PRODUCT MONOGRAPH

M.T.E.® - 6 CONCENTRATED

Multi-Trace Element

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NAME OF DRUG

M.T.E.®-6 CONCENTRATED

THERAPEUTIC CLASSIFICATION

Multi-Trace Element

ACTIONS AND CLINICAL PHARMACOLOGY

Zinc

Zinc is an essential nutritional element that plays a key role as a component of numerous metalloenzymes such as carbonic anhydrase, alkaline phosphatase, lactic dehydrogenase and carboxypeptidase. At least one zinc metalloenzyme has been identified in each of the six major categories of enzymes; i.e., oxidoreductase, transferase, hydrolase, lyase, isomerase and ligase. Zinc is also necessary for the synthesis of RNA and DNA, making it important in the normal growth and development process. Zinc helps maintain normal skin hydration and the senses of taste and smell and facilitates wound healing.

Zinc resides in muscle, bone, skin, kidney, liver, pancreas, retina, prostate and particularly in red and white blood cells. Calculations from data indicate that 75 to 88% of the total zinc of normal blood is contained in red cells (primarily in the zinc metalloenzyme carbonic anhydrase), 12 to 22% in the plasma and 3% in the leukocytes. Normal plasma levels of zinc vary from approximately 88 to 122 μg/100 ml.

Practically all zinc in serum is protein bound including plasma albumin, α2-macroglobulin and some plasma amino acids including histidine, cysteine, threonine, glycine and asparagine. Infection influences the uptake of zinc by the liver and reduces plasma concentration. This process is stimulated by leukocyte endogenous mediator (LEM).

Absorption of zinc occurs mainly in the small intestine, predominantly in the duodenum. The primary excretory pathway for zinc is the faeces and pancreatic secretion. The largest component comes from direct transfer of zinc through the intestinal wall. Several researchers showed that diarrhea, stomal and fistula losses were major sites of abnormal losses of zinc from endogenous sources in patients receiving

TPN solely. Small amounts of zinc may be lost in the urine (300-700 μg per 24 hrs). A striking increase in urine zinc levels occurs in post-operative procedures, major long bone fractures, burns, chronic malabsorption states and patients on long-term TPN. The excessive urinary loss of zinc following these kinds of stresses must be replaced in order to insure proper nutritional rehabilitation of the patients. Zinc is also lost through sweat, in hair and sloughing skin.

The first syndrome of zinc deficiency in adult human beings on TPN was reported in 1975. Four patients with severe gastrointestinal disorders who underwent zinc-free TPN therapy developed paranasal, perioral and periorbital dermatitis, diarrhea, alopecia and mental depression. Plasma zinc concentrations ranged from 9 to 12 μg/100 mL. Urinary zinc was high with values as high as 23,600 μg/day. Intravenous or oral administration of zinc sulphate in doses of 40 to 200 mg daily, rapidly reversed skin lesions, diarrhea and mental depression. The alopecia was resolved more slowly.

Numerous reports of all or some of the zinc deficiency symptoms in adults, children and premature infants then followed. The most predominant clinical manifestations of zinc deficiency in TPN reported were the skin lesions and diarrhea which resembled that found in 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, hypogensia, anorexia, dysosmia, geophagia, hypogonadism, growth retardation and hepatosplenomegaly.

COPPER

Copper plays a key role as a component of numerous metalloenzymes and proteins such as: cytochrome oxidase, ferroxidases, amine oxidases, superoxide dismutase, ceruloplasmin and metallothioneine. Specific biological functions for which copper is responsible are hemoglobin synthesis, growth and development, pigmentation, fertility and reproduction, coordination and nerve function, protection against oxygen radicals, connective tissue maturation, cardiovascular integrity, bone formation and

immunocompetence. The highest concentrations of copper content in the human body are in the liver, brain and heart.

Absorption of copper occurs predominantly in the stomach and upper small intestine. The exact mechanism of copper absorption from the gastro-intestinal tract into the blood is elusive. Normal serum copper values range from 80 to 163 μg/dl (mean, approximately 110 μg/dl). A report stated that copper concentrations are higher in serum than in plasma. After absorption, copper exists loosely bound to albumin in the plasma for transport and exchange with tissues. In circulation toward the liver, copper may be stored or combined with ceruloplasmin or erythrocuprein. The α2-globulin, ceruloplasmin, harbours greater than 90% of serum copper. More than 60% of the copper in erythrocytes is associated with erythrocuprein. The daily turnover of copper through ceruloplasmin is approximately 0.5 mg. Diet, age, hormones and pregnancy influence the concentration of copper in the liver.

The liver is responsible for the excretion of copper, primarily bile (80%). Eighteen and 4% of the trace element is eliminated through the intestinal wall and in the urine, respectively. Biliary copper is known to form a complex with the bile salt taurochenodeozylate and bilirubin. Small amounts of copper are also lost through menstruation and in sweat. Copper losses in the urine of normal subjects amounted to 0.0l to 0.06 mg/day.

Human copper deficiency was first documented in 1964. Infants who were recovering from marasmus or milk diets with no food sources exhibited deficiency manifestations such as anemia, decreased plasma copper and ceruloplasmin levels, intermittent neutropenia, severe osteoporosis and pathological fractures.

This deficiency syndrome with laboratory and clinical manifestations has now been recognized in adults and children who were receiving parenteral nutrition without copper supplementation. A consistent decline in plasma copper content can be seen without copper supplementation.

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

MANGANESE

Manganese is an essential nutrient that serves as an activator for enzymes such as polysaccharide polymerase, liver arginase, cholinesterase and pyruvate carboxylase.

Manganese is bound to a specific transport protein, transmanganin, a β-1-globulin. Manganese is widely distributed but concentrates in mitochondria-rich tissues such as brain, kidney, pancreas and liver. The concentration in skeletal muscle is very low. Manganese is also found in bone but cannot be mobilized to meet body needs. Newborns do not have a special store. Assays for manganese in whole blood result in concentrations ranging from 6 to 12 μg per litre.

Excretion of manganese occurs mainly through the bile. The liver appears to maintain manganese homeostasis. In the event of obstruction and overload, ancillary excretion routes include pancreatic juice or crossing the intestinal lumen of the duodenum, jejunum or ileum. Urinary excretion is negligible.

Providing manganese during TPN helps to maintain manganese serum levels and to prevent depletion of endogenous stores. Administration of manganese helps prevent deficiency symptoms such as nausea and vomiting, weight loss, dermatitis and changes in growth and colour of hair.

Besides animal experiment results, there exists one human case of manganese deficiency. A volunteer patient was observed for Vitamin K deficiency under metabolic ward conditions. Weight loss, transient dermatitis, occasional nausea and vomiting, hair and beard colour change and slow growth of hair and beard were noted and recorded. Protein synthesis was not affected. Remarkably, hypercholesterolemia was evident. It was later discovered that the addition of manganese to the purified mixture was overlooked.

CHROMIUM

Trivalent chromium is part of glucose tolerance factor (GTF), an essential activator of insulin-mediated reactions. Chromium helps to maintain normal glucose metabolism and peripheral nerve function. Its mode of action is described as facilitating the reaction of insulin by fine tuning the receptor sites of sensitive tissues.

Serum chromium is bound to transferrin (siderophilin) in the β-globulin fraction. Typical blood levels range from 1 to 5 μg per litre, but blood levels are not considered a meaningful index of tissue stores. 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 nutriture than serum chromium levels.

Excretion of chromium is via the kidneys, ranging from 3 to 50 μg/day. Several researchers reported urinary chromium loss in subjects not receiving TPN to be within the range of <1.0 to 7.0 μg per litre, with an average output of <5 μg/24 hours. In contrast, those patients receiving TPN excreted much higher amounts of chromium, within a range of 10 to greater than 100 μg of chromium per day.

Biliary excretion via the small intestine may be an ancillary route but it is believed that only small amounts of chromium are excreted in this manner. When insulin-requiring diabetics are given Cr-labelled chromic chloride intravenously, an increase in urinary excretion is observed when compared to normal subjects.

Providing chromium 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 is part of glutathione peroxidase which protects cell components from oxidative damage due to peroxides produced in cellular metabolism.

Prolonged TPN support in humans has resulted in selenium deficiency symptoms which include muscle pain and tenderness. The symptoms have been reported to respond to supplementation of TPN solutions with selenium. Pediatric conditions Keshan disease and Kwashiorkor have been associated with low dietary intake of selenium. The conditions are endemic to geographical areas with low selenium soil content.

Dietary supplementation with selenium salts has been reported to reduce the incidence of the conditions among affected children.

Normal blood levels of selenium in different human populations have been found to vary and depend on the selenium content of the food consumed. Results of surveys carried out in some countries as per the attached table:

COUNTRY	NO. OF SAMPLES	WHOLE BLOOD	SELENIUM (µg/100 ml)[a] BLOOD CELLS	PLASMA/ SERUM
Canada	254 adults	(37.9±7.8)	(23.6±6.0)	(14.4±2.9)
England	8[b]	26-37	-	-
Guatemala & South. USA	10 adults 9 children[c]	19-28 (23±5)	- (36±12)	- (15 ± 5)
N. Zealand[d]	113 adults	(5.4±0.1)	(6.6±0.3)	(4.3±0.1)
Thailand	3 adults 9 children[e]	14.4-20.2 (12±3.6)[f]	17.8-35.8 (19.5±8.2)	8.1-12.5 (8.3±2.2)
USA	210 adults	15.7-25.6 (20.6)	-	-

a Mean values with or without standard deviation in parentheses, all other ranges.
b Age group unknown
c Three children recovered from Kwashiorkor, the other six under treatment for other diseases.
d Low selenium-content soil area.
e Well nourished children, 3 recovered from kwashiorkor and the other six under treatment for other diseases.
f Mean values from 7 subjects

Plasma selenium levels of 0.3 and 0.9 µg/100 ml have been reported to produce deficiency symptoms in humans.

Selenium is eliminated primarily in urine. However, significant endogenous losses through faeces also occur. The rate of excretion and the relative importance of two routes varies with the chemical form of selenium used in supplementation. Ancillary routes of elimination are lungs and skin.

Negative selenium balance and decreased selenium blood levels have been reported in patients receiving Total Parenteral Nutrition (TPN). A trace element balance study was conducted on 4 adult male subjects fed only by parenteral nutrition. The result of this study showed that all 4 patients were in negative

selenium balance. Also the serum concentrations decreased in 3 out of 4 cases. The first case report of clinical signs of low selenium in a TPN patient came from New Zealand. Another case was described in which a 37-year-old patient developed bilateral muscular discomfort in her hamstring and quadriceps 30 days after initiation of TPN. Within 1 week of selenium supplementation, the patient regained full mobility with no discomfort. The selenium status of 23 adult surgical patients receiving TPN was also studied. Again, whole blood selenium levels were found to be less than what was observed in the normal local population.

A recent report measured plasma and erythrocyte levels of selenium in 7 long-term patients. Significantly lower levels ($p<0.001$) were found in the TPN population compared to normal adults. Three cases, 2 fatal, of selenium deficiency and cardiomyopathy in TPN patients have been reported. The selenium and glutathione peroxidase levels in the blood, liver, heart and skeletal muscle upon autopsy were found to be extremely low.

IODIDE

Iodide is an integral part of thyroid hormones triiodothyronine (T_3) and thyroxine (T_4). The hormones regulate basal metabolism. Persistent iodide deficiency results in histological changes in thyroid gland and impaired thyroid function which may culminate in goitre. Iodide deficiency in early stages in life has been reported to produce cretinism. Iodide is utilized as iodide or iodated organic complexes and is specifically concentrated by thyroid gland, which in humans is estimated to contain 7 to 8 mg total iodine. The circulating iodine is hormonal thyroxine of which 30-70 µg is protein bound and 0.5 µg is free thyroxine. The normal plasma inorganic iodide levels are estimated between 0.5 and 1.5 µg/100 ml.

INDICATIONS

M.T.E.®-6 CONCENTRATED is indicated for use as a supplement to intravenous solutions given for TPN. It's administration in TPN solutions help to maintain plasma zinc, copper, manganese, chromium, iodide and selenium levels and to prevent depletion of endogenous stores of these trace elements and subsequent deficiency symptoms.

CONTRAINDICATIONS

M.T.E.®-6 CONCENTRATED (Multiple Dose) is not for use in newborns. Benzyl alcohol, a preservative in this product, has been associated with toxicity of newborns. Data is unavailable on the toxicity of other preservatives in this age group.

M.T.E.®-6 CONCENTRATED is contraindicated for patients with known hypersensitivity to any of the constituent elements, especially iodide, in the formulation.

WARNINGS

M.T.E.®-6 CONCENTRATED is a hypotonic solution which should be administered in admixtures only.

If toxicity symptoms occur due to any one of the trace elements in M.T.E.®-6 CONCENTRATED, discontinue supplementation of TPN solutions immediately.

Do NOT give undiluted M.T.E.®-6 CONCENTRATED by direct injection into a peripheral vein because of the potential of infusion phlebitis.

PRECAUTIONS

Before administering M.T.E.®-6 CONCENTRATED in TPN solutions, the physician must assess the metabolic requirements for trace elements and disease state of the patient. Frequent determinations of serum levels of the various trace elements are suggested as a guideline for adjusting the dosage or completely omitting M.T.E.®-6 CONCENTRATED.

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

The possibility of copper and manganese retention is a consideration in patients with biliary obstruction since both of these trace elements are eliminated via the bile. Manganese ancillary routes of excretion include the following: pancreatic juice or absorption in the lumen of the duodenum, jejunum or ileum.

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.

As selenium is eliminated in urine and feces, selenium supplements may be adjusted, reduced or omitted in renal dysfunction and/or gastrointestinal malfunction. In patients receiving blood transfusions, contribution from such transfusions should also be considered. Frequent selenium plasma level determinations are suggested as a guideline.

Selenium should be used during pregnancy only if potential benefit justifies the potential risk to the fetus. Presence of selenium in placenta and umbilical cord blood has been reported in humans. There are no adequate and well-controlled studies to date in pregnant women.

ADVERSE REACTIONS

The amounts of zinc, copper, manganese, chromium, selenium and iodide in M.T.E.®-6 CONCENTRATED are very small and toxicity due to these trace elements in normal patients (see CONTRAINDICATIONS) are not likely to occur at the suggested dosage level.

Hypersensitivity to iodide may result in angioneurotic edema, cutaneous and mucosal haemorrhages, fever, arthralgia, lymph node enlargement and eosinophilia. If the patient develops a reaction, TPN supplementation with M.T.E.®-6 CONCENTRATED should be immediately withdrawn and appropriate measures taken.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

ZINC

Zinc is a relatively non-toxic 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. Two cases of oral ingestion of zinc sulfate in large amounts (30 and 44 grams, respectively) have resulted in death. Symptoms included nausea, vomiting, dehydration, electrolyte imbalances, dizziness, abdominal pain, lethargy and incoordination. 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 five days. The ill effects were tachycardia, hypothermia, profuse sweating and blurred vision. Single intravenous doses of 1 to 2 mg zinc/kg body weight have been given to adult leukemic patients without toxic manifestations.

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 1683 mg (7.4 g) dose of zinc infused over a 60 hour period.

Analysis of her serum zinc showed a zinc level of 4184 μg/100 ml. Clinical manifestations were edema, jaundice, vomiting, diarrhea and oliguria. Treatment included sodium calcium edetate (discontinued because of poor renal function), i.v. fluids, furosemide and hemodialysis.

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

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

MANGANESE

There have been no manganese toxicity reports in the literature of patients on TPN or from oral intake. Chronic poisoning due to manganese contaminated drinking water has resulted in lethargy, edema and extra-pyramidal effects. There is no specific therapy for manganese poisoning.

CHROMIUM

Chromium toxicity symptoms include nausea, vomiting, ulcers of the gastrointestinal tract, renal and hepatic damage, convulsions and coma.

A woman who received only 5.3 μg of chromium daily in her TPN solution for years as a protein hydrosylate contaminant began to exhibit signs of chromium deficiency. As treatment she received 250 μg/day for two consecutive weeks without toxic effects.

SELENIUM

Chronic toxicity in humans resulting from exposure to selenium in industrial environments, intake of foods grown in seleniferous soils, use of selenium-contaminated water and application of cosmetics containing selenium has been reported in the literature. Toxicity symptoms include hair loss, weakened nails, dermatitis, dental defects, gastrointestinal disorders, nervousness, mental depression, metallic taste, vomiting and garlic odour of breath and sweat. Acute poisoning due to ingestion of large amounts of selenium compounds has resulted in death with histopathological changes including fulminating peripheral vascular collapse, internal vascular congestion, diffusely hemorrhagic, congested and edematous lungs and brick red colour gastric mucosa. The death was preceded by coma. No effective antidote to selenium poisoning in humans is known.

IODIDE

The symptoms of chronic iodide poisoning in humans include metallic taste, soreness of the mouth, increased salivation, coryza, sneezing, swelling of the eyelids, severe headache, pulmonary edema, tenderness of salivary glands, acneform skin lesions and skin eruptions. Abundant fluids and salt intake help in elimination of iodides.

DOSAGE AND ADMINISTRATION

DOSAGE

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

For premature infants weighing up to 3 kg in body weight, 300 μg 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: For pediatric patients the suggested dosage level is 20 μg copper/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: A dosage level of 2 to 10 μg of manganese per kg daily is recommended.

CHROMIUM

Adults: For the metabolically stable adult receiving TPN, 10 to 15 μg of chromium per day is suggested as the additive dosage level. The metabolically stable adult with intestinal fluid loss may require 20 μg of chromium daily with frequent monitoring of blood levels as a guideline for subsequent administration.

Pediatrics: For pediatric patients, 0.14 to 0.20 μg/kg/day is suggested as the additive dosage level.

SELENIUM

Adults: For metabolically stable adults receiving TPN, the suggested additive dosage level is 20 to 60 μg selenium/day.

However, higher dosage levels up to 100 μg selenium/day for over 4 weeks have been reported to be used without adverse reactions.

Pediatrics: For pediatric patients, the suggested additive dosage is 3 μg/kg/day.

IODIDE

Adults: For metabolically stable adults receiving TPN, the suggested additive dosage level is 1 to 2 μg iodine/kg/day (normal adults 75-150 μg daily).

For pregnant and lactating mothers, the suggested additive level is 2 to 3 μg iodine/kg/day.

Pediatric: For pediatric patients, the suggested additive level is 2 to 3 μg iodine/kg/day.

ADMINISTRATION

Periodic monitoring of zinc, copper, manganese, chromium, iodide and selenium plasma levels is suggested as a guideline for administration.

Periodic monitoring of thyroid function is suggested as a guideline for adjusting the dosage level of iodide.

Normal plasma levels for zinc vary from approximately 88 to 112 μg/100 ml. Frequently monitor the blood zinc levels for those patients receiving more than the usual maintenance dosage level of zinc.

The normal plasma range for copper is approximately 80 to 160 μg/100 ml.

Frequent monitoring of plasma selenium levels is suggested as a guideline for subsequent administration. The normal whole blood range for selenium is approximately 10 to 37 μg/100 ml.

M.T.E.®-6 CONCENTRATED should be aseptically added to the TPN solution under the laminar flow hood. The trace elements present in M.T.E.®-6 CONCENTRATED are physically compatible with electrolytes and vitamins usually present in the amino acid/dextrose solution used for TPN. Compatability studies were conducted using FreAmine III 10% and Aminosyn 8.5% as the amino acid component. It is recommended that the dilute IV infusion be administered within 24 hours.

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

PHARMACEUTICAL INFORMATION

Trade Name: M.T.E.®-6 CONCENTRATED

Proper Names: Multi-Trace Element-6 CONCENTRATED

Drug Substance:

CHEMICAL NAME	MOLECULAR FORMULA	MOLECULAR WEIGHT
Zinc Sulfate Heptahydrate	$ZnSO_4.7H_2O$	287.54
Copper Sulfate Pentahydrate	$CuSO_4.5H_20$	249.68
Manganese Sulfate Monohydrate	$MnS0_4.H_20$	169.01
Chromic Chloride Hexahydrate	$CrCl_3.6H_20$	266.45
Selenium Metal (as Selenious acid)	Se	78.96
Iodide (as Sodium Iodide)	NaI	149.89

Description: M.T.E.®-6 CONCENTRATED is a sterile, non-pyrogenic solution of six trace elements for use as an additive for Total Parenteral Nutrition (TPN). Zinc Sulfate is chemically designated $ZnS0_4$, a white crystalline compound freely soluble in water. Cupric Sulfate is chemically designated $CuS0_4$, a blue crystalline compound very soluble in water. Manganese Sulfate is chemically designated $MnS0_4$, a pale red compound soluble in water. Chromic Chloride is chemically designated $CrCl_3$, a greenish compound soluble in water. Selenium is a lustrous grey or black crystalline metal chemically designated Se and is converted into selenious acid (H_2SeO_3) by Nitric Acid. Sodium Iodide is chemically designated NaI, a white crystalline or granular powder very soluble in water.

Composition: Each ml contains:

INGREDIENTS	M.T.E.®-6 CONCENTRATED 1 ml Fill	M.T.E.®-6 CONCENTRATED 10 ml Fill
Zinc (as Zinc Sulfate heptahydrate)	5.0 mg	5.0 mg
Copper (as Cupric Sulfate pentahydrate)	1.0 mg	1.0 mg
Manganese (as Manganese Sulfate monohydrate)	0.5 mg	0.5 mg
Chromium (as Chromic Chloride hexahydrate)	10.0 µg	10.0 µg
Selenium (as Selenious Acid)	60.0 µg	60.0 µg
Iodide (as Sodium Iodide)	75.0 µg	75.0 µg
Benzyl Alcohol NF	-	0.9%
Water for Injection USP	q.s.	q.s.

The pH is adjusted with 10% nitric acid.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15 to 30°C (59 to 86°F). Do not permit to freeze. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If such abnormalities are observed the drug should not be administered.

Parenteral Products

Dilution for Intravenous Use:

Aseptic addition of M.T.E.®-6 CONCENTRATED to the TPN solution under a laminar flow hood is recommended. The trace elements in M.T.E.®-6 CONCENTRATED are physically compatible with the electrolytes and vitamins usually present in the amino acid/dextrose solution used for TPN. Compatability studies were conducted using FreAmine III 10% and Aminosyn 8.5% as the amino acid component. The dilute IV infusion should be administered within 24 hours.

DILUTION TABLE FOR M.T.E.®-6 CONCENTRATED			
Ingredient	**Dose (per 1 mL)**	**Diluent (mL)**	**Approximate Final Concentration (µg/mL)**
Zinc	5.0 mg	1000	5.0
Copper	1.0 mg	1000	1.0
Manganese	0.5 mg	1000	0.5
Chromium	10.0 µg	1000	0.01
Selenium	60.0 µg	1000	0.06
Iodide	75.0 µg	1000	0.075

AVAILABILITY OF DOSAGE FORMS

M.T.E.®-6 CONCENTRATED is a sterile, nonpyrogenic solution containing six trace elements intended for IV use after dilution. The solution is available in the following formulations:

C2201	**M.T.E.®-6 Concentrated supplied in 1 mL single-dose, flip-top, glass vials in boxes of 25 vials.**
C3610	**M.T.E.®-6 Concentrated supplied in 10 mL multi-dose, flip-top, glass vials in boxes of 10 vials.**

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