PRODUCT MONOGRAPH

# Zinc Sulfate Injection, USP

Zinc Sulfate Injection

($Zn^{2+}$ 1 mg/mL and 5 mg/mL)

Electrolyte

Fresenius Kabi Canada Ltd.
165 Galaxy Blvd, Suite 100
Toronto, ON M9W0C8

Date of Initial Authorization:
November 21, 2022

Submission Control Number: 262908

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## CLINICAL PHARMACOLOGY

Zinc is an essential nutritional element that is important in many enzyme systems either as a metalloenzyme or as an enzyme activator. More than 70 different zinc metalloenzymes have been characterized including carbonic anhydrase, alkaline phosphatase, alcohol dehydrogenase, procarboxypeptidase, superoxide dismutase, glyceraldehydes-3-P dehydrogenase and retinene reductase.

A zinc metalloenzyme is also involved in the synthesis of RNA and DNA, making it important in the normal growth and development process. Zinc facilitates wound healing and helps maintain the senses of taste and smell and normal skin hydration.

The distribution of zinc is wide and nonuniform with the highest concentrations found in the eye, prostate, kidney, liver, muscle, bones, teeth (dental enamel), hair, nails and skin. Zinc is also present in the blood with 75-88% of the total zinc of normal human blood in the red cells, 12-22% in the plasma and 3% in the leukocytes. Normal zinc levels are 8.8 mcg/mL in whole blood, 1.21 mcg/mL in plasma, 14.4 mcg/mL in erythrocytes and 1.0 mcg/mL in serum.

In a study with 99 healthy young men, a mean serum zinc concentration of 102 mcg/100 mL (range 68-136) was reported. Thirty to forty percent of plasma zinc is bound to alpha 2 macroglobulin and sixty to seventy percent is loosely bound to albumin.

Profound changes in zinc blood levels are seen in various disease states and under stress conditions. Subnormal plasma zinc levels have been reported in patients with malignant tumours, atherosclerosis, postalcoholic cirrhosis of the liver and other liver diseases, tuberculosis and leprosy, untreated pernicious anemia, chronic and acute infections, and after acute tissue injury, regardless of origin.

Zinc is absorbed primarily from the small intestine. The main route of zinc excretion is in the feces, which contains the total endogenously excreted zinc (pancreatic and intestinal secretions) and zinc not absorbed from the diet. Small amounts of zinc are lost in urine (0.3 to 0.6 mg/day). However, accumulative zincuria has been observed following major operations, severe burns, nephrosis, postalcoholic hepatic cirrhosis, hepatic porphyria and starvation. Zinc is also lost through sweat, in hair and sloughing skin.

In patients with gastrointestinal disease receiving total parentral nutrition (TPN), abnormal zinc excretion occurred from the gastrointestinal tract in diarrheal stools and intestinal fluid lost through suction and fistulous discharge.

Zinc deficiency occurs during long term TPN and, in some cases, during short term TPN, particularly in patients with long standing enteropathies. TPN patients with zinc deficiency are characteristically apathetic, depressed, and develop diarrhea, alopecia and a moist eczematous rash in the nasolabial fold, followed by bullous or pustular lesions on other parts of the face, in the groin, and on the hands and feet. These conditions are reversed or relieved by zinc administration. All or some of these zinc deficiency symptoms have been reported in adults,

children and premature infants, the most predominant clinical manifestations reported being skin lesions and diarrhea resembling symptoms of acrodermatitis enteropathica.

Plasma zinc levels also declined in premature infants maintained on TPN without supplementation. During the last 10 to 12 weeks of pregnancy, two-thirds of the infant's zinc stores are transferred from the mother. This patient population is at high risk of developing zinc deficiency because they are born with low body stores, need zinc for growth and may be in negative zinc balance up to 60 days after birth.

Therefore, providing zinc during TPN prevents development of the following deficiency symptoms: parakeratosis, hypogenusia, anorexia, dysosmia, geophagia, hypogonadism, growth retardation and hepatosplenomegaly.

## INDICATIONS AND CLINICAL USE

Zinc Sulfate Injection, USP (Zinc Sulfate Injection) is indicated as a supplement to intravenous solutions given for TPN. Its administration in TPN solutions helps to maintain plasma zinc levels and to prevent depletion of endogenous stores of zinc and subsequent deficiency symptoms.

## WARNINGS AND PRECAUTIONS

Zinc Sulfate Injection, USP is a hypotonic solution which should be administered in admixtures only.

If toxicity symptoms occur due to zinc, discontinue supplementation of TPN solutions immediately.

Do not give undiluted Zinc Sulfate Injection, USP by direct injection into a peripheral vein because of the potential of infusion phlebitis.

The possibility of zinc retention should be a consideration in patients with renal dysfunction and caution should be exercised since zinc is excreted via the kidneys.

### Pulmonary Embolism due to Pulmonary Vascular Precipitates

Pulmonary vascular precipitates causing pulmonary vascular emboli and pulmonary distress have been reported in patients receiving parenteral nutrition. The cause of precipitate formation has not been determined in all cases; however, in some fatal cases, pulmonary emboli occurred as a result of calcium phosphate precipitates. Precipitation has occurred following passage through an in-line filter; in vivo precipitate formation may also have occurred. If signs of pulmonary distress occur, stop the parenteral nutrition infusion and initiate a medical evaluation. In addition to inspection of the solution the infusion set and catheter should also periodically be checked for precipitates.

### Vein Damage and Thrombosis

In addition, consider the osmolarity of the final parenteral nutrition solution in determining peripheral versus central administration. Solutions with an osmolarity of 900 mOsmol/L or

greater must be infused through a central catheter. The infusion of hypertonic nutrient solutions into a peripheral vein may result in vein irritation, vein damage, and/or thrombosis. The primary complication of peripheral access is venous thrombophlebitis, which manifests as pain, erythema, tenderness or a palpable cord. Remove the catheter as soon as possible, if thrombophlebitis develops.

### Aluminum Toxicity

Zinc Sulfate Injection contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Preterm infants are particularly at risk for aluminum toxicity because the kidneys are immature, and they require large amounts of calcium and phosphate solutions, which also contain aluminum.

Patients with impaired kidney function, including preterm infants, who receive greater than 4 to 5 mcg/kg/day of parenteral aluminum can accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

Exposure to aluminum from Zinc Sulfate Injection is not more than 0.6 mcg/kg/day. When prescribing Zinc Sulfate Injection for use in parenteral nutrition containing other small volume parenteral products, the total daily patient exposure to aluminum from the admixture should be considered and maintained at no more than 5 mcg/kg/day.

## ADVERSE REACTIONS

### Copper Deficiency

Several post-marketing cases have reported that high doses of supplemental zinc (approximately 10 times the recommended dosage of 3 mg/day Zinc Sulfate Injection in adults) taken over extended periods of time (i.e., months to years) may result in decreased enteral copper absorption and copper deficiency. The cases reported the following complications of copper deficiency: anemia, leukopenia, thrombocytopenia, myeloneuropathy, and nephrotic-range proteinuria.

If a patient develops signs and symptoms of copper deficiency during treatment with Zinc Sulfate Injection, interrupt zinc treatment and check zinc, copper, and ceruloplasmin levels. Copper deficiency should be treated with supplemental copper administration and discontinuation of zinc supplementation.

### Hypersensitivity Reactions

Hypersensitivity reactions to subcutaneously administered zinc-containing insulin products were identified in postmarketing case reports. Reported reactions included injection site induration, erythema, pruritus, papular rash, generalized urticaria, facial swelling, and dyspnea. Patients did not manifest symptoms after changing to zinc-free insulin or another insulin product with a reduced amount of zinc. In some cases, allergy testing confirmed the allergy to the zinc component of the insulin product. If hypersensitivity reactions occur, discontinue Zinc Sulfate Injection and initiate appropriate medical treatment.

## OVERDOSAGE

Zinc is a relatively nontoxic compound, but toxicity can occur by oral administration, inhalation and hemodialysis. Ingestion of excess zinc has usually resulted from storage of food or beverages in galvanized containers, which results in diarrhea, vomiting and fever. One report of intoxication following inhalation of zinc oxide fumes causing fever, headache and vomiting has been reported in the literature. In 1972, a case of zinc poisoning was reported in a patient on hemodialysis with zinc-contaminated water. The patient developed nausea, fever and severe anemia.

Infusions of 40 to 80 mg/day of zinc have been used with no apparent ill effects. No adverse effects were reported when a group of 22 patients received a 20 mg infusion before and after surgery. One case of ill effects was reported when a daily 10 mg dose of zinc was infused over one hour for 5 days. The ill effects were tachycardia, hypothermia, profuse sweating and blurred vision.

One death resulted from an overdose of intravenous zinc which was due to a local prescribing error. A 72 year old woman with a high output enterocutaneous fistula inadvertently received a 46 mmol (7.4 g) of zinc sulfate infused over a 60-hour period. Analysis of her serum zinc showed a zinc level of 4184 mcg/100 mL. Clinical manifestations were edema, jaundice, vomiting, diarrhea and oliguria.

Seven patients who received an accidental overdosage (25 mg zinc/litre TPN solution; equivalent to 50 to 70 mg zinc/day) exhibited hyperamylasemia (557 to 1850 Klein Units; normal 130 to 310).

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

## DOSAGE AND ADMINISTRATION

### Dosage

The suggested dosage ranges are:

#### Adults

For the metabolically stable adult receiving TPN, the suggested intravenous dosage level is 2.5 to 4 mg of zinc per day.

For acute catabolic states an additional 2 mg of zinc per day is suggested.

For the stable adult with fluid loss from the small bowel, an additional 12.2 mg of zinc per litre of TPN solution; or an additional 17.1 mg of zinc per kg of stool or ileostomy output is recommended.

#### Pediatrics

For full-term infants and children up to 5 years of age, 100 mcg zinc/kg/day is recommended.

For premature infants weighing up to 3 kg in body weight, 300 mcg zinc/kg/day is recommended.

**Administration**

Routine monitoring of zinc plasma levels is suggested as a guideline for administration.

Normal plasma levels for zinc vary from approximately 68 to 136 mcg per 100 mL. Frequently monitor the blood zinc levels for those patients receiving more than the usual maintenance dosage level of zinc.

Zinc Sulfate Injection, USP is for intravenous use after dilution only.

## PHARMACEUTICAL INFORMATION

| | |
|---|---|
| Proper Name: | Zinc Sulfate |
| Chemical Name: | Zinc Sulfate Heptahydrate |
| Molecular Formula: | $ZnSO_4 \cdot 7H_2O$ |
| Molecular Weight: | 287.54 g/mol |
| Description: | Zinc sulfate is colorless, transparent prisms or small needles and may occur as a white, granular, crystalline powder. Zinc sulfate is odorless and is efflorescent in dry air. Its solutions are acid to litmus. Zinc sulfate heptahydrate is very soluble in water, freely soluble in glycerin, insoluble in alcohol. 4.4 mg of zinc sulfate heptahydrate is approximately equivalent to 1 mg of zinc. |

### Dilution for Intravenous Use

Aseptic addition of Zinc Sulfate Injection, USP to the amino acid/dextrose component of a TPN solution under a laminar flow hood is recommended. Any other additions to the IV bag should be evaluated by a pharmacist for compatibility. Questions about compatibility may be directed to Fresenius Kabi Canada.

After dilution, the solution must be used within 24 hours.

Visually inspect parenteral drug products for particulate matter and discolouration prior to administration whenever container and solution permit.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

Each mL of Zinc Sulfate Injection, USP contains:

| | **Zinc Sulfate 1 mg/mL** | **Zinc Sulfate 5 mg/mL** |
|---|---|---|
| Zinc (as zinc sulfate heptahydrate) | 1 mg | 5 mg |
| Water for injection | q.s. | q.s. |

Sulfuric acid is used to adjust the pH.

Zinc Sulfate Injection, USP (Zinc Sulfate Injection) is available in two strengths:

1 mg/mL of zinc in single use vials of 10 mL, boxes of 10
5 mg/mL of zinc in single use vials of 5 mL, boxes of 10

The vial stopper is not made with natural rubber latex.

## STORAGE AND STABILITY

Store at 20 ºC to 25 ºC. Protect from freezing.

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This product monograph can be found at:

https://www.fresenius-kabi.com/en-ca/

or by contacting the sponsor, Fresenius Kabi Canada, Ltd.at: 1-877-821-7724

Prepared by: Fresenius Kabi Canada, Ltd.

Last Approved: November 21, 2022