PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

MICRO +6 CONCENTRATE

6 Trace Elements Injection

Zinc	5 mg/mL
Copper	1 mg/mL
Manganese	0.5 mg/mL
Chromium	10mcg/mL
Selenium	60 mcg/mL
Iodide	75 mcg/mL

USP

Intravenous

Combination of Electrolytes

Sandoz Canada Inc.
110 Rue de Lauzon
Boucherville, (Québec), Canada
J4B 1K6

Date of Initial Authorization:
APR 25, 1994

Date of Revision:
JAN 19, 2022

Control No.: 250302

RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment (Pediatrics)	05/2021
7 WARNINGS AND PRECAUTIONS, General	05/2021

TABLE OF CONTENTS

Sections and Subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MICRO +6 CONCENTRATE (6 Trace Elements Injection USP) is indicated for:

- use as a supplement to intravenous solutions given for TPN. Its administration in TPN solutions helps to maintain plasma zinc, copper, manganese, chromium, selenium and iodide levels and to prevent depletion of endogenous stores of these elements and development of subsequent deficiency symptoms.

1.1 Pediatrics (≤ 18 years of age): MICRO +6 Concentrate is indicated for use in pediatric patients (see 4.2 Recommended Dose and Dose Adjustments).

1.2 Geriatrics (≥ 65 years of age): MICRO +6 Concentrate is indicated for use in geriatric patients. No dosage adjustments are required.

2 CONTRAINDICATIONS

- MICRO +6 CONCENTRATE is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Routine monitoring of zinc, copper, manganese, chromium, selenium and iodine plasma levels is suggested as a guideline for administration. For iodine, routine monitoring of thyroid function is also indicated.

Zinc

Normal plasma levels 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.

Copper

While the normal adult plasma levels range from 90 to 130 mcg/100 mL, the normal full-term newborn's serum levels are about one-third of this. These values were found to rise gradually during the first week of life, fall to below adult levels at two months of age, rise to within the adult range at three months of age, and to rise still higher above the adult range at eight months of age, at which levels the values persisted throughout the remainder of infancy.

Manganese

Manganese is bound in both the serum and the erythrocytes. Normal human blood values have been recognized as 6 to 10 mcg/mL.

Chromium

Changes in serum chromium following glucose loading or insulin injection should be regarded with caution as indicators of chromium status. Serum levels of 1 to 31 ng/mL have been reported. Levels of chromium in hair may provide a more useful index of chromium status, with 900 ppb in newborn infants, 440 ppb in children 24-36 months of age, and 0.75 mcg chromium/g of hair in nulliparous women reported.

Selenium
The range for selenium blood levels has been reported as 78 to 157 ng/mL of plasma, and 70 to 229 ng/mL of whole blood.

Iodine
Serum levels of iodine for healthy subjects are 0.08 to 0.60 mcg/100 mL. Thyroid function is a more realistic indicator of iodine requirements, with the protein-bound iodine (PBI) or butanol extractable iodine (BEI) of the serum corresponding reasonably well with the level of thyroid activity; limits of normality have been placed at 3-8 mcg/100 mL of serum.

4.2 Recommended Dose and Dosage Adjustment

The suggested dosage ranges for the six trace elements are:

Zinc
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 (≤ 18 years of age)
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.

Copper
Adults
For the metabolically stable adult receiving TPN, the suggested additive dosage level is 0.5 to 1.5 mg copper per day.

Pediatrics (≤ 18 years of age)
For pediatric patients the suggested dosage level is 20 mcg copper per kg daily.

Manganese
Adults
For the metabolically stable adult receiving TPN, 0.15 to 0.8 mg/day is suggested as the additive dosage level for manganese.

Pediatrics (≤ 18 years of age)
The following dosage levels of manganese are recommended:

Infants up to 10 kg:	≤ 1 mcg per kg/day
Children ≤ 15 kg:	1 mcg per kg/day, with a maximum daily dose of 15 mcg
Children 15.1 to 40 kg:	15 mcg per kg/day
Children and adolescents > 40 kg:	the adult preparations of trace elements should be prescribed.

See 7 WARNINGS AND PRECAUTIONS.

Chromium
Adults
For the metabolically stable adult receiving TPN, 10 to 15 mcg of chromium per day is suggested as the additive dosage level.

The metabolically stable adult with intestinal fluid loss may require 20 mcg of chromium daily with frequent monitoring of blood levels as a guideline for subsequent administration.

Pediatrics (≤ 18 years of age)
For pediatric patients, 0.14 to 0.20 mcg/kg/day is suggested as the additive dosage level.

Selenium
Adults
For the metabolically stable adult receiving TPN, the suggested additive dosage level is 20 to 40 mcg selenium per day.

Pediatrics (≤ 18 years of age)
For pediatric patients, the suggested dosage level is 3 mcg selenium per kg per day.

Iodine
Adults
For adults who are metabolically stable, the recommended dosage level is 1 to 2 mcg iodine/kg/day. For normal adults this would be 75-150 mcg/day.

Pediatrics (≤ 18 years of age)
For growing children, the recommended dosage level is 2 to 3 mcg iodine/kg/day.

Pregnant or Lactating Women
For pregnant or lactating mothers, the recommended dosage level is 2 to 3 mcg iodine/kg/day.

4.3 Reconstitution
Not applicable

4.4 Administration
Aseptic addition of MICRO +6 CONCENTRATE to the amino acid/dextrose component of a TPN solution under a laminar flow hood is recommended. After dilution, the solution must be used within 24 hours, see 11 STORAGE, SATBILITY AND DISPOSAL.

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

5 OVERDOSAGE

Zinc
Zinc 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, vomiting, 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).

Copper
Ingestion of excess copper due to the storage of food or beverages in copper or brass vessels, and beverage vending machines has resulted in acute gastro¬intestinal illness. Adverse reactions experienced following the ingestion of large doses of copper sulfate (1 to 50 g) include nausea, vomiting, metallic taste, burning sensation in the œsophagus and stomach, colic, bloody diarrhea, convulsions, hypotension and coma, renal damage with acute kidney necrosis, jaundice associated with liver injury and hæmolysis, anuria/oliguria, and hemolytic anemia.

Symptoms of copper toxicity that have been reported include prostration, behavior change, diarrhea, progressive marasmus, hypotonia, photophobia and peripheral edema.
D-penicillamine has been reported effective as an antidote.

Manganese
Manganese toxicity (manganism), a rare central nervous system disease, can occur following chronic occupational exposure to the dust from manganese ore fumes in steel processing. A metal fume fever syndrome can occur after exposure to high concentrations of manganese oxide; a few cases of pneumonitis have been associated with manganese exposure.

High doses of manganese can lead to deposition in the basal ganglia of the brain and cause toxic events that manifest symptomatically as Parkinson-like signs and symptoms, in addition to neuropsychiatric symptoms. If treatment lasts more than 4 weeks, manganese levels must be checked and if there is an excess of manganese, the administration of the parenteral nutrition should be stopped and corrective measures should be initiated.

Chromium

Trivalent chromium has been administered to TPN patients exhibiting chromium deficiency at dosage levels up to 250 mcg/day for two weeks with no signs of chromium toxicity.

Symptoms of chromium toxicity that have been reported for other compounds include nausea, vomiting, anemia, gastroenteritis and renal and hepatic damage.

Selenium
Chronic selenium toxicity due to occupation related exposure, high selenium content in food, water or oral supplements resembles arsenic toxicity. Hair loss, white horizontal streaking on fingernails, paronychia, fatigue, irritability, hyperreflexia, nausea, vomiting, garlic odour on breath, and metallic taste characterize toxicity. Muscle tenderness, tremor, lightheadedness, and facial flushing are observed in selenite poisoning. Serum selenium levels are elevated but do not correlate well with symptoms. Blood chemistries, hematology, and liver and renal function tests are usually normal.

Acute selenious acid ingestions are almost invariably fatal. Stupor, respiratory depression, hypotension, and death can result several hours postingestion. Severe hypotension develops secondary both to decreased contractility from a toxic cardiomyopathy and to inappropriately low peripheral vascular resistance. Laboratory abnormalities include thrombocytopenia, moderate hepatorenal dysfunction, and elevated serum creatine kinase levels. The electrocardiogram may demonstrate ST elevations and T wave changes characteristic of myocardial infarction. The urinary excretion of selenium is rapid. Terminal respiratory failure developed after a selenious acid ingestion (15 mL gun bluing solution) despite the use of an extracorporeal membrane oxygenator. Death occurred on the 18th hospital day. The plasma selenium level reached 285 mcg/mL on the first hospital day and returned to normal levels by day 4.

There are no antidotes to selenious acid toxicity; treatment is expectant (cardiopulmonary monitoring in an intensive care setting) and supportive (intravenous infusion, supplemental oxygen and ventilation as needed).

Iodine
The symptoms of acute poisoning from ingestion of iodine are mainly due to its corrosive effects on the gastrointestinal tract: a disagreeable metallic taste, vomiting, abdominal pain, and diarrhea occur. Anuria may occur 1 to 3 days later; death may result from circulatory failure, edema of the glottis resulting in asphyxia, aspiration pneumonia, or pulmonary œdema. Œsophageal stricture may occur if the patient survives the acute stage. The fatal dose is usually 2 or 3 g.

Acute iodine poisoning should be treated with abundant fluids and electrolyte. The symptoms of iodism disappear soon after administration of the drug is discontinued.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form/ Strength	Non-medicinal Ingredients
Intravenous	Liquid /	Nitric acid, water for injection.

Route of Administration	Dosage Form/ Strength	Non-medicinal Ingredients
	zinc: 5 mg/ mL copper: 1 mg/ mL manganese: 0.5 mg/ mL chromium: 10 mcg/ mL selenium: 60 mcg/mL iodide: 75 mcg/mL	

COMPOSITION: MICRO +6 CONCENTRATE contains 5 mg/mL of zinc as zinc sulfate heptahydrate, 1 mg/mL copper as cupric sulfate penthydrate, 0.5 mg/mL manganese as manganese sulfate monohydrate, 10 mcg/mL chromium as chromium chloride hexahydrate, 60 mcg/mL selenium as selenium dioxide monohydrate, and 75 mcg/mL iodide as sodium iodide.

PACKAGING:
Available in single use vials of 10 mL, boxes of 10.

The stopper is not made with natural rubber latex.

7 WARNINGS AND PRECAUTIONS

General
MICRO +6 CONCENTRATE is a hypotonic solution which should be administered in admixtures only.

If toxicity symptoms occur due to any one of the trace elements in MICRO +6 CONCENTRATE, discontinue supplementation of TPN solutions immediately.

Do not give undiluted MICRO +6 CONCENTRATE by direct injection into a peripheral vein because of the potential of infusion phlebitis.

Endocrine and Metabolism
In diabetic patients, the contribution of chromium supplementation for maintenance of normal glucose homeostasis has to be taken into account. In all diabetic patients, the hyperglycemia should also be controlled with appropriate therapy

Hepatic / Biliary / Pancreatic
The possibility of copper and manganese retention should be a consideration in patients with biliary obstruction and caution should be exercised since copper and manganese are eliminated *via* the bile.

Neurologic
Excess of manganese can lead to deposition in the basal ganglia of the brain and cause toxic events that manifest symptomatically as Parkinson-like signs and symptoms, in addition to neuropsychiatric symptoms.

Renal
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.

The possibility of selenium retention should be considered in patients with renal dysfunction and/or gastrointestinal malfunction since selenium is eliminated in the urine and to a smaller extent in the feces.

Because iodide is mostly eliminated in the urine, iodine may accumulate to toxic levels in patients with renal dysfunction. Consideration should be given to other sources of iodine, such as topical disinfectants or coastal air, as iodine is absorbed through the skin and mucous membranes.

Sensitivity / Resistance
Occasional sensitization to iodine can result in anaphylactic shock. Patients should be evaluated for sensitivity to iodine before administration of MICRO +6 CONCENTRATE.

7.1 Special Populations

7.1.1 Pregnant Women
It is not known whether MICRO +6 CONCENTRATE can cause fetal harm when administered to a pregnant woman or if it can affect reproductive capacity.

7.1.2 Breast-feeding
It is unknown if MICRO +6 CONCENTRATE is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview
No adverse reactions have been reported for the amount of zinc, copper, manganese, chromium, or selenium present in this product. The amounts are small and toxicity symptoms are not likely to occur at the suggested dosage level. However, adverse reactions have been reported for iodine.

Iodine and iodides can produce goitre and hypothyroidism as well as hyperthyroidism. Goiter and hypothyroidism have also occurred in infants born to mothers who had taken iodides during pregnancy.

Iodine can give rise to allergic reactions which may include urticaria, angioedema, cutaneous hæmorrhage or purpuras, fever, arthralgia, lymphadenopathy, and eosinophilia.

Prolonged administration may lead to iodism, although some of the effects could be considered to be due to hypersensitivity. These include adverse effects on the mouth such as metallic taste, increased salivation, burning or pain, and coryza; there may be swelling and inflammation of the throat. Eyes may be irritated and swollen. Pulmonary œdema may develop. Skin reactions include acneform or severe eruptions (iododerma). Other reported effects include gastrointestinal upsets and diarrhea.

Symptomatic treatment may be required for allergic reactions and iodism, although symptoms usually subside rapidly when administration of iodine is discontinued.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview
No drug interactions have been established.

9.4 Drug-Drug Interactions
Interactions with drugs have not been established.

9.5 Drug-Food Interactions
Interactions with food have not been established.

9.6 Drug-Herb Interactions
Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action
Zinc
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, glyceraldehyde-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.

Copper
Copper is an essential nutritional element that is important in many enzyme systems either as a metalloenzyme or an enzyme activator such as: cytochrome-c-oxidase, dopamine-β-hydroxylase, monamine oxidase, superoxide dismutase, tyrosinase, urate oxidase, ceruloplasmin, ferroxidases and metallothionine.

The clinical importance of copper is related to the development and maintenance of collagen protein cross-linkage, structure and function of the central nervous system, iron metabolism, erythropoiesis and pigmentation.

Manganese
Manganese, an essential nutrient, is a component of several metalloenzymes, pyruvate carboxylase and superoxide dismutase, and a cofactor of a large number of enzyme systems including polymerase, galactotransferase, arginase and cholinesterase.

Manganese deficiency has been demonstrated in numerous animals and in one human subject with vitamin K deficiency whose symptoms included a delayed blood clotting response, mild evanescent dermatitis, reddening of hair and beard, slowed growth of hair, nails and beard, occasional nausea and vomiting, coincident decrease of serum phospholipids and triglycerides, and moderate weight loss.

Chromium
Trivalent chromium, an essential element, is a component of glucose tolerance factor which facilitates the reaction of insulin with receptor sites of insulin-sensitive tissues. Chromium helps to maintain normal glucose metabolism and peripheral nerve function.

Administration of chromium supplements to chromium deficient patients can result in normalization of the glucose tolerance curve from the diabetic-like curve typical of chromium deficiency. This response is viewed as a more meaningful indicator of chromium levels.

When chromium was administered intravenously to diabetics, increased chromium urinary levels were observed as compared to normal persons.

Selenium
Selenium is an essential component of glutathione peroxidase, which helps prevent oxidative damage to cells by peroxides and free radicals.

Keshan disease, a cardiomyopathy of children and young women in China is the only clinical condition that has been firmly linked to selenium deficiency. Plasma selenium levels have been shown to decrease during total parenteral nutrition; however symptoms of selenium deficiency are not seen in all TPN patients. Several factors may influence the development of selenium deficiency including geographical location, nutritional and clinical status, excessive GI losses, age, volume of fluid administered and duration of selenium deficient TPN. Several cases of cardiomyopathy have occurred in patients receiving total parenteral nutrition. Muscle pain and weakness have been reported during total parenteral nutrition and have responded to selenium supplementation.

Iodine
Iodine is an essential trace element in the human diet. It is an important factor in cellular oxidation processes and is necessary for the formation of thyroid hormones thyroglobulin, thyroxine and triiodothyronine. The manifestations of iodine deficiency are those of a deficiency of thyroid hormones. Where dietary iodine limits thyroid output, the basal metabolic rate is reversibly lowered.

10.2 Pharmacodynamics
Zinc
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 after acute tissue injury, regardless of origin.

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, hypogeusia, anorexia, dysosmia, geophagia, hypogonadism, growth retardation and hepatosplenomegaly.

Copper
Copper deficiency has been recognized in infants on cow's milk diets and in malnourished infants being rehabilitated on high-calorie low copper diets. Symptoms experienced include anemia, hypoproteinemia, low serum copper and iron levels, neutropenia, diarrhea and "scurvy-like" bone changes.

Adults and children receiving total parenteral nutrition without copper supplementation have shown these same symptoms along with a parallel decline in plasma copper.

Copper supplementation during TPN helps prevent development of the following deficiency symptoms: leukopenia, neutropenia, anemia, depressed ceruloplasmin levels, impaired transferrin formation and secondary iron deficiency.

Manganese
Administration of manganese helps prevent deficiency symptoms such as nausea and vomiting, weight loss, reduced phospholipid and triglyceride plasma levels, dermatitis and changes in growth and colour of hair.

Chromium
Chromium supplementation during TPN helps prevent deficiency symptoms which include impaired glucose tolerance, ataxia, peripheral neuropathy and a confusional state similar to mild/moderate hepatic encephalopathy.

Selenium
Selenium supplementation during TPN helps prevent development of the following deficiency symptoms: cardiomyopathy, muscle pain and weakness.

Iodine
The hypothalamus secretes the thyrotropin releasing factor, or TRF, a peptide which provokes the secretion of the thyroid stimulating hormone, or TSH. TSH stimulates the thyroid gland to release its hormone and trap iodide. The thyroid hormones in turn inhibit the release of both TRF by the hypothalamus and TSH by the pituitary, thus keeping the plasma level of the thyroid

hormones normal.

The fact that the thyroid hormones play an important role in animal metamorphosis, growth and cell differentiation suggests that these hormones have a primary effect on the control of gene expression.

Thyroid hormones and thus iodine are essential for growth during early life. Athyreosis can lead to a type of dwarfism found in severely goitrous areas, and can be treated with iodine administration.

Endemic goiter, when severe, is frequently associated with endemic cretinism, which is characterized by mental retardation, deafness and deaf-mutism, retarded growth, and neurological abnormalities, as well as hypothyroidism.

Thyroid hormones are important for the development of the gonads and secondary sex organs.

Changes in the skin and hair are among the most constant features of iodine deficiency.

Iodine concentrations in human foods vary with the availability of iodine in the soil or with the amount and nature of fertilizers applied. Overall iodine intakes are determined more by the source of foods composing dietaries than by the choice or proportion of different foods, except for those of marine origin, or where there is iodine enrichment such as iodized salt.

During short term total parenteral nutrition, iodine deficiency is unlikely to occur, except perhaps in patients with long-standing enteropathies; however, long term TPN may require supplementation of iodine.

10.3 Pharmacokinetics

Absorption:
Zinc
Zinc is absorbed primarily from the small intestine.

Copper
Copper is absorbed primarily from the stomach and jejunum; however the exact mechanism of absorption is not clear.

Manganese
Dietary manganese is poorly absorbed.

Selenium
Selenium absorption, retention and distribution within the body and the amounts, forms and routes of excretion vary with the chemical forms and amounts of the element ingested and with the dietary levels of other elements such as arsenic and mercury.

Selenium is absorbed from the small intestine and distributed widely to tissues including liver, skin, muscle, kidney, lung, brain, testis, ovary, heart, spleen, thyroid, pancreas, dental enamel and fingernails.

Iodine
Iodine, as inorganic iodide, is absorbed rapidly and almost completely from all levels of the GI

tract. Iodinated amino acids are more slowly and less completely absorbed, or are broken down and absorbed as iodide.

Distribution:

Zinc

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, and 14.4 mcg/mL in erythrocytes.

Copper

In man, the highest concentrations of copper are found in the liver and brain. Normal serum plasma levels range from 90 to 130 mcg/100 mL (mean, approximately 110 mcg/100 mL).

Manganese

It is estimated that the body of a normal 70 kg man contains 12 to 20 mg of manganese. This relatively small amount is widely distributed without notable concentration. However manganese concentration tends to be higher in tissues rich in mitochondria (liver, kidney and pancreas). Reserve manganese stores do not normally occur.

Chromium

The distribution of chromium occurs throughout the body in low concentrations without special concentration in any one tissue. Plasma chromium is bound to siderophilin (transferrin) a β1 globulin. Serum levels of 1 to 31 ng chromium per mL have been reported. Tissue uptake is rapid with plasma clearance occuring in several days. Since there does not appear to be an equilibrium between plasma and tissue chromium, blood levels are not considered to accurately indicate body chromium status.

Selenium

Blood levels have been shown to vary geographically due to selenium levels of soil and food. Reported values of selenium levels in whole blood vary from 150 ng/mL in selenium deficient areas to 3200 ng/mL in a seleniferous zone (in China). Studies in North America have reported whole blood levels of 70 to 229 ng/mL and plasma levels of 78 to 157 ng/mL.

Iodine

The healthy human adult body contains a total of 15-20 mg iodine, of which 70-80% is present in the thyroid gland. The skeletal muscles contain the next largest proportion of total body iodine. Iodine is also present in the pituitary gland, salivary glands, and bile. Iodine in the tissues is present in both inorganic and organically bound forms. The salivary iodine concentration is proportional to the plasma in organic iodine concentration. The protein-bound iodine of the serum (PBI), or the butanol extractable iodine (BEI) of the serum corresponds reasonably well with the level of thyroid activity in man. In adults the normality has been placed at 4-8 or 3-7.5 mcg/100 mL with a mean close to 5-6 mcg/100 mL. Human colostrum has been reported to contain 50-240 mcg/litre, with 40-80 mcg/litre in human milk, once lactation is established.

Metabolism:

Copper

Absorbed copper is loosely bound to serum albumin and amino acids for transport and exchange with tissues. After reaching the liver, copper is either stored or released for incorporation into erythrocuprein, ceruloplasmin and the numerous copper containing enzymes.

About 60% of the copper in red blood cells is associated with erythrocuprein while the remainder is more loosely bound to protein.

Copper in plasma is present in two main forms of which 90% is firmly bound to ceruloplasmin and a small percentage is loosely bound to albumin. The remainder is bound to amino acids and enzymes.

Age, diet, hormones and pregnancy influence liver and plasma concentrations of copper.

Manganese
Plasma manganese is bound to a β1 globulin, transferrin. Normal whole blood levels of manganese range from 6 to 10 mcg/L.

Iodine
The iodide pool is replenished continuously, exogenously from the diet, and endogenously from the saliva, the gastric juice, and the breakdown of thyroid hormones. The rate of removal of iodide from the plasma inorganic iodide pool by the thyroid and kidneys is expressed as thyroid and renal clearances. In normal man the total clearance occurs at the rate of about 50 mL/min over all ranges of plasma iodide examined. Thyroid clearance is sensitive to changes in plasma concentrations and varies with the activity of the gland. In normal adults, the thyroid clears 10-20 mL/min.

Elimination:
Zinc
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 parenteral nutrition (TPN), abnormal zinc excretion occurred from the gastrointestinal tract in diarrheal stools and intestinal fluid lost through suction and fistulous discharge.

Copper
Copper is excreted primarily via the bile (approximately 80%) in the form of a nonabsorbable protein complex with a further 18% via the intestinal wall and 2-3% via urine. Consequently, ingestion of 2-5 mg of copper per day, would result in copper losses of 0.6 to 2 mg per day, with 0.01 to 0.06 mg in urine. Comparatively small amounts are lost through menstruation and in sweat.

Manganese
Bile is the major route of manganese excretion with the liver apparently maintaining manganese homeostasis. However, when the biliary route is blocked or overloaded, auxiliary routes, pancreatic juices and the walls of duodenum, jejunum and ileum, increase. Urinary excretion, which is negligible, can be increased by the administration of chelating agents.

Chromium

Chromium is excreted mainly in the urine (5-10 mcg/day) with small amounts lost in the feces via the bile and small intestine. In subjects not receiving total parenteral nutrition urinary chromium has been reported to be less than 5 mcg/day, whereas, patients receiving TPN excreted much higher levels ranging from 10 to more than 100 mcg chromium/day. A chromium balance in TPN patients can be assessed by the measurement of chromium input and output.

Selenium
Excretion occurs mainly *via* the kidneys. However a small amount of the endogenous stores is lost through the feces.

Iodine
Iodine is excreted mainly in the urine, with smaller amounts appearing in the feces and sweat. The level of urinary iodine excretion correlates well with plasma iodide concentration and labelled iodine thyroid uptakes. The lower limit of normal urinary levels has been suggested to be 75 mcg/g creatinine for adult man, 50 mcg/g for adolescents, and 32.5 mcg/g for children 5-10 years of age. Most of the hormonal iodine is degraded by the liver and the iodide returned to the body iodide pool, with little appearing in the feces.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15 and 30ºC. Protect from light. Protect from freezing.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Zinc

Proper name:	Zinc sulfate
Chemical name:	Zinc sulfate heptahydrate
Molecular formula and Molecular mass:	$ZnSO_4 \cdot 7H_2O$, 287.5 g/mol
Physicochemical properties:	Zinc sulfate is an odourless, colourless, transparent, effloresce nt crystal or white crystalline powder with an astringent metallic taste and freely soluble in water.

Copper

Proper name:	Copper sulfate
Chemical name:	Copper sulfate pentahydrate
Molecular formula and molecular mass:	$CuSO_4 \cdot 5H_2O$, 249.68 g/mol
Physicochemical properties:	Copper sulfate occurs as a blue crystal powder. It effloresces slowly in dry air. Its solution is acid to litmus. It is freely soluble in water and in glycerin, very soluble in boiling water and slightly soluble in alcohol.

Manganese

Proper name:	Manganese sulfate
Chemical name:	Manganese sulfate monohydrate
Molecular formula and molecular mass:	$MnSO_4 \cdot H_2O$, 169.01 g/mol
Physicochemical properties:	Manganese sulfate is a pale red, slightly efflorescent crystal or purple odourless powder. It is soluble in water and insoluble in alcohol.

Chromium

Proper name:	Chromic choride
Chemical name:	Chromic chloride (III) hexahydrate

Molecular formula and molecular mass:	$CrCl_3 \cdot 6H_2O$, 266.5 g/mol
Physicochemical properties:	Chromic chloride is a dark green, odourless, slightly deliquescent crystal. It is soluble in water and in alcohol, slightly soluble in acetone, and practically insoluble in ether.

Selenium

Proper name:	Selenium dioxide
Chemical name:	Selenium dioxide monohydrate
Molecular formula and molecular mass:	H_2SeO_3, 128.97 g/mol
Physicochemical properties:	Selenious acid is a colourless or white crystal, efflorescent in dry air and hygroscopic in moist air. It is insoluble in water and alcohol.

Iodine

Proper name:	Sodium iodide
Chemical name:	Sodium iodide
Molecular formula and molecular mass:	NaI, 149.89 g/mol
Physicochemical properties:	Sodium iodide occurs as colourless, odourless crystals, or white crystalline powder. It is deliquescent in moist air, and develops a brown tint upon decomposition. It is very soluble in water, and freely soluble in alcohol and in glycerin.

14 CLINICAL TRIALS

This information was not available at the time of authorization.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

This information was not available at the time of authorization.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
MICRO +6 CONCENTRATE
6 Trace Elements Injection USP

Read this carefully before you start taking **MICRO +6 CONCENTRATE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MICRO +6 CONCENTRATE.**

What is MICRO +6 CONCENTRATE used for?
MICRO +6 CONCENTRATE is used with other nutrition products that are given to you through an infusion into your vein. It is given when you cannot eat normally. It helps maintain normal levels of nutrients (zinc, copper, manganese, chromium, selenium and iodide).

How does MICRO +6 CONCENTRATE work?
Zinc, copper, manganese, chromium, selenium and iodide are essential nutrients for your body. MICRO +6 CONCENTRATE works by maintaining normal levels of these nutrients in your blood. This helps prevent problems when these levels of nutrients are low.

What are the ingredients in MICRO +6 CONCENTRATE?
Medicinal ingredients: zinc (as zinc sulfate heptahydrate), copper (as cupric sulfate pentahydrate), manganese (as manganese sulfate monohydrate), chromium (as chromium chloride hexahydrate), selenium (as selenium dioxide monohydrate) and iodide (as sodium iodide).
Non-medicinal ingredients: nitric acid, water for injection.

MICRO +6 CONCENTRATE comes in the following dosage form: liquid (5 mg zinc / mL, 1 mg copper / mL, 0.5 mg manganese / mL, 10 mcg chromium / mL, 60 mcg selenium / mL, 75 mcg iodide / mL).

Do not use MICRO +6 CONCENTRATE if you:
- are allergic to zinc, copper, manganese, chromium, selenium, iodide or to any of the other ingredients of MICRO +6 CONCENTRATE or to a component of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MICRO +6 CONCENTRATE. **Talk about any health conditions or problems you may have, including if you:**
- have a liver condition where there is a blockage of the bile duct.
- have kidney disease.
- have diabetes.
- are sensitive or allergic to iodine.
- are pregnant or plan to become pregnant.
- are breastfeeding of plan to breastfeed. It is not known if MICRO +6 CONCENTRATE passes into breastmilk.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

There are no known relevant interactions at this time.

How to take MICRO +6 CONCENTRATE:

- MICRO +6 CONCENTRATE will be given to you into your vein by a healthcare professional.
- Your healthcare professional will make sure that MICRO +6 CONCENTRATE is prepared correctly before it is given to you.
- Your healthcare professional will routinely monitor the nutrient levels in your blood.

Usual dose:
Your healthcare professional will decide on the actual dose of MICRO +6 CONCENTRATE that is right for you based on your age, body weight and medical condition.

Overdose:

If you think you, or a person you are caring for, have taken too much **MICRO +6 CONCENTRATE**, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using MICRO +6 CONCENTRATE?
These are not all the possible side effects you may have when taking MICRO +6 CONCENTRATE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:
- goitre (swelling in the neck)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN			
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, fever, joint pain, swollen lymph nodes			√
Hyperthyroidism (overactive thyroid): nervousness, anxiety, irritability, trouble sleeping, sensitivity to heat, weight loss, irregular or fast heartbeat		√	
Hypothyroidism (underactive thyroid): fatigue, increased sensitivity to cold, constipation, dry skin, weight gain, thinning hair, slow heartbeat		√	
Iodine poisoning: metallic taste in the mouth, increased saliva, mouth and/or throat pain, eye irritation, shortness of breath, rash, stomach problems, diarrhea		√	

If you have a troublesome symptoms or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Your healthcare professional will store MICRO +6 CONCENTRATE at 15 - 30°C. Protect from light. Protect from freezing.
Keep out of sight and reach of children.

If you want more information about MICRO +6 CONCENTRATE:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada web site (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.sandoz.ca or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

Revised on JAN 19, 2022.