitoring of serum calcium and sodium as well as renal function is recommended.

Drug Interactions

Concurrent use with thiazides may cause renal damage.

Pregnancy Category C

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.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sodium phosphate is administered to a nursing woman.

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 ions are known to be substantially excreted by the kidney, and the risk of toxic reactions 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 phosphate intoxication. Phosphate 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 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, inorganic 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 of phosphate and milli-equivalents of sodium.

In patients on TPN, approximately 10 to 15 mmol of phosphorus (equivalent to 310 to 465 mg elemental phosphorus) per liter bottle of TPN solution is usually adequate to maintain normal serum phosphate, though larger amounts may be required in hypermetabolic states. The amount of sodium which accompanies the addition of 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 mmol/kg/day.

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

HOW SUPPLIED:

Product No.	NDC No.	Volume
17005PX	63323-170-05	5 mL in a 10 mL vial
17015PX	63323-170-15	15 mL in a 30 mL vial
11850	63323-118-50	50 mL in a 50 mL vial

These vials are flip-top, Single Dose Vials, packaged 25 vials per tray. The vials marked with "PX" are partially filled to facilitate transfer of the contents.

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

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

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Revised: August 2017

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