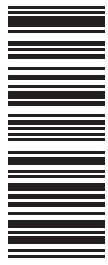
TRALEMENT®
(trace elements injection 4*, USP)
for intravenous use



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(trace elements injection 4*, USP)
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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRALEMENT® safely and effectively. See full prescribing information for TRALEMENT®.

TRALEMENT® (trace elements injection 4*), for intravenous use
Initial U.S. Approval: 2020

---------- INDICATIONS AND USAGE ----------

Tralement is a combination of trace elements (zinc sulfate, cupric sulfate, manganese sulfate and selenious acid) indicated in adult and pediatric patients weighing at least 10 kg as a source of zinc, copper, manganese, and selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- *Single-dose vial. Not for direct intravenous infusion.* (2.1)
- See full prescribing information for information on preparation, administration and general dosing considerations. (2.1, 2.2, 2.3, 2.4)

Recommended Dosage

- Each mL of Tralement provides zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg. (2.5)
- *Adults and Pediatric Patients Weighing at Least 50 kg:* The recommended dosage of Tralement is 1 mL per day added to parenteral nutrition. Tralement is not recommended for patients who may require a lower dosage of one or more of the individual trace elements. (2.5)
- *Pediatric Patients Weighing 10 kg to 49 kg:* The recommended dosage of Tralement based on body weight is 0.2 mL to 0.8 mL per day added to parenteral nutrition. Tralement does not provide the recommended daily dosage of zinc (in heavier patients in some weight bands), copper or selenium. Additional supplementation using single trace element products may be needed for these patients. For complete dosing information see table in the full prescribing information. (2.4, 2.5)
- Monitor trace element concentrations in blood during long-term administration of parenteral nutrition. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 1 mL in a single-dose vial. Each mL contains zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg. (3)

---------- CONTRAINDICATIONS ----------

Hypersensitivity to zinc or copper (4, 5.7)

---------- WARNINGS AND PRECAUTIONS ----------

- Pulmonary Embolism due to Pulmonary Vascular Precipitates: If signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation. (5.1)
- Vein Damage and Thrombosis: Solutions with osmolarity of 900 mOsmol/L or more must be infused through a central catheter. (2.1, 5.2)
- Neurologic Toxicity with Manganese: Monitor for clinical signs and symptoms of neurotoxicity, whole blood manganese concentrations and liver function tests in patients receiving long-term Tralement. Discontinue Tralement and consider brain magnetic resonance imaging (MRI) if toxicity suspected. (5.3)
- Hepatic Accumulation of Copper and Manganese: Assess for development of hepatic or biliary dysfunction. Monitor concentrations of copper and manganese in patients with cholestasis, biliary dysfunction or cirrhosis receiving Tralement long-term. (5.4)
- Aluminum Toxicity: Increased risk in patients with renal impairment, including preterm infants. (5.5, 8.4)
- Monitoring and Laboratory Tests: Monitor blood zinc, copper, manganese, and selenium concentrations, fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, blood count and coagulation parameters. (5.6, 2.4)
- Hypersensitivity Reactions with Zinc and Copper: If reactions occur, discontinue Tralement and initiate appropriate medical treatment. (5.7)

To report SUSPECTED ADVERSE REACTIONS, contact American Regent, Inc. at 1-800-734-9236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

Pediatric Patients Weighing Less than 10 kg: Tralement is not approved for use in this subpopulation because the product does not provide an adequate dosage of zinc, copper, or selenium and exceeds the recommended dosage of manganese. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Tralement® is indicated in adult and pediatric patients weighing at least 10 kg as a source of zinc, copper, manganese, and selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

Tralement is supplied as a single-dose vial for *admixture use* only. It is *not for direct intravenous infusion*. Prior to administration, Tralement *must be transferred to a separate parenteral nutrition container* and used as an admixture in parenteral nutrition solution.

The final parenteral nutrition solution is for intravenous infusion into a central or peripheral vein. The choice of a central or peripheral venous route should depend on the osmolarity of the final infusate. Solutions with osmolarity of 900 mOsmol/L or greater must be infused through a central catheter *[see Warnings and Precautions (5.2)]*.

2.2 Preparation and Administration Instructions

- Tralement is not for direct intravenous infusion. Prior to administration, Tralement *must be prepared and used as an admixture* in parenteral nutrition solution.
- Add Tralement to the parenteral nutrition solution in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area). The key factor in the preparation is careful aseptic technique to avoid inadvertent touch contamination during mixing of solutions and addition of other nutrients.
- Inspect the parenteral nutrition solution containing Tralement for particulate matter before admixing, after admixing, and prior to administration.

2.3 Preparation Instructions for Admixing Using a Parenteral Nutrition Container

- Inspect Tralement single-dose vial for particulate matter.
- Transfer Tralement to the parenteral nutrition container after the admixture of amino acids, dextrose, lipid emulsion (if added), and electrolytes solutions is prepared.
- Because additives may be incompatible, evaluate all additions to the parenteral nutrition container for compatibility and stability of the resulting preparation. Consult with pharmacist, if available. For introducing additives to the parenteral nutrition container, use aseptic technique.
- An interaction may occur between cupric ion and ascorbic acid; therefore, multivitamin additives should be added to the admixed parenteral nutrition solution shortly before infusion.
- Inspect the final parenteral nutrition solution containing Tralement to ensure that:
  - Precipitates have not formed during mixing or addition on additives.
  - The emulsion has not separated, if lipid emulsion has been added. Separation of the emulsion can be visibly identified by a yellowish streaking or the accumulation of yellowish droplets in the admixed emulsion.
  - Discard if any precipitates are observed.

Stability and Storage

- Single-dose vial. Discard unused portion.
- Use parenteral nutrition solutions containing Tralement promptly after mixing. Any storage of the admixture should be under refrigeration from 2°C to 8°C (36°F to 46°F) and limited to a period of no longer than 9 days. After removal from refrigeration, use promptly and complete the infusion within 24 hours. Discard any remaining admixture.
- Protect the parenteral nutrition solution from light.

2.4 Overview of Dosing

- Prior to administration of parenteral nutrition solution containing Tralement, correct severe fluid, electrolyte, and acid-base disorders.
- The dosage of the final parenteral nutrition solution containing Tralement must be based on the concentrations of all components in the solution, the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral intake.
- For pediatric patients weighing 10 to 49 kg, Tralement does not provide the recommended daily dosage of zinc (in heavier patients in some weight bands), copper or selenium. Additional supplementation using single trace element products may be needed for these patients *[see Dosage and Administration (2.5)]*.
- Monitor fluid and electrolyte status during treatment use of Tralement and adjust the parenteral nutrition solution as needed.

2.5 Recommended Dosage in Adults and Pediatric Patients and Monitoring Considerations

Tralement is a fixed-combination product. Each mL of Tralement provides zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg.

Tralement is recommended only for patients who require supplementation with all four of the individual trace elements (i.e., zinc, copper, manganese and selenium).

Adults and Pediatric Patients Weighing at least 50 kg:

The recommended dosage of Tralement is 1 mL per day added to parenteral nutrition (zinc 3 mg/copper 0.3 mg/manganese 55 mcg/selenium 60 mcg). Tralement is not recommended for those patients who may require a lower dosage of one or more of the individual trace elements.

Pediatric Patients Weighing 10 kg to 49 kg:

The recommended dosage of Tralement by volume to be added to parenteral nutrition is based on body weight and ranges from 0.2 mL to 0.8 mL per day as shown in Table 1.

Table 1. Recommended Weight-Based Daily Dosage of Tralement (mL) for Pediatric Patients Weighing 10 kg to 49 kg and Corresponding Amount of Each Trace Element (mcg)

Body Weight	Recommended Weight-Based Dosage of Tralement in Volume	Amount of Trace Element Provided by the Corresponding Tralement Volume			
		Zinc	Copper	Manganese	Selenium
10 kg to 19 kg	**0.2 mL**	600 mcg	60 mcg	11 mcg	12 mcg
20 kg to 29 kg	**0.4 mL**	1,200 mcg	120 mcg	22 mcg	24 mcg
30 kg to 39 kg	**0.6 mL**	1,800 mcg	180 mcg	33 mcg	36 mcg
40 kg to 49 kg	**0.8 mL**	2,400 mcg	240 mcg	44 mcg	48 mcg

Use Additional Supplementation with Tralement

For pediatric patients weighing 10 kg to 49 kg, additional zinc (in heavier patients in some weight bands), copper and selenium may be needed to meet the recommended daily dosage of these trace elements, shown below. To determine the additional amount of supplementation that is needed, compare the calculated daily recommended dosage based on the body weight of the patient to the amount of each trace element provided by Tralement (Table 1) and other dietary sources.

- Zinc: 50 mcg/kg/day (up to 3,000 mcg/day)
- Copper: 20 mcg/kg/day (up to 300 mcg/day)
- Selenium: 2 mcg/kg/day (up to 60 mcg/day)

Do not supplement Tralement with additional manganese. Accumulation of manganese in the brain can occur with long-term administration with higher than the recommended dosage of 1 mcg/kg/day (up to 55 mcg/day) *[see Warnings and Precautions (5.3)]*.

Monitoring

- Monitor serum zinc, copper, and selenium concentrations and manganese whole blood concentrations during long-term administration of parenteral nutrition.
- Trace elements concentrations may vary depending on the assay used and the laboratory reference range. The collection, processing, and storage of the blood samples should be performed according to the laboratory's sample requirements for analysis.
  - *Zinc:* In serum, the reported concentration range in healthy adults is 60 to 140 mcg/dL. Zinc concentrations in hemolyzed samples may be falsely elevated due to release of zinc from erythrocytes.
  - *Copper:* In serum, the reported concentration range in healthy adults is 70 to 175 mcg/dL; consider obtaining concentrations of ceruloplasmin along with serum copper.
  - *Manganese:* In whole blood, the reported concentration range in healthy adults is 4 to 16 mcg/L.
  - *Selenium:* In serum, the reported concentration range in healthy adults is 7 to 19 mcg/dL.

3 DOSAGE FORMS AND STRENGTHS

Injection: 1 mL clear, colorless to slightly blue solution in a single-dose vial. Each mL contains zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg.

4 CONTRAINDICATIONS

Tralement is contraindicated in patients with hypersensitivity to zinc or copper *[see Warnings and Precautions (5.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 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 *[see Dosage and Administration (2.2, 2.3)]*, the infusion set, and catheter should also periodically be checked for precipitates.

5.2 Vein Damage and Thrombosis

Tralement must be prepared and used as an admixture in parenteral nutrition solution. It is not for direct intravenous infusion. In addition, consider the osmolarity of the final parenteral nutrition solution in determining peripheral versus central administration. Solution with an osmolarity of 900 mOsmol/L or greater must be infused through a central catheter *[see Dosage and Administration (2.1)]*. The infusion of hypertonic nutrient solution 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.

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5.3 Neurologic Toxicity with Manganese

Manganese accumulation in the basal ganglia has been reported in adult and pediatric patients on long-term parenteral nutrition receiving manganese at higher than recommended dosages and in association with cholestatic liver disease. Some adult patients with brain MRI findings reportedly experienced neuropsychiatric symptoms, including changes in mood or memory, seizures and/or parkinsonian-like tremors, dysarthria, mask-face, and halting gait. Some pediatric patients experienced dystonic movements or seizures. Brain MRI findings and clinical symptoms have also been observed in patients who received manganese at or below the recommended dosage and with normal blood manganese concentrations. Regression of symptoms and MRI findings have occurred over weeks to months following discontinuation of manganese in most patients but have not always completely resolved.

Monitor patients receiving long-term parenteral nutrition solutions containing Tralement for neurologic signs and symptoms and routinely monitor whole blood manganese concentrations and liver function tests. In case of suspected manganese toxicity or new neuro-psychiatric manifestations, temporarily discontinue Tralement, check manganese whole blood concentrations, and consider brain MRI evaluation.

Monitor patients receiving Tralement for cholestasis or other biliary liver disease. Consider individual trace element products as an alternative to Tralement in patients with hepatic and/or biliary dysfunction *[see Warnings and Precautions (5.4)]*.

5.4 Hepatic Accumulation of Copper and Manganese

Copper is primarily eliminated in the bile and excretion is decreased in patients with cholestasis and/or cirrhosis. Hepatic accumulation of copper and manganese have been reported in autopsies of patients receiving long-term parenteral nutrition containing copper and manganese at dosages higher than recommended.

Patients receiving parenteral nutrition with cholestasis and/or cirrhosis are at increased risk of manganese brain deposition and neurotoxicity *[see Warnings and Precautions (5.3)]*.

Administration of copper to patients with cholestasis, and/or cirrhosis may cause hepatic accumulation of copper. Administration of copper to patients with Wilson disease, an inborn error of copper metabolism with defect in hepatocellular copper transport, may cause both increased hepatic accumulation of copper and aggravation of the underlying hepatocellular degeneration.

For patients with cholestasis, biliary dysfunction, or cirrhosis, monitor hepatic and biliary function during long-term administration of Tralement. If a patient develops signs or symptoms of hepatic or biliary dysfunction during the use of Tralement, obtain serum concentrations of copper and ceruloplasmin as well as manganese whole blood concentrations. Consider using individual trace element products in patients with hepatic and/or biliary dysfunction *[see Use in Specific Populations (8.6)]*.

5.5 Aluminum Toxicity

Tralement contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Preterm infants, including preterm 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 preterm infants and 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 or lower daily amounts.

Exposure to aluminum from Tralement is not more than 0.1 mcg/kg/day. When prescribing Tralement 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)]*.

5.6 Monitoring and Laboratory Tests

Monitor blood zinc, copper, manganese, and selenium concentrations, fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, blood count, and coagulation parameters during use of parenteral nutrition containing Tralement *[see Dosage and Administration (2.4)]*.

5.7 Hypersensitivity Reactions with Zinc and Copper

Hypersensitivity reactions to subcutaneously administered zinc-containing insulin products and copper-containing intrauterine devices (IUD) were identified in postmarketing case reports. If hypersensitivity reactions occur in patients receiving Tralement in parenteral nutrition, discontinue Tralement, and initiate appropriate medical treatment *[see Contraindications (4)]*.

Zinc

For patients prescribed zinc-containing insulin products, 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.

Copper

For women with copper IUD implantation, reported reactions included diffuse eczematous dermatitis, maculopapular skin eruption, urticaria, and angioedema of the eyelids, face, and labia weeks or months after IUD insertion. In most cases, the patch test for copper was positive, and the adverse reactions resolved after IUD removal.

6 ADVERSE REACTIONS

The following adverse reactions were identified in clinical studies or post-marketing reports. Given that 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 (5.5)]*

Adverse reactions with the use of trace elements administered parenterally or by other routes of administration:

- Neurologic toxicity with manganese *[see Warnings and Precautions (5.3)]*
- Hepatic accumulation of copper and manganese *[see Warnings and Precautions (5.4)]*
- Hypersensitivity reactions with zinc and copper *[see Warnings and Precautions (5.7)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Administration of the recommended dose of Tralement in parenteral nutrition is not expected to cause major birth defects, miscarriage, or adverse maternal or fetal outcomes. Deficiency of trace elements may result in adverse pregnancy and fetal outcomes *(see Clinical Considerations)*. Animal reproduction studies have not been conducted with Tralement or with the individual trace elements.

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

Tralement is approved for use in pediatric patients weighing at least 10 kg as a source of zinc, copper, manganese, and selenium 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 products containing zinc, copper, manganese, and selenium *[see Dosage and Administration (2.2)]*.

Tralement is not approved for use in pediatric patients weighing less than 10 kg because the product does not provide an adequate dosage of zinc, copper, or selenium to meet the needs of this subpopulation and exceeds the recommended dosage of manganese.

8.5 Geriatric Use

Reported clinical experience has not identified a difference in requirements for zinc, copper, manganese, or selenium between elderly and younger patients.

8.6 Hepatic Impairment

Copper is primarily excreted in the bile. Excretion is decreased in patients with cholestasis and/or cirrhosis. Manganese is found, and presumed to be excreted, in bile *[see Clinical Pharmacology (12.3)]*. Hepatic accumulation of copper and manganese have been reported with long-term administration in parenteral nutrition at dosages higher than recommended *[see Warnings and Precautions (5.4)]*.

For patients with cholestasis, biliary dysfunction, or cirrhosis, monitor hepatic and biliary function during long-term administration of Tralement. If a patient develops signs or symptoms of hepatic or biliary dysfunction during use of Tralement, obtain serum concentrations of copper and ceruloplasmin as well as manganese whole blood concentrations. Consider using individual trace element products in patients with hepatic and/or biliary dysfunction.

10 OVERDOSAGE

There is no information on overdosing or toxicity with a fixed-combination trace element product. However, there are reports on overdosage in the literature for the individual trace elements. Management of overdosage is supportive care based on presenting signs and symptoms. Obtain blood samples for laboratory testing of the individual trace elements and ceruloplasmin for copper.

Zinc

Acute zinc toxicity was reported in an infant who received an inadvertent 1,000-fold overdose of zinc in parenteral nutrition that led to cardiac failure and death. Zinc toxicity in adult patients receiving 17 to 400-fold the recommended dosage in parenteral nutrition for 2.5 to 60 days reported signs and symptoms including vomiting, diarrhea, hyperamylasemia, thrombocytopenia, and anemia. The zinc serum concentration was 2 to 30-fold the upper end of the reported range in healthy subjects in these cases.

Copper

Acute copper toxicity was reported in patients with oral, intravenous, or subcutaneous administration. Clinical manifestations included metallic taste, nausea, vomiting, abdominal pain, and multi-organ failure involving kidney, liver, blood, and cardiovascular systems. Chelating agents can be used for treatment of acute toxicity. Long-term administration of parenteral copper above recommended dosage may result in significant accumulation of copper in the liver, brain, and other tissues with possible organ damage *[see Warnings and Precautions (5.4)]*.

Manganese

Acute manganese toxicity was reported in adult patients following infusion of manganese more than 10,000-fold the recommended dosage and after use of dialysis fluid contaminated with manganese. Signs and symptoms included skin flushing, acute pancreatitis, elevated whole blood manganese concentrations, and MRI evidence of brain accumulation of manganese. Chronic infusion and oral intake of manganese above recommended dosage have resulted in neuropsychiatric symptoms and MRI evidence of brain accumulation of manganese *[see Warnings and Precautions (5.3)]*.

Selenium

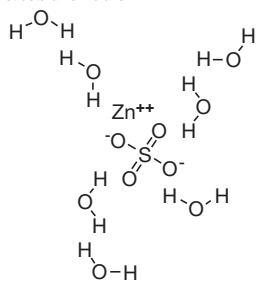
Acute selenium toxicity was reported with oral overdosage of greater than 1 g/day. Symptoms included nausea, vomiting, diarrhea, abdominal pain, garlic breath odor, and altered mental status. Death from circulatory collapse was reported after oral ingestion of 5 to 10 g of selenium with blood concentrations ranging 10 to 50-fold the upper end of the reported range in healthy subjects.

11 DESCRIPTION

Tralement® (trace elements injection 4*, USP) is a sterile, non-pyrogenic, clear, and colorless to slightly blue solution, intended for use as a combination of four trace elements and an additive to intravenous solutions for parenteral nutrition. It contains no preservative.

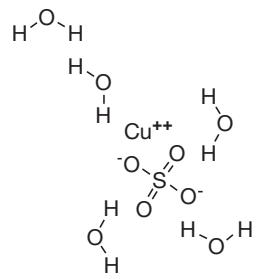
Each single-dose vial contains 1 mL. *Each mL contains zinc 3 mg (equivalent to zinc sulfate 7.41 mg), copper 0.3 mg (equivalent to cupric sulfate 0.75 mg), manganese 55 mcg (equivalent to manganese sulfate 151 mcg), selenium 60 mcg (equivalent to selenious acid 98 mcg), and water for injection. Sulfuric acid may be added to adjust pH between 1.5 and 3.5.

Zinc sulfate exists as a heptahydrate. The structural formula is:



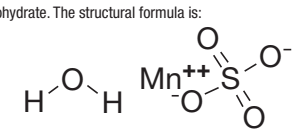
Molecular formula: $ZnSO_4 \bullet 7H_2O$.
Molecular weight: 287.54 g/mol.

Cupric sulfate exists as a pentahydrate. The structural formula is:



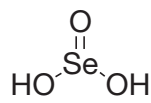
Molecular formula: $CuSO_4 \bullet 5H_2O$.
Molecular weight: 249.69 g/mol.

Manganese sulfate exists as a monohydrate. The structural formula is:



Molecular formula: $MnSO_4 \bullet H_2O$.
Molecular weight: 169.02 g/mol.

The structural formula of selenious acid is:



Molecular formula: H_2SeO_3.
Molecular weight: 128.97 g/mol.

Tralement contains no more than 6,000 mcg/L of aluminum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zinc

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 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.

Copper

Copper is a cofactor for many metalloenzymes acting as an oxidase to achieve reduction of molecular oxygen. Examples of copper metalloenzymes include but are not limited to lysyl oxidase, monoamine oxidase, ferroxidase, cytochrome C oxidase, dopamine beta monooxygenase, tyrosinase, and superoxide dismutase.

Manganese

Manganese is essential for the normal catalytic activity of several metalloenzymes including manganese superoxide dismutase, arginase, glutamine synthetase, phosphoenolpyruvate decarboxylase, and pyruvate carboxylase. Manganese contributes to the normal function of several other enzyme families including the oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases.

Selenium

Selenious acid is converted in vivo to hydrogen selenide via glutathione-involved electron reductions. Hydrogen selenide acts as a selenium pool to form selenoproteins which include, but are not limited to, glutathione peroxidase, iodothyronine deiodinase, peroxidase, and thioredoxins.

12.2 Pharmacodynamics

The exposure-response relationship and the time course of pharmacodynamic response are unknown for zinc, copper, manganese, and selenium.

12.3 Pharmacokinetics

Zinc

Over 85% of total body zinc is found in skeletal muscle and bone. In blood, zinc is mainly localized within erythrocytes. Approximately 80% of serum zinc is bound to albumin and the remainder to α-2-macroglobulin and amino acids. 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.

Copper

In plasma, about 7% of copper is bound to albumin and amino acids. In the liver, about 93% of copper is bound to ceruloplasmin and released to the serum. Copper is excreted in bile and into the gastrointestinal tract where it is not reabsorbed. Copper is also eliminated through the kidneys.

Manganese

Manganese is widely distributed in body tissues including liver and specific brain regions such as the basal ganglia. The concentrations of manganese are higher in erythrocytes compared to the plasma or serum concentrations. In human plasma, manganese is bound to albumin and β_1-globulin. Manganese is found in human bile suggesting biliary excretion.

Selenium

In humans, 85% of intravenous administered ^{75}Se was protein-bound within 4 to 6 hours and 95% by 24 hours.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tralement (trace elements injection 4*, USP) is a clear, colorless to slightly blue solution supplied in 1 mL single-dose vials (NDC 0517-9305-01).

*Each mL of Tralement contains zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg.

It is packaged in trays containing 25 vials per tray (NDC 0517-9305-25).

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°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Store admixed solution at 2°C to 8°C (36°F to 46°F) *[see Dosage and Administration (2.3)]*.

17 PATIENT COUNSELING INFORMATION

Inform patients, caregivers, and home healthcare providers of the following risks of Tralement:

- Pulmonary embolism due to pulmonary vascular precipitates *[see Warnings and Precautions (5.1)]*
- Vein damage and thrombosis *[see Warnings and Precautions (5.2)]*
- Neurologic toxicity with manganese *[see Warnings and Precautions (5.3)]*
- Hepatic accumulation of copper and manganese *[see Warnings and Precautions (5.4)]*
- Aluminum toxicity *[see Warnings and Precautions (5.5)]*
- Hypersensitivity reactions with zinc and copper *[see Warnings and Precautions (5.7)]*

Distributed by:

AMERICAN REGENT, INC.
SHIRLEY, NY 11967

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