

5.3 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 [see Use in Specific Populations (8.4)].

5.4 Monitoring and Laboratory Tests

Monitor zinc concentrations, fluid and electrolyte status, serum osmolality, blood glucose, liver and kidney function, blood count and coagulation parameters throughout treatment [see Dosage and Administration (2.4)].

5.5 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 [see Adverse Reactions (6)].

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.

5.6 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 [see Contraindications (4)].

6 ADVERSE REACTIONS

No zinc-related adverse reactions have been reported in clinical studies or post-marketing reports in patients receiving intravenously administered parenteral nutrition solutions containing zinc sulfate within the recommended dosage range.

The following were identified in clinical studies or post-marketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Adverse reactions with other components of parenteral nutrition solutions:

- Pulmonary embolism due to pulmonary vascular precipitates [see Warnings and Precautions (5.1)]
- Vein damage and thrombosis [see Warnings and Precautions (5.2)]
- Aluminum toxicity [see Warnings and Precautions (5.3)]

Adverse reactions with the use of zinc-containing products administered by other routes of administration:

- Copper deficiency [see Warnings and Precautions (5.5)]
- Hypersensitivity reactions [see Warnings and Precautions (5.6)]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Administration of the approved recommended dose of Zinc Sulfate Injection in parenteral nutrition is not expected to cause major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with intravenous zinc sulfate.

The estimated background risk of major birth defects and miscarriage for the indicated populations is 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

Deficiency of trace elements, including zinc, is associated with adverse pregnancy and fetal outcomes. Pregnant women have an increased metabolic demand for trace elements, including zinc. Parenteral nutrition for zinc should be considered if a pregnant woman's nutritional requirements cannot be fulfilled by oral or enteral intake.

8.2 Lactation

Risk summary

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

8.4 Pediatric Use

Zinc Sulfate Injection is approved for use in the pediatric population, including neonates, as a source of zinc for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. Safety and dosing recommendations in pediatric patients are based on published literature describing controlled studies of zinc-containing products in pediatric patients [see Dosage and Administration (2.2)].

Because of immature renal function, preterm infants receiving prolonged parenteral nutrition treatment with Zinc Sulfate Injection may be at higher risk of aluminum toxicity [see Warnings and Precautions (5.3)].

8.5 Geriatric Use

Reported clinical experience with intravenous zinc sulfate has not identified a difference in zinc requirements between elderly and younger patients. In

general, dose selection should be individualized based on the patient's clinical condition, nutritional requirements, and additional nutritional intake provided orally or enterally to the patient.

10 OVERDOSAGE

There are reported cases of overdosage with intravenous zinc in parenteral nutrition:

- Seven adult patients received an inadvertent overdosage of 50 mg to 75 mg elemental zinc per day in parenteral nutrition solution for 26 to 60 days; 6 of the 7 patients developed hyperamylasemia (peak amylase values of 557 to 1850 Klein units; normal: 130 to 310). Amylase was not reported in one patient. Serum zinc concentrations ranged from 310 to 670 mcg/dL. None of the patients developed clinical signs of pancreatitis. Five of the 7 patients died of septic complications.
- One adult patient died of infectious complications after receiving an inadvertent overdosage of 7.4 grams of zinc sulfate (equivalent to 1.2 grams of elemental zinc per day for 2.5 days) in parenteral nutrition solution over 60 hours. The serum zinc concentration was 4184 mcg/dL. Symptoms of zinc overdosage also included hyperamylasemia, thrombocytopenia, anemia, vomiting and diarrhea.
- One preterm infant born at 26 weeks gestation died of cardiac failure following a medication error in which the parenteral nutrition solution contained 330 mg/100 mL instead of 330 mcg/100 mL of zinc sulfate (overdosage of 1000-fold).

Management

There is no known antidote for acute zinc toxicity. Management of zinc overdosage is supportive care based on presenting signs and symptoms.

11 DESCRIPTION

Zinc Sulfate Injection, USP is a sterile, non-pyrogenic, clear, colorless, and odorless solution intended for use as a trace element and an additive to intravenous solutions for parenteral nutrition.

30 mg/10 mL Pharmacy Bulk Package vial:

Each mL contains 3 mg of zinc present as 7.41 mg of zinc sulfate and water for injection q.s.

25 mg/5 mL Pharmacy Bulk Package vial:

Each mL contains 5 mg of zinc present as 12.32 mg of zinc sulfate and water for injection q.s.

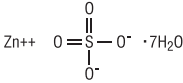
All presentations do not contain preservatives.

The pH range is 2 to 4; pH may be adjusted with sulfuric acid.

3 mg/mL of Zinc Sulfate Injection, USP contains no more than 2,500 mcg/L of aluminum and has a calculated osmolality of 96.5 mOsmol/L.

5 mg/mL of Zinc Sulfate Injection, USP contains no more than 2,500 mcg/L of aluminum and has a calculated osmolality of 157.2 mOsmol/L.

Zinc sulfate heptahydrate, USP has a molecular weight of 287.6 g/mol and a formula of ZnSO₄·7H₂O.



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zinc is an essential trace element. Zinc functions as a cofactor of various enzymes including DNA polymerases, RNA polymerases, alcohol dehydrogenase, and alkaline phosphatases. Zinc is a coordinator of protein structural folding, such as folding of "Zinc finger" motif that interacts with a variety of proteins, lipids, and nucleic acids. In addition, zinc is a catalyst of essential biochemical reactions, including activation of substrates of carbonic anhydrase in erythrocyte. Also, zinc is a signaling mediator modulating multiple signaling pathways.

12.2 Pharmacodynamics

Zinc sulfate exposure-response relationships and the time course of pharmacodynamic responses are unknown.

12.3 Pharmacokinetics

Distribution

Over 85% of total body zinc is found in skeletal muscle and bone. Other organs containing zinc are the liver, kidney, skin, brain, and heart. In blood, zinc is mainly localized within erythrocytes. Approximately 80% of serum zinc is bound to albumin and the remainder to alpha2-macroglobulin and amino acids.

Elimination

In adults, zinc is primarily excreted via the gastrointestinal tract and eliminated in the feces.

A smaller amount of zinc is excreted via the kidneys in the urine. Urinary zinc excretion rates in very low birth weight preterm infants are relatively high in the neonatal period, and they decline to a level on a body weight basis that is similar to that of normal adults by two months of age. Additionally, endogenous zinc loss occurs from hair, skin desquamation and sweat.

16 HOW SUPPLIED/STORAGE AND HANDLING

Zinc Sulfate Injection, USP is a clear, colorless solution supplied as:

- 30 mg/10 mL (3 mg/mL) of zinc in a 10 mL Pharmacy Bulk Package vial. Cartons of 25 vials (NDC 66794-240-42).
- 25 mg/5 mL (5 mg/mL) of zinc in a 5 mL Pharmacy Bulk Package vial. Cartons of 25 vials (NDC 66794-239-42).

Vial closure is not made with natural rubber latex.

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

For storage of admixed solution see Dosage and Administration (2.3).

17 PATIENT COUNSELING INFORMATION

Inform patients, caregivers or home healthcare providers of the following risks of Zinc Sulfate Injection:

- Pulmonary embolism due to pulmonary vascular precipitates [see Warnings and Precautions (5.1)]
- Vein damage and thrombosis [see Warnings and Precautions (5.2)]
- Aluminum toxicity [see Warnings and Precautions (5.3)]
- Copper deficiency [see Warnings and Precautions (5.5)]
- Hypersensitivity reactions [see Warnings and Precautions (5.6)]



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