NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	209376
Priority or Standard	Standard
Submit Date(s)	9/5/2019
Received Date(s)	9/5/2019
PDUFA Goal Date	7/5/2020
Division/Office	Division of Hepatology and Nutrition (DHN)
Review Completion Date	7/2/2020
Established/Proper Name	trace elements injection 4*
(Proposed) Trade Name	TRALEMENT
Pharmacologic Class	Trace Elements
Applicant	American Regent, Inc.
Dosage form	Injection
Applicant proposed Dosing Regimen	• Adults and Pediatric Patients (b) (4) • Pediatric Patients (b) (4) (b) (4) (b) (4)
Applicant Proposed Indication(s)/Population(s)	(b) (4) as a source of zinc, copper, manganese, and selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	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.
Recommended Dosing Regimen	Adults and Pediatric Patients ≥50 kg: 1 mL/day Pediatric Patients 40 kg to 49 kg: 0.8 mL/day Pediatric Patients 30 kg to 39 kg: 0.6 mL/day Pediatric Patients 20 kg to 29 Kg: 0.4 mL/day Pediatric Patients 10 kg to 19 kg: 0.2 mL/day

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Thao Vu, R.Ph.
Nonclinical Reviewer	Ke Zhang, Ph.D.
Nonclinical Team Leader	David Joseph, Ph.D.
Office of Clinical Pharmacology Reviewer	Elizabeth Shang, Pharm.D., Ph.D
Office of Clinical Pharmacology Team Leader	Insook Kim, Ph.D
Clinical Reviewer	Yao-Yao Zhu, M.D., Ph.D
Clinical Reviewer	Paolo Fanti, M.D.
Clinical Team Leader	Joseph Toerner, M.D., M.P.H.
Associate Director for Labeling	Joette Meyer, Pharm.D.
Cross-Disciplinary Team Leader	Joseph Toerner, M.D., M.P.H.
Division Director (*acting*)	Joseph Toerner, M.D., M.P.H.

Additional Reviewers of Application

OPQ	ATL:	Hitesh Shroff, Ph.D.
	DP:	Jane Chang, Ph.D Moo Jhong Rhee, Ph.D.
	DS:	Frederick Burnett, Ph.D. Donna Christner, Ph.D.
	Process &Facility:	Kenjun Cheng, Ph.D Aditi Thakur, Ph.D
	Micro:	Bethany Lee, Ph.D Jesse Wells, Ph.D.
Regulatory Policy Advisor	Julieann Dubeau, M.S.N, R.N. Richard Ishihara, Pharm.D.	
OPDP	Meeta Patel, Pharm.D.	
OSE SRPM **OSE SRPM Team Leader**	Alvis Dunson, M.S. Aleksander Winiarski, Pharm.D, R.Ph.	
OSE/DEPI	Joel Weissfeld, M.D. Catherine Callahan, Ph.D. Sandhu, Sukhminder, Ph.D., M.P.H., M.S.	
OSE/DMEPA	Sarah Vee, R.Ph. Idalia Rychlik, R.Ph.	
OSE/DPV-I	Jamie Klucken, Pharm.D. Ann Biehl, Pharm.D. Paolo Fanti, M.D. CDR Mona Munoz, Pharm.D., Ph.D., B.C.P.S.	
OPT	Gerri Baer, M.D. Suna Seo, M.D.	
DPMH RPM **DPMH RPM Team Leader**	Niquiche Guity George Greeley, M.S., M.B.A.	

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DPMH/Pediatrics	Erica Radden, M.D. Mona Khurana, M.D.
DPMH/Maternal	Carrie Caresa, M.D. Miriam Dinatale, M.D.
OUDLC	Anne C. Tobenkin, Pharm.D. Yelena Maslov, Pharm.D.

OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSE = Office of Surveillance and Epidemiology
SRPM = Safety Regulatory Project Management
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DPV = Division of Pharmacovigilance
OPT = Office of Pediatric Therapeutics
DPMH = Division of Pediatric and Maternal Health
OULDC = Office of Unapproved Drug and Labeling Compliance

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Glossary

ACD	automated compounding device
ADME	absorption, distribution, metabolism, excretion
ALP	alkaline phosphatase
API	active pharmaceutical ingredient
ASCN	American Society for Clinical Nutrition
ASPEN	American Society for Parenteral and Enteral Nutrition
AST	aspartate aminotransferase
BLA	biologics license application
CAERS	Center for Food Safety and Applied Nutrition Adverse Event Reporting System
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CMC	chemistry, manufacturing, and controls
DEPI	Division of Epidemiology I
DESI	Drug Efficacy Study Implementation
DGIEP	Division of Gastroenterology and Inborn Errors Products
DHN	Division of Hepatology and Nutrition
DMF	drug master file
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GC-MS	gas chromatography–mass spectrometry
GI	gastrointestinal
ICH	International Conference on Harmonisation
ICP-MS	inductively coupled plasma mass spectrometry
iPSP	initial pediatric study plan
IR	Information Request
IUD	intrauterine contraceptive device
IV	intravenous
HPN	home parenteral nutrition
LC-MS	Liquid chromatography–mass spectrometry
MPPRC	Medical Policy & Program Review Council
MRI	magnetic resonance imaging
MTE	multitrace element
NAG-AMA	Nutrition Advisory Group of the American Medical Association
[redacted]	(b) (4)
NDA	new drug application
PDE	Permitted Daily Exposure
PI	Prescribing Information
PK	pharmacokinetics
PMR	postmarketing requirement
PN	parenteral nutrition
PREA	Pediatric Research Equity Act

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Pre-IND	preinvestigational new drug application
RDA	recommended dietary allowance
RDI	reference dietary intake
SCT	Safety Concern Threshold
TE	trace element
TPN	total parenteral nutrition
USP	U.S. Pharmacopeia
WB	whole blood

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1. Executive Summary

1.1. Product Introduction

Tralement (trace elements injection 4*) is a combination of trace elements (zinc sulfate, cupric sulfate, manganese sulfate and selenious acid) supplied in 1 mL single-dose vials 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. Each mL of Tralement provides zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg. Tralement is administered intravenously after it is diluted and admixed with parenteral nutrition (PN) solution.

The Applicant proposed the following dosages (Prescribing Information, September 4, 2019):

(b) (4)

The Applicant's proposal for the dosage regimen was carefully reviewed by the clinical team and the team from pediatrics and maternal health, (b) (4)

The final agreed-upon dosing regimen recommended daily dosage of Tralement for adult and pediatric patients is as follows:

- Adult and pediatric patients weighing at least 50 kg: 1 mL
- Pediatric patients weighing at least 10 kg to 49 kg (weight-based):
  - 10 to 19 kg: 0.2 mL
  - 20 to 29 kg: 0.4 mL
  - 30 to 39 kg: 0.6 mL
  - 40 to 49 kg: 0.8 mL

For pediatric patients 10 kg to 49 kg, Tralement will not provide the required daily amounts of zinc, copper and/or selenium in some or all weight bands. Therefore, additional amounts of zinc, copper and selenium from single-ingredient trace element products are recommended. The dosage of manganese in Tralement approximates the required daily amount and additional manganese should not be added to the total parenteral nutrition (TPN), as 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). The product package insert provides for the appropriate precautions and mitigations regarding the required daily amounts of zinc, copper, and/or selenium and potential need for administration of single-ingredient

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trace element products. (b) (4)

The Applicant has been manufacturing and distributing marketed unapproved sterile injectable trace element products over several decades, including six different formulations of fixed combination trace element products for adult, pediatric, and neonatal patient populations containing either four trace elements (zinc, copper, manganese, chromium) or five trace elements (zinc, copper, selenium, manganese, chromium). (b) (4)

The Applicant currently markets the approved, single-ingredient products of zinc sulfate injection (New Drug Application [NDA] 209377) and selenious acid injection (NDA 209379) for a similar indication.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Per pre-NDA meetings with the Food and Drug Administration (FDA), the Applicant submitted NDA 209376 under a 505(b)(2) regulatory pathway, relying on published literature for its efficacy and safety without conducting clinical trials for Tralement. (b) (4) The evaluation of this NDA focuses on a systematic literature review of two of the four individual trace elements, copper and manganese, since zinc sulfate (NDA 209377) and selenious acid (NDA 209379) were approved on July 18, 2019 and April 30, 2019, respectively. Both products are manufactured by the Applicant. For additional details, refer to the reviews for both NDAs.

Tralement effectiveness as a source for parenteral nutrition is based on a totality of evidence of various types including published studies (prospective randomized or unrandomized, controlled or uncontrolled), retrospective case reports, review articles, book chapters, parenteral nutrition guidelines regarding appropriate scientific expert consensus, time and extent of use in clinical practice, and generally accepted scientific knowledge of zinc, copper, manganese and selenium as essential trace elements. The review is also in reference to established dietary standards such as recommended dietary allowance (RDA, Institute of Medicine 2001) and reference dietary intake (RDI, 21CFR final rule in 2016). Refer to Section 8 for detail of the literature review on evidence for each trace element.

Tralement is a fixed-combination product evaluated under 21 CFR 300.50. As compared to an alternative of preparation and administration of each of trace element separately from single trace element products, Tralement as a single dose of combination of four trace elements may provide: (1) safe and effective dosage of all four trace elements in a single administration for adult and pediatric patients weighing 10 kg and above; (2) simplified preparation and administration process with less steps and less resource consumed; (3) potential avoidance of medication errors from multiple dosing calculations; and (4) reduction in risk of contamination of infective agents by limiting preparation steps. Each component of Tralement provides for the claimed effects of the drug such that the combination provides for safe and effective dosing for

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patients requiring concurrent administration of these trace elements. However, Tralement as a fixed-combination may not be used in patients who are contraindicated to one of the trace elements or patients who may require different dose (s) of individual trace element (s) due to their developmental need and medical conditions. Furthermore, Tralement use alone in pediatric patients will not be sufficient for full replacement of all elements. The product's prescribing information clearly describes this concern for pediatric patients and provides for mitigation to add single-ingredient trace elements when Tralement is given to pediatric patients.

All four trace elements are essential for body metabolism as cofactors of various enzymes. Specific biological functions of each element are based on accumulated and consolidated knowledge obtained from decades of animal studies and human deficiency syndromes. Retrospective studies, case reports, and case series provided extensive evidence of distinctive deficiency manifestations due to lack of certain trace elements in patients on long-term parenteral nutrition or due to deficiency in oral intake. Such patients usually responded to the supplementation of the deficient trace element.

Controlled or randomized prospective studies provided substantial evidence of the daily requirement of each trace element for parenteral nutrition to maintain the element's homeostasis. Some trace elements were evaluated with balance studies regarding difference between intake (various doses) and output (urine, stool, body excretion). Others were evaluated based on intake and achieved blood levels. Sufficient evidence was available to support the recommended daily dosage for each of the four trace elements. Various retrospective, prospective, controlled or uncontrolled studies provided supportive evidence for appropriate supplementation of trace elements by measuring concentrations of trace elements in blood and by assessing accumulation of trace elements in organs and tissues (biopsy, autopsy or neuroimaging).

We concluded that the Applicant has provided the substantial evidence of effectiveness required by 21 CFR 314.126(a)(b) to support approval of Tralement.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Tralement (trace elements injection 4*) 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. The review team recommends approval of Tralement.

Tralement supplies the trace elements of zinc, copper, manganese, and selenium, which are cofactors of enzymes that play important roles in cellular metabolism, and in biological and physiological functions of the tissues and organs, such as zinc in DNA or RNA polymerases, copper in oxidases, manganese in enzymes of catalytic activity, and selenium in selenoproteins for glutathione-involved electron reductions. Deficiency in any of four trace elements from enteral or parenteral source may cause serious deficiency syndromes in adult, pediatric, and neonatal populations, such as skin lesions and growth retardation from zinc deficiency, anemia from copper deficiency, and cardiomyopathy from selenium deficiency. There is limited literature describing human manganese deficiency. Supplementation of the deficient trace elements often leads to resolution of the deficiency syndromes. For more than 30 years, the Applicant has marketed six different unapproved formulations of fixed combination trace elements for adult, pediatric, and neonatal populations to meet the needs of patients on parenteral nutrition. (b) (4)

Tralement is submitted under the 505(b)(2) regulatory pathway, relying on studies from published literature to support its efficacy and safety. Formulation of adequate daily dosages of each element in fixed combination is essential to meet the daily needs and to avoid excessive supplementation that may cause toxicity. The adequate daily dosage of each trace element is supported by balance studies (determination of input and output of trace element under different doses) and/or by clinical studies evaluating element concentrations in blood, tissue, and organ. The recommended dosages are consistent with published guidelines from the American Society for Parenteral and Enteral Nutrition (ASPEN). The benefit of this fixed combination product as compared to the alternative administration of single trace element products include: (1) a simplified preparation and administration process; (2) a reduced risk of dosage calculation errors; and (3) a reduced risk of contamination with infectious agents, owing to simpler preparation.

Identified risks associated with use of Tralement include: (1) inadequate provision of the recommended dosage of the four trace elements in pediatric populations; some pediatric patients may need additional supplementation of single trace element products such as zinc, copper and selenium; (2) inadequate provision of the four trace elements in certain patient populations or conditions, such as those with excessive gastrointestinal loss or burn lesions; (3) hepatic accumulation of copper and/or manganese in patients with liver diseases; (4) manganese neurotoxicity; despite reduction of the manganese dosage as compared to previous formulations, uncertainty remains about safety of the recommended manganese dosage. The Applicant has committed to conduct a postmarketing randomized, placebo-controlled trial as a

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postmarketing requirement (PMR); (4) risk of hypersensitivity to zinc and copper; (5) lack of flexibility in dosage adjustment due to a fixed-dose combination. Most risks can be mitigated by adhering to the Prescribing Information. Tralement is not recommended for those patients who may require a lower dosage of one or more of the individual trace elements. The risk of neurotoxicity will be further studied under a PMR.

In conclusion, this review establishes the safety and effectiveness of Tralement in adults and pediatric patients weighing 10 kg and above. A systemic literature review identified benefits, potential risks, and adequate daily dosage for Tralement, which are reflected in the Prescribing Information. A required postmarketing prospective randomized, controlled clinical study will address the uncertainty about the risk of neurotoxicity at the recommended manganese dosage.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pediatric and adult patients may depend on parenteral nutrition including trace elements as their only source of nutrition due to various diseases and conditions such as short bowel syndrome. • Deficiency of the trace elements zinc, copper, and selenium leads to specific clinical manifestations; information is limited about the manifestations of manganese deficiency. • Supplementation of deficient trace elements results in resolution of the specific manifestations of deficiency.	• Pediatric and adult patients with insufficient or no enteral intake dependent upon parenteral nutrition require trace element supplementation for their daily nutritional need. • A fix-dose combination of four trace elements may provide the safe and effective doses of the four elements in a single administration.
Current Treatment Options	• The Applicant has manufactured and marketed unapproved fixed-dose combination formulations for neonates, children, and adults for more than three decades, at times in the setting of drug shortage. • Approved single trace element products, i.e. cupric chloride, zinc sulfate, selenious acid, are available on the market	• Approved fixed combination trace element products are not available on the market • Marketed unapproved products have been used as an alternative to approved products during times of drug shortage • FDA has not evaluated unapproved products for adherence to quality standards • Approved single trace element may be used to supplement the Tralement or used in various combination in condition where Tralement is not indicated

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Trace element homeostasis maintains normal biological function. • New drug application (NDA) review and chemistry, manufacturing, and controls (CMC) inspection ensure the safety and efficacy of Tralement via a process that addresses standards of identity, strength, quality, and purity, and that replaces unapproved multitrace products. • Removal of chromium and reduction of manganese in Tralement prevent or mitigate potential toxicity, especially in pediatric patients. • Control of aluminum contaminant in Tralement to (b) (4) (b) (4) mcg/kg/day reduces the risk of toxicity in vulnerable populations (neonates and renal failure patients). • Fixed dose combination of four trace elements in a single dose provides effectiveness, increased safety by lowering the risks of contamination with infective agents and of medical error from multiple dose calculations, and convenience by requiring less preparation steps	• Rationale for approval of Tralement • Benefit may outweigh risks because identified risks may be mitigated via labeling and a PMR
Risk and Risk Management	• Tralement may not provide adequate dose of all 4 elements in some medical conditions such as excessive gastrointestinal loss or in pediatric patients. • Biliary obstruction and cholestatic liver diseases such as cirrhosis may cause brain accumulation of manganese with neurotoxicity, and liver accumulation of copper and manganese with possible consequent liver injury. • Systemic allergic reactions to zinc and copper.	• Use individual trace-element products if Tralement is not indicated or needed to be added • Addition of individual trace elements is clearly described in the prescribing information for pediatric dosing. • No new safety signals are anticipated postmarketing. Routine pharmacovigilance is recommended. • All risks are described in Contraindications; Warnings and Precautions for risk mitigation

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		• Blood concentration and clinical monitoring are emphasized in the label • An adequate, well-controlled clinical trial to study the impact of manganese dose on manganese deposition in the brain and neurological manifestation is agreed upon, and will be planned and conducted under PMR

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☒	**Patient experience data was not submitted as part of this application.**			

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2. Therapeutic Context

2.1. Analysis of Condition

This section provides background about the medical condition that Tralement is indicated for as parenteral nutrition supplement, along with biological functions, deficiency and toxicity manifestations, and laboratory monitoring standards of zinc, copper, manganese, and selenium. The section also summarizes the marketed experience of both fixed dose multitrace element (MTE) products (unapproved) and single trace element products (approved and unapproved).

2.1.1. Established Standard for Oral Intake: Recommended Daily Allowance and Reference Daily Intake

The first U.S. standard daily oral allowance of individual nutrients, named recommended dietary allowances (RDAs), were formulated in 1941 by the Food and Nutrition Board under the auspices of the U.S. National Academy of Science, and thereafter revised every 5 to 10 years. Following the congressional Dietary Supplement Act, the FDA introduced in 1993 the RDI as a new daily nutritional value that included the existing RDA values and new RDI values for nutrients without assigned RDA. In 1997, at the suggestion of the Institute of Medicine of the National Academy, the RDIs and RDAs became part of a broader set of dietary guidelines called the Dietary Reference Intake, with most recent update in 2001. Table 1 shows the RDI for zinc, copper, manganese, and selenium for adult and pediatric population.

Table 1. Reference Daily Intake

Trace Element	Adult & Children ≥4 Years	Infants Birth to 12 Months	Children 1 to 3 Years	Pregnant & Lactating Women
Zinc (mg)	11	3	3	13
Copper (mg)	0.9	0.2	0.3	1.3
Manganese (mg)	2.3	0.6	1.2	2.6
Selenium (mcg)	55	20	20	70

Source: Federal Register/Vol. 81, No. 103, May 27, 2016/Rule and Regulations, Page 33982

Reviewer's comments: *Although the oral intake standards do not directly determine the parental daily dosage, they serve along with measures of bioavailability to estimate parenteral daily needs of a given trace element.*

2.1.2. Parenteral Nutrition and Parenteral Supplementation of Trace Elements

Parenteral nutrition (PN) is intravenous administration of nutrition, which may include protein (amino acids), carbo hydrate (dextrose), fat (lipid emulsion), minerals and electrolytes, vitamins and trace elements (TE), including zinc, copper, manganese and selenium for patients who cannot consume or absorb enough food through oral or tube feedings to maintain an adequate nutrition status. PN may be needed for a variety of diseases or conditions that impair food intake, nutrient digestion or absorption, including premature delivery, short bowel syndrome, gastro-intestinal fistulas, bowel obstruction, critically ill patients, and severe acute pancreatitis.

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PN can be used short-term or long-term in the hospital or home settings and may be used as the exclusive means to deliver nutrition or in combination with some amount of oral/enteral intake. According to the 2014 National Inpatient Survey data, over 290,000 patients received PN during their hospital stay and about 43% of those patients were newborns and children. It is estimated that about 25,000 patients receive PN at home (Mundi et al. 2017).

TEs are essential for fundamental processes such as enzymatic reactions. Some TEs are well established as essential in human physiology while the role and requirement of others have yet to be defined.

In 1979, the Nutrition Advisory Group of the Department of Food and Nutrition and the American Medical Association recommended that 4 TEs, zinc, copper, manganese, and chromium be provided in adult PN formulas, while the addition of selenium was first recommended in 1984 (Shils et al. 1994). The practice of providing several essential trace elements as a single multitrace element preparation in long-term parenteral nutrition patients has been endorsed and recommended by the American Society of Clinical Nutrition since at least 1988 (Greene et al. 1988).

In 2012, the American Society for Parenteral and Enteral Nutrition (ASPEN) published a position paper with recommendations about adult and pediatric parenteral MTE products. As shown in Table 2, ASPEN recommended to eliminate or reduce the dosage of chromium to not more than 1 mcg per day in adult MTE products, to change copper to 0.3 to 0.5 mg/d, manganese to 55 mcg/d, and selenium to 60 to 100 mcg/d, and to maintain zinc at 2.5 to 5.0 mg/d. Regarding pediatric MTE products, ASPEN recommended to modify the manganese dosage to 1 mcg/kg/d for neonates and the selenium to 2 mcg/kg/d from birth through childhood, but to maintain copper at 20 mcg/kg/d and selenium at 1 to 3 mcg/kg/d.

Table 2. ASPEN Recommended Parenteral Dosage for Adult and Children (2012)

Trace Element	Adult	Infants and Children
Zinc	2.5-5 mg/day	Infant <3 mo: 250 mcg/kg/day Infant >3 mo: 50 mcg/kg/day Children: 50 mcg/kg/day (max =5000mcg/day)
Copper	0.3-0.5 mg/day	20 mcg/kg/day (max: 500mcg/day)
Manganese	55 mcg/day	1 mcg/kg/day (max =50 mcg/kg/day)
Selenium	60-100mcg/day	2 mcg/kg/d (max =100mcg/kg/d)

Source: ASPEN Position Paper, August 2012

Reviewer's comments: *The 2012 ASPEN position paper serves as a guideline for parenteral nutrition in medical practice. To determine the optimal daily dosages for adults and pediatric populations during this NDA review, the review team took an evidence-based approach, evaluating whether the data from the clinical studies support the ASPEN recommended dosages.*

2.1.3. Biological Functions of Zinc, Copper, Manganese, and Selenium

Zinc, copper, manganese and selenium are essential trace elements as cofactors (zinc, copper, and manganese) or structural constituents (selenium) of various enzymes, playing important roles in a variety of metabolic and structural functions, as summarized in Table 3.

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Table 3. Summary of Biological Functions of Zinc, Copper, Manganese, and Selenium

Element	Biological Function(s)
Zinc	Cofactor of proteins participating in metabolic, structural and regulatory functions: **Metabolic:** RNA polymerase, alcohol dehydrogenase, carbonic anhydrase, alkaline phosphatase, and copper-zinc superoxide dismutase **Structural:** zinc finger-like proteins (protein folding) **Regulatory:** metallothionein gene expression, protein kinase-C activity, apoptosis, synaptic signaling.
Copper	Cofactor of enzyme **catalytic functions**: **Amine oxidation**: diamine oxidase, monoamine oxidase (MAO), lysyl oxidase. **Iron oxidation**: ferroxidase I (ceruloplasmin), ferroxidase II, **Energy metabolism:** cytochrome *c* oxidase **Neurotransmission**: dopamine-beta monooxygenase **Redox balance**: copper/zinc superoxide dismutase
Manganese	Cofactor of enzyme **catalytic functions**: **Redox balance**: manganese superoxide dismutase **Proteoglycan synthesis**: glycosyltransferase, xylosyltransferase **Amino acid metabolism:** arginase, glutamine synthetase, Pyruvate carboxylase
Selenium	Constituent of selenocysteine in enzymes participating in: **Thiol metabolism:** glutathione peroxidase, thioredoxine reductases **Thyroid hormone synthesis**: iodothyronine deiodinase **Selenium metabolism**: selenophosphate synthase

Reviewer's comments: *The biological functions of zinc, copper, manganese, and selenium justify mechanistically the supplementation of these elements in the parenteral nutrition of patients with limited or absent enteral nutrition.*

2.1.4. Trace Element Deficiency and Toxicity

Table 4 below, summarizes the medical disorders reported in association with oral or parenteral nutritional deficiency of zinc, copper, manganese, or selenium.

Table 4. Summary of Trace Element Deficiency

Trace Element	Clinical Manifestations of Deficiency (Enteral or Parenteral Source)
Zinc (Livingstone 2015)	• Severe deficiency: growth failure, depressed muscle work capacity, bullous-pustular dermatitis, depressed immune function, frequent infections, neuropsychiatric disorders, impaired cognitive development. • Mild deficiency: anorexia, dysgeusia, dysosmia, diarrhea, eye and skin lesions, alopecia, growth delay, delayed sexual maturation and impotence • PN-dependent patients: acrodermatitis enteropathica-like syndrome.
Copper (Livingstone 2017)	• Anemia (hypochromic microcytic), neutropenia, and pancytopenia • B12 deficiency-like myelopathy and peripheral neuropathy, depressed cognitive function • Proteinuria, nephrotic syndrome • Osteoporosis, long-bone fractures, epiphyseal separation, growth delay • Pseudoscurvy • Immune dysfunction, Increased infection rate
Manganese (Livingstone 2018)	• Miliaria crystalline dermatitis • Hypocholesterolemia • Weight loss, decreased hair and nail growth • Decreased cognitive function, growth retardation, lowered seizure threshold. • Non-dietary manganese deficiency: short stature, intellectual impairment, developmental delay, hypotonia, ataxia, seizure.

Trace Element	Clinical Manifestations of Deficiency (Enteral or Parenteral Source)
Selenium (Institue of Medicine (US) Panel on Micronutrients 2000b)	• Keshan disease (pediatric population cardiomyopathy) • Kashin-Beck disease (preadolescence or adolescence, endemic osteoarthritis) • Skeletal myopathy, muscle weakness • Macrocytosis • Skin and nail changes (whitened nailbeds, loss of pigmentation of hair and skin) • In infants, alopecia and growth retardation

Reviewer's comments: *Case reports and small studies on trace element deficiency provide extensive evidence for zinc, copper and selenium and marginal evidence for manganese to further justify the parenteral supplementation of these trace elements in clinical practice.*

Table 5 below summarizes the clinical manifestations reported in association with zinc, copper, manganese, or selenium toxicity.

Table 5. Summary of Trace Element Toxicity

Trace Element	Clinical Manifestations of Toxicity (All Sources)
Zinc (Livingstone 2015)	Low toxicity (undefined upper limit of parenteral dosage). • Possible acute nausea, vomiting, abdominal pain and diarrhea with 300 mg/day oral dosage (20-fold U.S. RDA) • Interference of long-term oral or parenteral intake with copper and iron absorption, leading to anemia, neutropenia, impaired immunity, decreased HDL cholesterol.
Copper (Livingstone 2017)	Rare acute oral toxicity with: • Nausea, vomiting, diarrhea, gastrointestinal bleeding, acute liver injury and necrosis, acute kidney injury, rhabdomyolysis, encephalopathy, death • Hemolytic anemia In long-term PN, possible accumulation in liver and kidney
Manganese (Livingstone 2018)	• Accumulation in brain basal ganglia following parenteral/oral/inhalatory exposure, with or without high blood concentrations and/or neuropsychiatric manifestations • Neuropsychiatric manifestations: - Parkinson-like syndrome, with muscular hypertonia, ataxia, abnormal gait, weakness, dysphonia, tremors. - Visual disturbances, loss of appetite, headache, anxiety, memory loss, dysthymia, aggressive behavior, seizure. • Risk factors of neuropsychiatric toxicity: - Liver disease with cholestasis, - Pediatric age, - Genetic variation (deletion of the exon 4 of the PRKN gene, mutation of the SLC30A10 manganese transporter gene) - Concomitant critical illness
Selenium (Vinceti et al. 2014; Rae et al. 2018)	Oral toxicity only: • Alopecia, hair and nails brittleness, skin rash • Nausea, vomiting, halitosis (garlic breath) • Dizziness, paresthesia, ataxia • Visual problems, memory loss, convulsions, hyperreflexia, increased latency in visual evoked potentials

Reviewer's comments: *The clinical manifestations of toxicity of each trace element occurred mainly with oral and less often with parenteral overdose up to 1000-folds above the recommended dosage. These symptoms are described in section 10 (Overdosage) of the Prescribing Information, for the purpose of mitigating the risk of potential medical errors.*

2.1.5. Laboratory Monitoring

Table 6 below summarizes current laboratory monitoring standards for zinc, copper, manganese, or selenium.

Table 6. Laboratory Monitoring of Zinc, Copper, Manganese and Selenium

Trace Element	Laboratory Monitoring	Analytical Limitations
Zinc	• Serum and plasma concentrations are the most commonly reported measures of balance (Iyengar and Woittiez 1988). • Reference range: - Lower limit: 55 to 66 mcg/dL - Upper limit: 110 to 150 mcg/dL (Btaiche et al. 2011).	Low zinc concentrations correlate inconsistently with clinical manifestations of deficiency. Combined analysis of blood zinc concentrations and clinical response to treatment are a superior measure of treatment efficacy.
Copper	• Serum concentrations are the most common and reliable marker of balance. • Serum concentration of ceruloplasmin (transports ~95% of serum copper) is also used as a marker of balance.	Affected by liver disease, malignancy, inflammation, infections, pregnancy, an oral contraceptive.
Manganese	• Whole blood, serum, plasma, or red blood cell concentrations are the most commonly reported measures of balance (Ntihabose et al. 2018). • Reference range: - Whole blood: ~4 to 16 mcg/L - Serum or plasma: ~0.4 to 2.4 mcg/L - Red blood cells: ~11 to 23 mcg/L • T1-weighted magnetic resonance imaging (MRI) of the brain is the most accurate and clinically informative test of cerebral deposition in both asymptomatic and symptomatic patients (Uchino et al. 2007; Jin et al. 2018).	**Blood concentrations.** In 7 of 10 original studies blood concentrations were an unreliable predictor of cerebral deposits at the individual patient level (Bertinet et al. 2000). In the remaining 3 studies, only subjects with high blood concentrations were tested for cerebral deposits, biasing results and interpretation (Fell et al. 1996; Orimo and Ozawa 2001; Dastych et al. 2016a) (see Table 34 and Table 37). In conclusion, individual patients' blood manganese concentrations are an unreliable marker of solid tissue content or long-term intake (Jiang et al. 2007). **Brain MRI:** Less accessible than blood analysis and currently not recommended as a routine test.
Selenium	• Serum and plasma concentrations are the most commonly reported measures of balance (Institue of Medicine (US) Panel on Micronutrients 2000a). • Reference range in serum and plasma: - Lower limit: 4.6 - 10 mcg/dL - Upper limit: 10 - 16.5 mcg/dL • Reference range in whole blood (reflect intake over 3 months to 4 months): - 14.7 to 24.7 mcg/Dl (Jain and Choi 2015)	Concentrations may be affected by geographical location and age, and may decline in acute inflammatory states (lowered).

Reviewer's comments: *In patients on long-term PN, it is standard practice to monitor periodically the blood trace element concentrations and basic laboratory parameters such as complete blood count, electrolyte concentration, liver and renal function, for risk mitigation in the context of several medical conditions, including cholestasis, change of developmental need, liver or kidney failure, and burns. These conditions may require adjustment of trace element*

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dosage and monitoring of concentrations. Since blood trace element concentrations and clinical manifestations not always correlate and the reference levels can vary among laboratories, it is established practice to assess the blood trace element concentrations in combination with other laboratory parameters and with clinical manifestations. The Prescribing Information, 2. Dosage and Administration, provides the reference range of the four trace elements for risks mitigation.

2.1.6. Genetic Mutations in Copper Metabolism

Genetic mutations in copper exporter proteins cause unbalanced copper homeostasis and related clinical disorders. Mutation of ATP7B causes *Wilson disease*, a rare autosomal recessive disease, whereby hepatic copper cannot bind to ceruloplasmin to be released into serum and is therefore trapped in the liver and/or deposited into other tissues including neuronal tissue and cornea (Kayser-Fleisher rings), leading to cirrhosis and neurological damage. Copper chelation using D-penicillamine or administration of high dose zinc, to compete for copper intestinal absorption of, are the standard treatment.

Reviewer's comments: *Patients with Wilson disease on long-term PN should receive special care to minimize copper overload from parenteral sources. This risk is communicated in the Prescribing Information under Warnings and Precautions.*

In conclusion, all four trace elements are essential for body metabolism as cofactor of various enzymes as summarized in Table 3. Specific biological functions of each element are based on accumulated and consolidated knowledge obtained from decades of animal studies and human deficiency syndromes. Retrospective studies, case reports, and case series provided extensive evidence of distinctive deficiency syndrome due to lack of certain trace elements in patients on long-term parenteral nutrition or due to deficiency in oral intake, as summarized in Table 4. Such patients usually responded to the supplementation of the deficient trace element. Therefore, Tralement may provide the source of essential trace elements in a single administration to meet the developmental need of pediatric patients and need to maintain homeostasis in all patients dependent on PN under certain medical conditions.

2.2. Analysis of Current Treatment Options

2.2.1. Multi-Trace Element Products

Marketed unapproved MTE products have been the source of parenteral trace elements for most parenteral nutrition patients for more than three decades, since no parenteral fixed-combination MTE product has been approved in the United States. As shown in Table 7, Trace Elements Injection 4 products provide zinc sulfate heptahydrate, cupric sulfate, manganese sulfate, and selenious acid, which are available in standard, concentrated, pediatric and neonatal formulations. Trace Elements Injection 5 products provide the combination of the above elements plus chromic chloride, which are available in standard and concentrated formulations.

Reviewer's comments: (b) (4) *while removing chromium and reducing manganese to*

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minimize toxicity. The safety and efficacy of the proposed Tralement will be determined by supportive evidence identified from a systemic literature review.

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Table 7. Unapproved MTE-4 and MTE-5 Products Marketed by American Regents in the U.S.

	Trace Elements Injection 4					Trace Elements Injection 5	
	0517-7410-25	0517-7201-25 0517-7210-25	0517-9310-25	0517-9203-25	0517-6202-25	0517-8510-25	0517-8201-25 0517-8210-25
Element	**Adult**	**Adult** *	**Pediatric**	**Pediatric**	**Neonatal**	**Adult**	**Adult** *
Zinc	1 mg	5 mg	0.5 mg	1 mg	1.5 mg	1 mg	5 mg
Copper	0.4 mg	1 mg	0.1 mg	0.1 mg	0.1 mg	0.4 mg	1 mg
Manganese	0.1 mg	0.5 mg	30 mcg	25 mcg	25 mcg	0.1 mg	0.5 mg
Chromium	4 mcg	10 mcg	1 mcg	1 mcg	0.85 mcg	4 mcg	10 mcg
Selenium	--	--	--	--	--	20 mcg	60 mcg

Source: CMC reviewer Jane Chang
Column labels display NDC code pf products and their indications.
Symbols: (*) concentrated formulation
Abbreviation: MTE, multitrace element; NDC, national drug code

2.2.2. Single Trace Element Products

Approved and unapproved parenteral single TE zinc, copper, manganese, and selenium products currently marketed in the United States are listed in Table 8.

Reviewer's comments: *Single trace element zinc, copper, and selenium products are approved in the United States, while manganese is currently marketed as an unapproved product. Of these, the Division approved zinc sulfate and selenious acid last year. Some of the products were withdrawn. Approved single trace element products currently available on the market are listed in Table 8. These products can supplement Tralement if the latter is not sufficient for specific trace elements due to developmental need or certain disease conditions.*

Table 8. Approved and Unapproved Single Trace Element Products Marketed in the United States

Trace Element	Product	Manufacturer	NDC	NDA	Approval Date	Status
Zinc	Zinc sulfate	American Reagent, Inc.	0517-6103-01	209377	7/18/2019	Active
	Zinc chloride	Hospira, Inc.		018959	6/26/1986	Active
Copper	Cupric chloride	Hospira Inc.	0409-4092-01	18960	6/26/1986	Active
Manganese	Manganese sulfate	American Reagent, Inc.	0517-6410-25	Not approved		Active
Selenium	Selenious acid	American Reagent, Inc.	0517-6510-25	209379	4/30/2019	Active

Source: Drugs@FDA; DailyMed (NIH)
Extracted from:
1. Institute of Medicine (US) Panel on Micronutrients (2000). Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington (DC), National Academies Press (US).
2. Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds (2000) Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. DOI: 10.17226/9810.
Abbreviations: NDA, new drug application; NDC, national drug code

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This section summarizes approved or unapproved (due to shortage) marketing history of single trace element products or as a component of multitrace products.

3.1.1. Zinc

- Zinc Chloride Injection (NDA 018959, Hospira, Inc.) was approved as a single agent on June 26, 1986, and remains active on the market.
- Zinc Sulfate Injection (NDA 019229, Abraxis Pharm) was approved as a single agent on May 5, 1987 and withdrawn by the application holder on June 15, 2017.
- Zinc Sulfate, as a component of multitrace products such as TE-4 or TE-5 has been marketed unapproved by the Applicant (due to shortage) in adult, pediatric, and neonatal dosages

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- Zinc Sulfate Injection (NDA 209377, American Regent, Inc.) was approved as single agent on July 18, 2019

3.1.2. Copper

- Cupric chloride as a single agent was approved on June 26, 1985, (NDA 018960, Hospira) and remains active on the market.
- Cupric sulfate was approved (NDA 19350, Abraxis) on May 5, 1987, but withdrawn from the market effective on July 21, 2017.
- Copper, as a component of multitrace products such as TE-4 or TE-5 has been marketed unapproved by the Applicant (due to shortage) in adult, pediatric, and neonatal dosages.

3.1.3. Manganese

- Manganese Chloride Injection (NDA 018962, Hospira, Inc.) was approved on June 26, 1986
- Manganese Sulfate Injection (NDA 019228, Abraxis) was approved on May 5, 1987 and discontinued.
- Manganese Sulfate Injection (American Regent, Inc), is marketed unapproved.
- Manganese, as a component of multitrace products such as TE-4 or TE-5 has been marketed unapproved by the Applicant (due to shortage) in adult, pediatric, and neonatal dosages

3.1.4. Selenium

- Selenium, as a component of multitrace products such as TE-5 has been marketed unapproved by the Applicant (due to shortage) in adult dosages.
- Selenious Acid Injection (NDA 209379, American Regent, Inc) was approved as a new chemical entity on April 30, 2019

3.2. Summary of Presubmission/Submission Regulatory Activity

Since 2009, ASPEN has communicated with the Division of Gastroenterology and Inborn Errors Products (DGIEP) on multiple occasions to express concern about the lack of approval of certain parenteral nutrition products, the shortage of certain drug products, and the marketing of unapproved products. ASPEN has urged the Agency to approve safe and effective injectable TE products that comply with the current standards of clinical practice, fulfill the Agency's quality standards, and meet the supply and demand of the market.

DGIEP communicated with the Applicant, American Regent, Inc., for a marketing application under Preinvestigational New Drug Application (Pre-IND) 123432 and Pre-NDA 209376 for the MTE Injection product, as summarized below:

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Pre-NDA Submission History

- Pre-IND Meeting – November 12, 2014 (Pre-IND 123432)
  - The Division acknowledged the Applicant's plan to file a marketing application under the 505(b)(2) pathway relying on published literature to support the safety and efficacy each trace element component and dose in adult and pediatric populations.
- Type C Meeting – September 1, 2015 (Pre-IND 123432)
  - The Division advised the Applicant to submit the published literature in a framework organized according to route of administration and individual trace element.
  - Submit any position papers regarding parenteral dosing
  - The Division acknowledged that the Applicant may request a Pre-NDA meeting prior to submission of the marketing application which should include the proposed framework for the organization of the literature and the table of contents.
- Pre-NDA Meeting – August 3, 2016 (Pre-NDA 209376)
  - The Division agreed in principle with the Applicant's proposal to use the totality of evidence by integrating efficacy information from multiple sources to support the indication for each trace element. The Applicant agreed to provide, where available, primary source publications for any data used to support dosing recommendations, including bioavailability data, described in book chapters or review articles.
  - Submit an initial pediatric study plan (iPSP) prior to NDA submission
  - Chromium should not be included in the product
  - Integrated analyses of efficacy and safety were requested for each of the trace element but not required for the combined elements
  - Address the requirement of fixed combination product per 21 CFR 300.50; but a factorial design study was not required
  - A proposed framework for organizing the summarized literature identified in the Systemic Review (Section 14.2) was sent to the Applicant in a post-meeting communication.
- Fast Tract Designation was granted for multitrace element as additives to parenteral nutrition on April 17, 2017. Request for rolling submission of NDA was accepted.
- Medical Policy & Program Review Council (MPPRC) meeting was held on February 27, 2019 (see Section 9.1)
  - Division sought MPPRC's recommendation on the planned review for 505(b)(2) applications regarding selenious acid (NDA 209379), zinc sulfate (NDA 209377), and multitrace elements (zinc sulfate, copper sulfate, manganese sulfate, and selenious acid, NDA 209376)
  - Council agreed with Division's approach of approving the indication as "source" for PN in adult and pediatric patients based on collective evidence of clinical PN data, known enteral nutrition requirement (RDA, RDI), bioavailability, clinical PN guidelines, and toxicity data

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  - Council recommended considering PMR study to obtain additional data to support dosing in population if there is uncertainty

NDA 209376 Submission History

- Clinical and nonclinical data were submitted on October 12, 2018
- CMC data was submitted on September 15, 2019 (review clock starting)
- Major Information Request (IR) and IR response during 10-month standard review
  - October 15, 2019: Division of Pediatric and Maternal Health IR regarding labeling for PLLR (pregnancy, lactation, and reproductivity)
  - October 24, 2019: filing letter: no filing issues and the standard review with PDUFA due date on July 5, 2020
  - November 4, 2019 (74-Day letter): additional literature review for efficacy and safety of four elements from 2015 to 2019 with full-text of publications; rationale with references for proposed adult and pediatric dosing; addressing fixed combination rule per 21 CFR 300.50
  - December 12, 2019: pharmtox IR regarding elemental impurities of (b) (4) (b) (4)
  - January 6, 2020: additional information regarding benefit/risk and risk mitigation of fix combination therapy for Tralement
  - February 14, 2020: update of new information regarding drug-drug interaction; information about copper hypersensitivity and toxicity from other source such as copper-containing intrauterine contraceptive device (IUD); laboratory references ranges of four trace elements from top five frequently used laboratories in the United States for adults and pediatric patients.
  - March 13, 2020 information regarding copper pharmacokinetics (PK) and copper interaction with ascorbic acid in PN
  - April 20, 2020, and May 14, 2020: labeling change for pediatric dosing.
  - May 24, 2020, and June 4, 2020: agreement, milestones, and protocol synopsis for prospective, controlled manganese safety study under postmarketing requirement (PMR)
- PDUFA goal date: July 5, 2020

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4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

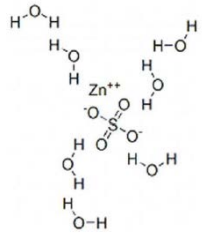
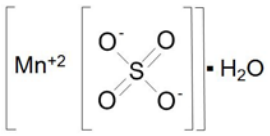
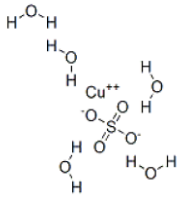
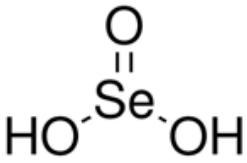
4.1. Office of Scientific Investigations

An Office of Scientific Investigations audit was not requested or performed given that the Applicant did not conduct any clinical trials.

4.2. Product Quality

The active ingredients in Tralement (trace elements injection 4*) are Zinc sulfate, U.S. Pharmacopeia (USP); Cupric sulfate, USP; Manganese sulfate, USP and Selenious acid, USP.

Table 9. Active Ingredients in Tralement

Drug Substance	Structure	Manufacturer	Physico/Chemical Properties
Zinc sulfate, USP $ZnSO_4 . 7H_2O$ MW: 287.54 g/mol		(b) (4)	• Colorless, odorless, granules or crystals • Soluble in water, insoluble in alcohol, efflorescent in dry air • log P = -0.84 • Two polymorphs reported in literature
Manganese sulfate, USP MnSO4. H2O MW: (b) (4) g/mol			• Pale pink odorless crystalline powder • Soluble in water, insoluble in alcohol • Slightly efflorescent • pKa = -3
Cupric sulfate, USP $CuSO_4 . 5H_2O$ MW: 249.69 g/mol			• Deep blue triclinic crystals or blue granules or powder • Solubility varies with pH. Insoluble hydroxides form above pH 7.0 • Hygroscopic at high humidity • pKa = -3
Selenious Acid, USP H_2SeO_3 MW: 128.97 g/mol			• Colorless, white crystals • Soluble in water and alcohol • Hygroscopic • pKa_1=2.62 • pKa_2=8.32

Abbreviations: MW, molecular weight

All four drug substances used in the drug product formulation are of USP grade. The identity, strength, purity and quality of the drug substances are controlled by their specification. The particle size and polymorphs of the drug substances are not important because the drug product is an injection. The CMC information regarding the drug substance manufacturing process, specification and stability was reviewed, and it was deemed adequate to support the drug product, Tralement.

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Tralement is a sterile, non-pyrogenic, clear and colorless to slightly blue solution for intravenous use to deliver zinc, copper, manganese and selenium. It is supplied as 1 mL vials. Each mL of solution 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. There are no preservatives or (b) (4) in the drug product formulation.

The drug product is manufactured by American Regent, Inc.; NY by a typical injection manufacturing process. The drug product manufacturing process, in-process controls, drug product release tests and executed batch records were reviewed and deemed satisfactory.

The identity, strength, purity and quality is deemed adequate based on raw material controls and drug product specification including description, identity and assay of zinc, copper, manganese and selenium; elemental impurities (b) (4) Aluminum content, volume in vial, bacterial endotoxin, particulate matter and sterility.

As demonstrated by the compatibility studies when used as recommended in the Package Insert the drug product appeared to be compatible with common TPNs containing lipids and amino acids such as Kabiven and Clinimix E solutions.

The Applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Tralement (trace elements injection 4*). * Each mL provides: zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg.

The Office of Pharmaceutical Manufacturing Assessment has made a final overall “Approval” recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling is acceptable from the CMC perspective.

The Office of Pharmaceutical Quality Review team has assessed NDA 209376 with respect to CMC and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such the Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective.

4.3. Clinical Microbiology

The environmental monitoring at (b) (4) manufacturing process buildings/facilities, component/ equipment sterilization, depyrogenation of vials and stoppers, container closure integrity, drug product (b) (4) , as well as microbiology related attributes of the drug product specification including bacterial endotoxins and sterility etc. were reviewed and deemed adequate. Based on the satisfactory sterility assurance this NDA was recommended for approval from the microbiology perspective.

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5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No nonclinical studies were conducted to support the approval of Tralement, which is a combination of zinc (as zinc sulfate), copper (as cupric sulfate), manganese (as manganese sulfate), and selenium (as selenious acid) for use in parenteral nutrition. Clinical experience exists for the use of zinc sulfate (currently approved), cupric sulfate (previously approved and then withdrawn), manganese sulfate (previously approved and then withdrawn), and selenious acid (currently approved) in parenteral nutrition. Tralement is intended for administration via admixing in parenteral nutrition solutions. The Applicant provided summaries of published nonclinical and clinical studies with each of the four trace elements.

The proposed adult dose for each element does not exceed the dose in adult parenteral nutrition products approved by the Agency. (b) (4) The Applicant agreed to revise the pediatric dosing to address the Agency's concerns, and this revision assures that the pediatric dose for each of the four trace elements does not exceed the pediatric dose in parenteral nutrition products approved by the Agency (amendment dated May 15, 2020).

The dose levels of zinc, copper, manganese, and selenium delivered by Tralement are expected to restore and/or maintain the normal body levels of these trace elements, thereby promoting and maintaining an adequate nutritional status for patients receiving parenteral nutrition. Aside from this function, no other pharmacological activity is expected from these trace elements at the recommended dose levels. Based on these considerations, the safety assessment of Tralement is best informed by the clinical experience with the use of zinc, copper, manganese, and selenium as additives in parenteral nutrition.

Safety testing of the four trace elements in animals (e.g. general toxicology, developmental studies) is not expected to provide clinically relevant information for the intended use of Tralement, because the adverse effects in animal studies are usually attributed to accumulation of abnormally high body levels of the administered element(s), such that the body's capacity to safely store the element(s) is exceeded. The published nonclinical studies tested zinc, copper, manganese, and selenium at extremely high multiples of the proposed doses in Tralement, and the exposure to the administered elements was supplemental to normal dietary intake. Therefore, data from safety testing in animals does not add value to the overall safety assessment of Tralement.

From a nonclinical perspective, the safety assessment of Tralement is focused on the drug product quality attributes (i.e. elemental impurity limits), the supporting batch analysis data for

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elemental impurities, and the leachables evaluation (see Section 14.10). Although we identified safety concerns related to the potential levels of [redacted] (b) (4), the Applicant's proposal to address these issues post-approval by submission of additional batch data in the first annual report is acceptable. We also identified a safety concern for the [redacted] (b) (4) in the drug product, however the Applicant resolved this issue by agreeing to the Agency's request [redacted] (b) (4). Therefore, we recommend approval of Tralement.

5.2. Referenced NDAs, BLAs, DMFs

NDA 209379, Selenious Acid and NDA 209377, Zinc Sulfate

5.3. Pharmacology

The functions of zinc, copper, manganese, and selenium in nutrition are described in the label (12.1 Mechanism of Action).

5.4. ADME/PK

Not applicable (see Section 5.1).

5.5. Toxicology

5.5.1. General Toxicology

Not applicable (see Section 5.1).

5.5.2. Genetic Toxicology

Not applicable (see Section 5.1).

5.5.3. Carcinogenicity

Not applicable (see Section 5.1).

5.5.4. Reproductive and Developmental Toxicology

Not applicable (see Section 5.1).

5.5.5. Other Toxicology Studies

Not applicable (see Section 5.1).

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6. Clinical Pharmacology

6.1. Executive Summary of Clinical Pharmacology

Tralement is a fixed-dose combination product to provide a source of zinc, copper, manganese, and selenium for PN when oral or enteral nutrition is not possible, insufficient, or contraindicated. Zinc (NDA 209377 Zinc Sulfate Injection) and selenium (NDA 209379 Selenious Acid for Injection) have been approved as individual products. The proposed dose of Tralement in adults provides the same amounts of zinc and selenium as those individual products. Thus, the review of clinical pharmacology focused on copper and manganese only. Given that the proposed product is a solution to be added to PN for intravenous use, in vivo bioavailability of copper and manganese provided as cupric sulfate and manganese sulfate, respectively, is self-evident. The Applicant did not conduct any clinical studies using the proposed product, thus, no clinical PK and pharmacodynamics data for the proposed product were available. The Clinical Pharmacology information on copper and manganese in this section of the review was sourced from nonproduct-specific literature data related to these two components.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The bioavailability of copper and manganese as components of Tralement injectable solution for intravenous use is self-evident.

Copper

In plasma, about 7% of copper is bound to albumin and amino acids (Neuman and Sass-Korstak 1963; Shike 1984). In the liver, about 93% of copper is bound to ceruloplasmin (Cartwright and Wintrobe 1964; Shike 1984). The copper-ceruloplasmin complex is then released to serum where copper binds to serum proteins and delivered to cells of the body. Data generated from animal studies indicate that nearly 80% of the copper is excreted in bile (Winge and Mehra 1990), through the intestinal wall (16%) and in urine (4%) (Baumgartner 1997). Minimal amount of copper is reabsorbed after excretion into the intestines (Winge and Mehra 1990; Baumgartner 1997).

The amount of copper (0.09±0.005 mg) (Shike et al. 1981) excreted into urine following PN therapy containing copper 0.25 mg/day which was close to 0.3 mg/day proposed for Tralement, is higher than that in healthy subjects (0.01 to 0.06 mg) on a regular diet (Cartwright and Wintrobe 1964). The difference is probably due to first-pass hepatic binding of most of the intestinally absorbed copper to ceruloplasmin, while copper administered intravenously is eliminated through the kidney before it reaches the liver (Shike et al. 1981).

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Manganese

Manganese is widely distributed in tissues including the liver and basal ganglia in the brain (Livingstone 2018). Whole-body retention study after oral administration of manganese in healthy subjects showed that manganese was found in the liver region with small amounts in the intestinal tract (Davidsson et al. 1989).

The concentration of manganese was found to be higher in erythrocytes (60% to 80%) than in plasma (Cotzias et al. 1966; Milne et al. 1990; Bertinet et al. 2000). In human plasma, manganese is bound to albumin (Foradori et al. 1967) and β_1-globulin (Papavasiliou et al. 1966).

Studies conducted in rats showed that manganese was mainly excreted in bile (Bertinchamps et al. 1966; Papavasiliou et al. 1966). Manganese was detected in hepatic bile from three Japanese patients who suffered from cholelithiasis or cholecystolithiasis and had undergone surgery which allowed a T-tube for hepatic bile drainage to be installed (Ishihara and Matsushiro 1986). This suggested the biliary excretion of manganese in humans.

Patients with cholestasis can have high erythrocyte concentrations of manganese (Fitzgerald et al. 1999), although elevated levels have also been observed in patients with normal liver function (Jin et al. 2017). Case reports (Hauser et al. 1994) suggested that a risk for manganese toxicity was the highest in patients with biopsy-proven hepatic cirrhosis (N=3) where biliary excretion could be low even though none of these patients was given PN therapy. The source of manganese was presumably from their diet.

Manganese was measurable in human urine from those who had normal diet (Fitzgerald et al. 1999) while study conducted in rats, rabbits, and dogs showed that renal excretion of manganese was negligible (Klaassen 1974).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

For adults and pediatric patients with body weight ≥50 kg, there is only one dose level (1 mL) to be added to PN. Tralement is a fixed-combination product recommended only for patients who require supplementation with all four of the individual trace elements (i.e., zinc, copper, manganese and selenium).

Table 10. Amount of Trace Element Provided by Corresponding Tralement Volume for Adults and Pediatric Patients Weighing ≥50 kg

		Amount of Trace Element			
Body Weight	**Dosage of Tralement**	**Zinc**	**Copper**	**Manganese**	**Selenium**
≥50 kg	1 mL	3000 mcg	300 mcg	55 mcg	60 mcg

The doses for zinc and selenium are the same as those single ingredient products. On the other hand, the doses for copper and manganese are recommended based on the following information.

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Copper

The proposed adult dose for copper is 0.3 mg/day to be added to PN. The identified pivotal study in the literature (Weissfeld 2019) supporting this dosing regimen was a copper balance study conducted by Shike and his colleagues (Shike et al. 1981) where they found that copper requirement was 0.3 mg/day to achieve the balance for patients with normal amounts of gastrointestinal excretion on the PN therapy. The copper balance was determined by the amount of copper provided in the PN and the amount of copper found in stool, gastrointestinal drainage if applicable, urine, and hair.

The review team considered using relative bioavailability of copper in diet to estimate the dose of copper for parenteral supplement. However, the oral absorption of copper appears to be affected by the amount of copper in the diet and other factors (Bertinet et al. 2000; Collins 2014). In addition, the percentage of copper absorbed decreased to slightly lower than 60% to less than 20% when the dietary copper intake was increased from 0.785 and 7.53 mg/day possibly due to the saturation of the oral absorption (Turnlund et al. 1989; Turnlund 1998). Therefore, it is unreliable to use oral bioavailability to estimate the amount of copper to be supplemented via intravenous route.

Manganese

The proposed adult dose for manganese to be added to PN is 55 mcg/day. This dose is derived from empirical experience in the use of manganese and the identified pivotal study in the literature (Weissfeld 2020) discussed below. No manganese balance study was found in the published literature. The pivotal study supporting this dosing regimen was conducted by Takagi and his colleagues (Takagi et al. 2002) where adult Japanese patients (N=12) received sequential daily doses of manganese via PN therapy: 1100 mcg (20 mcmol, 9.4 months, n=12) → 0 mcg (0 mcmol, 14.6 months, n=9) → 110 mcg (2 mcmol, 15 months, n=12) → 55 mcg (1 mcmol, 17 months, n=12). Note that three out of 12 patients did not receive 0 mcg dose during the dose change. The duration of each dose for each subject varied, thus average duration is presented here. Also note that for the 0 mcg group, patients did receive 3 to 6 mcg (0.05 to 0.11 mcmol)/day manganese due to its presence as a contaminant in PN solution. Patients' whole-blood concentrations of manganese were within the normal range when they received either 55 mcg/day or 0 mcg/day dose. On the other hand, the whole-blood concentrations of manganese exceeded normal levels in 91% of the patients receiving 1100 mcg/day of manganese while 17% of patients receiving 110 mcg/day of manganese had a whole-blood concentrations of manganese exceeded normal range. No manganese brain deposits (0 out of 11 patients) were found when patients received no additional manganese (0 mcg/day) while the whole-blood manganese levels were normal in these patients. This study also suggested that fewer number of patients had manganese brain deposits after 55 mcg dose (2 out of 10) compared to those received 110 mcg dose (6 out of 11). The caveat is that this was a sequential design where patients received 110 mcg/day for an average of 15 months followed by 55 mcg/day. Even though evidence showed that it took at least 5 months for the high-intensity T1-weighted images to disappear when patients were withdrawn from manganese administration via PN (Takagi et al. 2001), a potential deposit of manganese after 55 mcg dosing

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may not be completed ruled out. Also refer to Section 8.5 for additional review comments regarding Takagi's study published in 2002.

The potential of manganese brain deposit after administration of 55 mcg/day of manganese provided by Tralement will be further studied in a prospective randomized trial as a PMR (Section 12). It is noteworthy that accumulation of manganese resulting in brain deposits is also reported in other published article such as Bertinet et al. (Bertinet et al. 2000) where 10 out of 15 patients receiving manganese (median dose 100 mcg/day for an average 3.8 years, n=15) showed paramagnetic accumulation on cerebral magnetic resonance imagining (MRI).

Therapeutic Individualization

Tralement is not recommended for those patients who may require a lower dosage of one or more of the individual trace elements.

If an individual component in Tralement needs to be adjusted, the prescriber needs to use the individual product for each element.

Pediatric Patients Weighing 10 kg to 49 kg

The daily recommended dosage for each trace element for pediatric patients 10 kg to 49 kg is as follows:

- Zinc: 50 mcg/kg/day (maximum daily dose is 3000 mcg/day)
- Copper: 20 mcg/kg/day; for those weighing ≥15 kg, 300 mcg/day
- Manganese: 1 mcg/kg/day (maximum daily dose is 55 mcg/day)
- Selenium: 2 mcg/kg/day; for those weighing ≥30 kg, 60 mcg/day

Weight-based dosing of Tralement is recommended for pediatric patients weighing less than 50 kg (Table 11). Refer to Section 10 for details.

Table 11. Weight-Based Daily Dosage (mL) of Tralement and Corresponding Amount of Each Trace Element

		Amount of Trace Element Provided by the Corresponding Tralement Volume			
Body Weight	**Dosage of Tralement**	**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

Since Tralement does not provide the recommended daily amount of zinc (in heavier patients in some weight bands), copper, and selenium in pediatric patients receiving a lower volume of Tralement, additional supplementation using single ingredient products is recommended.

The daily recommended manganese for pediatric patients is 1 mcg/kg/day (up to 55 mcg/day). Tralement 0.2 mL to 0.8 mL will provide 0.9 mcg/kg/day to 1.1 mcg/kg/day for pediatric patients ≤49 kg. Although some patients may be slightly underdosed depending on their body weight, no additional supplementation is recommended due to the concerns of accumulation

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of manganese in the brain with long-term administration with higher than the recommended dosage.

Additional Supplementation for Zinc, Copper, and Selenium for Pediatric Patients 10 kg to 49 kg

To determine the additional amount of supplementation for zinc, copper, and selenium 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 11). Table 12 through Table 15 show the additional amount of zinc, copper, and selenium needed for each body weight.

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Table 12. The Additional Daily Amount of Zinc, Copper, and Selenium Needed to Meet the Recommended Daily Amount for 10 kg to 19 kg

		Body Weight (kg)									
Element	**Amount**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Zinc	Total daily need (mcg)*	500	550	600	650	700	750	800	850	900	950
	Zn from Tralement (mcg)	600	600	600	600	600	600	600	600	600	600
	Additional Zn needed (mcg)	0	0	0	50	100	150	200	250	300	350
Copper	Total daily need (mcg)*	200	220	240	260	280	300	300	300	300	300
	Cu from Tralement (mcg)	60	60	60	60	60	60	60	60	60	60
	Additional Cu needed	140	160	180	200	220	240	240	240	240	240
Selenium	Total daily need (mcg)*	20	22	24	26	28	30	32	34	36	38
	Se from Tralement (mcg)	12	12	12	12	12	12	12	12	12	12
	Additional Se needed (mcg)	8	10	12	14	16	18	20	22	24	26

* Total daily need (mcg) is calculated based on the recommended dosage: Zn: 50 mcg/kg/day, max 3000 mcg/day; Cu: 20 mcg/kg/day, max 300 mcg/day; Se: 2 mcg/kg/day, max 60 mcg/day

Table 13. The Additional Daily Amount of Zinc, Copper, and Selenium Needed to Meet the Recommended Daily Amount for 20 kg to 29 kg

		Body Weight (kg)									
Element	**Amount**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
Zinc	Total daily need (mcg) *	1000	1050	1100	1150	1200	1250	1300	1350	1400	1450
	Zn from Tralement (mcg)	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200
	Additional Zn needed (mcg)	0	0	0	0	0	50	100	150	200	250
Copper	Total daily amount (mcg)*	300	300	300	300	300	300	300	300	300	300
	Cu from Tralement (mcg)	120	120	120	120	120	120	120	120	120	120
	Additional Cu needed (mcg)	180	180	180	180	180	180	180	180	180	180
Selenium	Total daily need (mcg)*	40	42	44	46	48	50	52	54	56	58
	Se from Tralement (mcg)	24	24	24	24	24	24	24	24	24	24
	Additional Se needed (mcg)	16	18	20	22	24	26	28	30	32	34

* Total daily need (mcg) is calculated based on the recommended dosage: Zn: 50 mcg/kg/day, max 3000 mcg/day; Cu: 20 mcg/kg/day, max 300 mcg/day; Se: 2 mcg/kg/day, max 60 mcg/day

Table 14. The Additional Daily Amount of Zinc, Copper, and Selenium Needed to Meet the Recommended Daily Amount for 30 kg to 39 kg

		Body Weight (kg)									
Element	**Amount**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**
Zinc	Total daily need (mcg)*	1500	1550	1600	1650	1700	1750	1800	1850	1900	1950
	Zn from Tralement (mcg)	1800	1800	1800	1800	1800	1800	1800	1800	1800	1800
	Additional Zn needed (mcg)	0	0	0	0	0	0	0	50	100	150
Copper	Total daily need (mcg)*	300	300	300	300	300	300	300	300	300	300
	Cu from Tralement (mcg)	180	180	180	180	180	180	180	180	180	180
	Additional Cu needed (mcg)	120	120	120	120	120	120	120	120	120	120
Selenium	Total daily need (mcg)*	60	60	60	60	60	60	60	60	60	60
	Se from Tralement (mcg)	36	36	36	36	36	36	36	36	36	36
	Additional Se needed (mcg)	24	24	24	24	24	24	24	24	24	24

* Total daily need (mcg) is calculated based on the recommended dosage: Zn: 50 mcg/kg/day, max 3000 mcg/day; Cu: 20 mcg/kg/day, max 300 mcg/day; Se: 2 mcg/kg/day, max 60 mcg/day

Table 15. The Additional Daily Amount of Zinc, Copper, and Selenium Needed to Meet the Recommended Daily Amount for 40 kg to 49 kg

		Body Weight (kg)									
Element	**Amount**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**
Zinc	Total daily need (mcg)*	2000	2050	2100	2150	2200	2250	2300	2350	2400	2450
	Zn from Tralement (mcg)	2400	2400	2400	2400	2400	2400	2400	2400	2400	2400
	Additional Zn needed (mcg)	0	0	0	0	0	0	0	0	0	50
Copper	Total daily need (mcg)*	300	300	300	300	300	300	300	300	300	300
	Cu from Tralement (mcg)	240	240	240	240	240	240	240	240	240	240
	Additional Cu needed (mcg)	60	60	60	60	60	60	60	60	60	60
Selenium	Total daily need (mcg)*	60	60	60	60	60	60	60	60	60	60
	Se from Tralement (mcg)	48	48	48	48	48	48	48	48	48	48
	Additional Se needed (mcg)	12	12	12	12	12	12	12	12	12	12

* Total daily need (mcg) is calculated based on the recommended dosage: Zn: 50 mcg/kg/day, max 3000 mcg/day; Cu: 20 mcg/kg/day, max 300 mcg/day; Se: 2 mcg/kg/day, max 60 mcg/day

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Refer to Section 6.2.1.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The indication for Tralement is a source of zinc, copper, manganese, and selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. Tralement is added to the PN given intravenously. The bioavailability is self-evident. The concentrations of these trace elements are monitored to routinely keep them in the normal range in humans. Refer to Section 2.1.5 for the normal range of manganese and copper.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. Refer to General Dosing in Section 6.2.2.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Copper

Hepatic Impairment

As the major elimination pathway for copper is through biliary secretion, the dose of copper should be reduced in patients with cholestasis and/or cirrhosis (Foradori et al. 1967; Shike 1984). The dose reduction is more important in patients with cholestatic liver disease receiving long-term PN with copper as excessive infusion of copper may result in deposition in the liver and other organs resulting in organ damage (Cartwright and Wintrobe 1964). Hepatic accumulation of copper has been reported in autopsies of patients receiving long-term PN containing copper at dosage (1.4 mg/day) higher than currently recommended dose of 0.3 mg/day (Howard et al. 2007).

In the product label, the following recommendation will be included “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.”

Copper balance study from Shike et al. (Shike et al. 1981) showed that the patients with elevated serum bilirubin or elevated alkaline phosphatase (ALP) was associated with a decrease

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in copper excretion in feces. In six patients with elevated ALP, the mean daily copper excretion in the stool was 0.078 ± 0.021 mg, much lower than other patients without evidence of cholestasis (0.211 ± 0.037 mg, N=22). In addition, one patient received 0.25 mg copper as a trace element while his/her copper excretion in the stool was 0.279 mg on Day 1. On Day 3, the bilirubin rose to 1.6 mg/dL and the copper excretion in the stool decreased to 0.087 mg. Taken together, Shike et al. recommended 0.2 mg/day of copper in PN for these patients with cholestasis if they are on long-term PN therapy (Shike et al. 1981).

Diseases Related to the Genetic Defects in Copper Metabolism

Copper dose should be reduced or withheld in patients with Wilson Disease and Indian Child Cirrhosis where genetic defects in copper metabolism result in copper accumulation in the liver (Shike 1984; Turnlund 1999). In Wilson Disease, the defect in the ATP7B gene encoding a copper-transporting ATPase result in systemic copper accumulation in liver, brain and cornea. Indian Child Cirrhosis is a hereditary disease with at least one known mutation in the UTP4 gene encoding for cirhin (a protein) accompanied by rapid copper accumulation in the liver (National Institutes of Health 2020). However, it is unclear why the effects of North American Indian childhood cirrhosis appear to be limited to the liver.

Conditions With Increased Gastrointestinal Excretion

Copper dose should be increased to 0.4 to 0.5 mg/day in patients with increased gastrointestinal fluid loss (>300 gm/day) such as diarrhea, fistula and ostomy secretions. Copper balance study suggested that the copper loss to stool in these patients was 0.336±0.022 mg/day while patients with gastrointestinal (GI) excretion ≤300 gm/day had copper loss of 0.219±0.031 mg/day.

Manganese

Manganese is found in human bile and presumably excreted in the bile and into the gastrointestinal tract. Hepatic accumulation of manganese has been reported in autopsies of patients receiving long-term PN containing manganese at dosage (700 mcg/day) higher than recommended.

Thus, for patients with cholestasis, biliary dysfunction, or cirrhosis, monitoring of hepatic and biliary function during long-term administration of Tralement is recommended. If a patient develops signs or symptoms of hepatic or biliary dysfunction during use of Tralement, obtain manganese whole blood concentrations. We recommend using individual trace element products in patients with hepatic and/or biliary dysfunction to individualize the dose for each element as Tralement is a fixed-dose combination product.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Since Tralement is administered by intravenous (IV) infusion, a food-effect study was not conducted as food-drug interaction is not expected.

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There is a potential for drug interaction between intravenous zinc and copper hemostasis. Case reports showed that copper deficiency occurred following parenteral zinc supplementation in patients requiring dialysis, presumably due to zinc affecting the oral absorption of copper. For details, refer to the Agency's review of NDA 209377 Zinc sulfate. Overall, this is not an issue for Tralement as the product contains both zinc and copper.

7. Sources of Clinical Data and Review Strategy

7.1. Source of Review Materials

Review of the Tralement 505(b)(2) application is based on analysis of the existing literature and applicant's submission. Table 16 summarizes the main source of review material from the Applicant's submission.

Table 16. Summary of Review Material for NDA 209376

Review Materials	Date	Module
Draft Prescribing Information	9/4/2019	1.14
Major Information Request (IR) Response • IR 11/4/2019: provide literature review gap between 2015-2019; rationale for pediatric dosing >10 kg; address the fixed combination rule • IR 1/6/2020: further address fixed-dose combination requirement • IR 2/14/2020: drug interaction; copper contraindication; blood concentration reference range of copper and manganese from five companies • IR 4/20/2020, 5/14/2020: pediatric dose revision in Prescribing Information • IR 4/24/2020, 6/4/2020: agreement, milestones and protocol synopsis for prospective, controlled manganese safety study under PMR	2018-2020	1.2
Financial Certification and Disclosure	10/12/2018	1.34
Meetings (Pre-IND, Pre-NDA)	2014-2016	1.6
Clinical Overview for Trace Element Injection (adult & pediatric)	10/14/2017	2.5
Summary of Clinical Efficacy (adult & pediatric)	10/14/2017	2.7.3
Summary of Clinical Safety (adult & pediatric)	10/14/2017	2.7.4
Systematic Literature Review for Trace Elements in Parenteral Nutrition Copper in the Adult Population (by (b) (4))	6/2/2016	5.3.5.4
Systematic Literature Review for Trace Elements in Parenteral Nutrition Manganese in the Adult Population (by (b) (4))	6/10/2016	5.3.5.4
Literature Reference (ASPEN position paper; FDA and IOM oral daily intake standards; clinical studies (randomized, controlled, uncontrolled, retrospective), case reports, book chapters	1966-2019	5.4

7.2. Overall Review Strategy

The following summarizes the overall review strategies for NDA 209376

- Safety and efficacy were reviewed for each of the trace elements
- As the indication of Tralement is a nutritional source for patients on PN, the efficacy review focuses on the identification and confirmation of the effective dose based on literature review rather than focusing on the disease conditions/indications.

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- Safety review evaluates literature of four-decade market experience under different exposure conditions: patient population of various ages and various diseases, doses of below, same or well-above the recommendation doses, advertent or inadvertent overdose, administration from intravenous, enteral, or other route such as intrauterine exposure to copper containing contraception device.
- The reviews of zinc and selenium are limited to brief summaries in reference to reviews of zinc sulfate (NDA 209377) and selenious acid (NDA 209379), which were approved by the Division in 2019
- Copper was reviewed by Yao-Yao Zhu, clinical reviewer (Division of Hepatology & Nutrition); and manganese by Paolo Fanti, clinical reviewer (Division of Pharmacovigilance)
- Joel L. Weissfeld, M.D., MPH et al. from Division of Epidemiology provided consultation regarding the selection of literature on effective dose for copper and manganese (see Section 9.2).

7.3. Copper Review Strategies

- Main data source: the Applicant commissioned (b) (4) to conduct the systemic literature review of clinical studies for parenteral use of trace element in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al. 2009). Publication for copper studies in adults:
  - Dated up to 2015: 39 publications (total patients included in the publication=1137), including 9 copper-only publications; 5 randomized controlled trials; 7 prospective cohorts, 5 retrospective cohorts, 3 case-control studies, and 10 case reports/case series.
  - Dated from 2015 to 2019 (total patients included in the publication=410): 6 additional papers were submitted per IR request at Review Day 74, including 2 prospective cohort study and 4 retrospective studies
- Assessment of safety focused primarily of the review of case reports of copper deficiency and toxicity.
- Assessment of efficacy focused on the review of clinical studies providing key or supportive evidence in favor of the proposed copper dosage of Tralement consistent with the 2012 ASPEN recommendations.

7.4. Manganese Review Strategies

- The largest data source was a systematic review of literature on parenteral, oral and enteral manganese in adults up to 2019, commissioned by the Applicant and conducted by (b) (4) identified 51 publications reporting on parenteral manganese exposure in adults. In addition, the Division, in consultation with Office of Surveillance and Epidemiology/Division of Epidemiology I (DEPI), identified 7 more publications in adult patients receiving parenteral manganese (Consult Review filed in Document Archiving,

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Reporting and Regulatory Tracking System by Drs. J. Weissfeld, C. Callahan, and S.K. Sandhu on January 28, 2020), bringing to 58 the total number of available publications.

- The Division excluded 21 of the above 58 publications due to inadequate or insufficient information on blood manganese concentrations, including 8 controlled studies, 4 uncontrolled studies, and 9 case reports. In addition, the Division found misclassification of the study design characteristics in several of the remaining 37 publications (Bruce et al. 2018). For example, the Applicant labeled 19 publications as controlled studies, when only 7 actually fulfilled the minimal design requirement of a controlled study (Shenkin et al. 1987; Fitzgerald et al. 1999; Bertinet et al. 2000; Iwase et al. 2002; Takagi et al. 2002; Siepler et al. 2003; Akutsu et al. 2012), while the remaining 12 were uncontrolled (Wolman et al. 1979; Lowry et al. 1981; Main et al. 1982; Lane et al. 1987; Mirowitz et al. 1991; Winnefeld et al. 1995; Braunschweig et al. 1997; Reimund et al. 1999; Wardle et al. 1999; Reimund et al. 2000; Papageorgiou et al. 2002; Liu et al. 2015).
- Assessment of safety focused primarily on evidence of manganese toxicity in retrospective and prospective studies, case series and case reports. Evidence of manganese deficiency was limited to one small short term prospective study and one case reports.
- Assessment of efficacy focused on the review of clinical studies that provided key or supportive evidence in favor of the proposed manganese dosage. Notably, in the absence of any evidence of manganese deficiency in the general population, all publications on parenteral supplementation of manganese have equated efficacy of treatment with the preservation of normal manganese blood levels rather than with the treatment or prevention of symptomatic deficiency.

8. Clinical Evaluation

This section evaluates the efficacy and safety of individual trace elements, zinc, copper, manganese, and selenium based on review of published literature. As the indication of Tralement is a nutritional source for patients on PN, the efficacy review focuses on the identification and confirmation of the effective dose based on literature review. While this section focuses on copper and manganese, a brief summary for zinc and selenium is described here. Refer to UniReview of approved zinc sulfate under NDA 209377 and approved selenious acid under NDA 209379 for further detail.

8.1. Review of Efficacy: Zinc

Zinc efficacy was reviewed in the Multi-Disciplinary Review and Evaluation of Zinc Sulfate on July 18, 2019 (July 2019a).

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Timetable of Inclusion of Zinc Supplementation in Parenteral Nutrition

In 1979, the Nutrition Advisory Group of the Department of Food and Nutrition and the American Medical Association recommended that zinc 2.4 to 4 mg/day be provided in adult PN formulas, as part of a MTE product (1979b; 1979a). The ASPEN reviewed these recommendations in 2009, 2012, and 2019, with most recent recommendation for parenteral zinc 3 to 5 mg/day (Vanek et al. 2012; American Society for Parenteral and Enteral Nutrition 2019). Currently, zinc supplementation in PN, especially in long-term PN, is standard practice.

Prospective Controlled Balance Study (Wolman et al. 1979)

Objective of this prospective, randomized, dose-response, crossover study was to determine the effect of parenteral zinc (as zinc sulfate) on the zinc balance in patients on TPN. Twenty-four stable TPN-dependent adult patients not receiving enteral nutrition were assigned to receive one week each of 3 randomly sequenced doses of zinc. 17 patients (Group 1) received zinc 0.0 mg/day, 1.5 mg/day, and 3.0 mg/day, while the remaining 7 patients (Group 2) received 6.0 mg/day, 12.0 mg/day, and 23.0 mg/day. Plasma zinc concentration, and 24-hour urine and stool content were measured on days 1, 3, and 7 of each zinc dose period. Objective of this prospective, randomized, dose-response, crossover study was to determine the effect of parenteral zinc (as zinc sulfate) on the zinc balance in patients on TPN. Twenty-four stable TPN-dependent adult patients not receiving enteral nutrition were assigned to receive one week each of 3 randomly sequenced doses of zinc. 17 patients (Group 1) received zinc 0.0 mg/day, 1.5 mg/day, and 3.0 mg/day, while the remaining 7 patients (Group 2) received 6.0 mg/day, 12.0 mg/day, and 23.0 mg/day. Plasma zinc concentration, and 24-hour urine and stool content were measured on days 1, 3, and 7 of each zinc dose period.

Results

Twelve mg/day of supplemental zinc were necessary to achieve balance in the 24 participants, although 3 mg/day were sufficient in the 10 participants with stool mass <300 g/day. In regression analysis, the GI losses of zinc were proportional to the stool mass ($p<0.001$). Patients with and without ileostomy required respectively 17.1 and 12.2 mg/day of zinc supplementation for each kg/day of stool or ileostomy output.

Reviewer's comments: *The study offers strong evidence in support of supplementation of zinc 3 mg/day, at a minimum, during long-term PN. Parenteral supplementation with this zinc dose maintained the element metabolic balance in subjects who did not have ileostomy output or excessive stool volumes.*

Prospective Controlled Study (Lowry et al. 1981)

Objective of this prospective non-randomized controlled study was to define an intake of zinc and copper that preserves serum levels and provides consistently positive urinary retention of zinc and copper. Twenty-four adult TPN patients were allocated to receive either an MTE supplement (2.0 mL/day) with zinc 2.0 mg/mL, copper 1.4 mg/mL, manganese 0.2 mg/mL, and iodine 0.05 mg/mL (active treatment, n=20), or no supplement (control, n=4) for a mean

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duration of 22 days. Parenteral zinc supplementation varied from 1.3 to 5.5 mg/day depending at least in part on the patient body size. Serum zinc concentration was measured before and during the intervention.

Results

Serum zinc concentration increased transiently during the first two weeks of intervention and it remained within the reference range throughout in the group receiving the MTE supplement, but it dropped below the reference range in the non-supplemented group.

Reviewer's comments: *This study confirms the need for zinc supplementation to maintain blood levels within the reference range. The amount of element supplemented varied between subjects, but it roughly centered around 3 mg/day.*

Conclusion

The Applicant needed to demonstrate efficacy of Zinc Sulfate Injection as an adequate source of zinc in standard PN regimens. The Division finds the original studies cited by the Applicant to be sufficient and in general alignment with the approach agreed upon prior to NDA submission. Overall, the literature supports the notion that intravenous zinc sulfate is an effective source of the element and it maintains blood zinc levels in patients who cannot receive adequate nutrition through oral/enteral intake. These studies acquire expanded significance when interpreted in the context of the physiological functions of zinc and the role of its supplementation in preventing and treating clinical deficiency.

8.2. Review of Safety: Zinc

Zinc safety was reviewed in the Multi-Disciplinary Review and Evaluation of Zinc Sulfate on July 18, 2019 (July 2019a).

Four publications included safety information. The dose and duration of zinc supplementation in these 4 studies are summarized in Table 17.

Table 17. Adult Dose and Duration of Zinc Supplementation

Author Year	No. of Patients	Daily IV Dose	Duration of Therapy
Braunschweig 1997	21	30 mg	3 days
Berger 1998	10 in trace element group	26 mg	8 days
	10 in control group	7 mg	8 days
Main 1982	10	8 mg	64 weeks
Liu 2015	76	3 mg	Mean of 5.2 days

Source: From NDA 209377 submission, Section Trace Element Injection (Adult), Module 2.7.4 Summary of Clinical Safety, Table 2, Page 13/110.
Abbreviations: IV, intravenous

The cumulative number of patients was 127, with duration of zinc supplementation ranging from ≤8 days in 3 studies to 64 weeks in one study, and the parenteral zinc dose ranging from 3 to 30 mg/day. Diarrhea was reported in all 4 studies at the stated doses. Otherwise, these publications did not report other significant adverse events.

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Analysis of multiple postmarketing data sources by the Division of Pharmacovigilance-I (DPV-I) did not identify any postmarketing reports of zinc-related adverse events in patients receiving intravenously administered PN solutions containing zinc sulfate within the recommended dosage range. However, DPV-I identified multiple adverse event reports in the literature, including cases of hypocupremia, cardiac failure, and hypersensitivity with zinc-containing insulin products. The involved zinc preparations were most often used at high doses, via the oral or parenteral (subcutaneous, intravenous or hemodialysis-related) route of administration.

Conclusion

The published trials and the clinical and post-marketing experience provide extensive knowledge on safety of intravenous administration of zinc sulfate as an additive to PN in patients on long-term PN, although with noted limitations. This evidence has not conclusively identified zinc-related adverse events in patients receiving intravenously administered PN-solutions containing intravenous zinc sulfate within the recommended dosage range. Therefore, there appear to be few, if any, adverse reactions at the recommended dose.

8.3. Review of Efficacy: Copper

The review for copper efficacy evaluates evidence of effective dose based on a systemic literature review for a 505(b)(2) product.

Literature Search Methodology

The Applicant contracted (b) (4) for conducting an independent parenteral protocol-based systemic literature review, searching publication for three categories of studies: controlled, uncontrolled, and case series (Module 2.7.3. Summary of Clinical Efficacy Adult, page 26; Module 5.3.5.4. Systematic Literature Review for Trace Elements in Parenteral Nutrition Copper in the Adult Population by (b) (4)). There are total of 45 papers for parenteral copper studies.

Rationale for Copper Parenteral Supplementation and Recommended Dose

Several levels of evidence are discussed in the review:

- Copper is essential for body metabolism
- Extrapolation for parenteral dose from the established oral intake standard (RDI)
- ASPEN dosing guideline
- Copper balance study: key evidence
- Supportive evidence
  - Evidence of supplementation with recommended dose maintains the blood copper concentration
  - Evidence of supplementation with higher doses increases the blood copper concentration

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- Evidence of supplementation of lower doses decrease the blood copper concentration
- Evidence of chronic over-supplementation above the recommended dose led to hepatic excessive accumulation of copper
- Evidence of decrease in copper blood concentration when copper is not supplemented and response to supplementation with increased copper blood concentration and correction of deficiency disorders.

Copper is Essential for Body Metabolism

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 (Institute of Medicine 2001, dietary reference, copper).

Extrapolation From the RDI

Copper RDI is 0.9 mg for adults (Section 2.1.1). Assuming 35% absorption of copper in the intestine (Institue of Medicine (US) Panel on Micronutrients 2000a),the daily parenteral allowance of copper is calculated to be 0.32 mg. The proposed dose of copper 0.3 mg per day as part of trace element injection formulation is within the range of 0.3 mg to 0.5 mg.

Parenteral Dosing Guideline

Since 1979, ASPEN has been published guideline for copper and other trace element parenteral supplementation. Copper dosing recommendation has been rather stable without much changes. Table 18 below summarizes the recommendations and its basis. ASPEN's parenteral guideline are endorsed by other organizations (Vanek et al. 2015)

Table 18. Copper Parenteral Dosing Guideline

Organization	Year	Adult Dose	Cited Supporting Evidence
NAG/AMA (1979a)	1979	0.5–1.5 mg/day	Expert opinion, clinical experience, balance studies
ASPEN (1998b)	1998	0.3–0.5 mg/day	Balance studies and supporting studies
ASPEN (Vanek et al. 2012)	2012	0.3–0.5 mg/day	Shike 1981, Howard 2007, Blaszyk 2005
ASPEN (Vanek et al. 2015)	2015	0.3–0.5 mg/day	Same as above

Abbreviations: AMA, American Medical Association; ASPEN, American Society for Parenteral Nutrition; NAG, Nutrition Advisory Group.

Copper Balance Study: Key Evidence for Copper Dosing in PN

The Shike study (Shike et al. 1981) is the basis for ASPEN recommended dose at 0.3 mg daily for adult, which has been unchanged for more than 20 years. The publication is summarized as follows.

Shike 1981 concluded from this study:

- Daily dose of 0.3 mg/day for adult to achieve balance
- Increase dose to 0.4 to 0.5 mg/day for excessive GI loss
- Decrease dose to 0.15 mg/day for abnormalities of liver excretory system/cholestasis
- No correlation between plasma copper concentration and the dose level.
- Higher than the recommended dose may cause significant accumulation of copper in liver, brain and other tissues for chronic PN
- Problem of trace element contaminant in PN solution

Study Design

- Prospective, 3-week randomized crossover study of three doses, balance study
- N=28 adult (22 to 73 years old, one 15 yo) with gastrointestinal diseases (bowel resection, malnutrition, short bowel) requiring TPN
- Copper doses (copper chloride): 0.25 mg, 1.05 mg/day; 1.85 mg/day (contaminant of 0.25 mg/day added)
- Duration: three weeks; one week for each dose
- Procedure: copper sampling from body output: stool, GI drainage, urine; copper blood level, liver chemistry, ceruloplasmin etc.
- Endpoint: copper balance defined as copper intake matching losses in body output (stool, urine, GI drainage)

Result (Figure 1)

- Daily dose of 0.25 mg resulted in a balance status; other higher doses had positive balance; patients with GI loss has negative balance
- No correlation between dose and plasma level of copper (data not shown)
- Average daily copper contaminant is 0.25 mg/day for the PN product in this study

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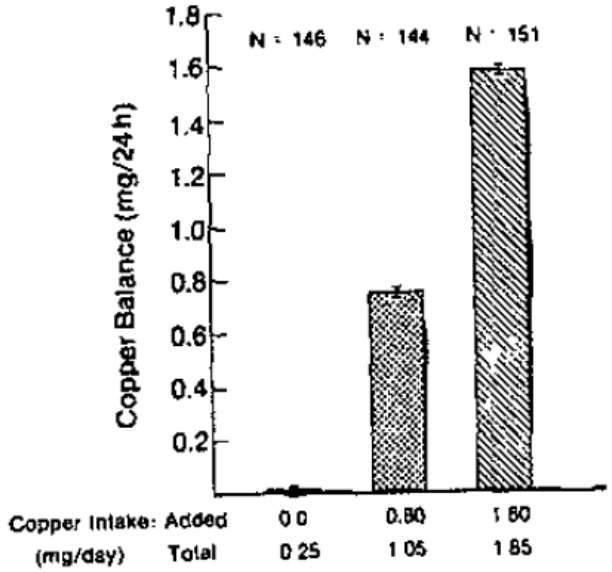
Figure 1. Mean Daily Copper Balance in Relation to Amount of Copper Infused



Source: Figure 2, page 5, Shike 1981

Higher Copper Dose in Long-Term PN Causes Copper Accumulation in Liver (Retrospective Study; Case Report/Case Series): Supportive Evidence

Howard et al. (Howard et al. 2007) studied copper level as well as other 5 trace elements in autopsy tissues of heart, muscle, liver and kidney comparing patients (n=8) with short bowel syndrome on long-term TPN (2 years to 21 years) with chronic copper supplementation at 1.4 mg per day in TPN and patients (n=45) who died without GI disorder and not on TPN. The results showed significant elevation of hepatic copper. Two patients who died of liver failure had liver copper levels comparable to Wilson disease (>250 mcg/g). See detail on Section 8.4 subsection "Hepatic Accumulation of Copper." Also see Section 8.4.

Lack of Copper Supplementation in PN Causes Copper Deficiency Disorder: Supportive Evidence

Evidence from case report/case series (see detail on Section 8.4. subsection "Copper Deficiency") confirmed: (1) without copper supplementation or prolonged holding of copper due to reasons of cholestasis or liver function abnormality may lead to copper deficiency causing pancytopenia or neuropathy in these patients; (2) copper supplementation in PN result in increased serum copper concentration and correction of the deficiency syndrome; and (3) monitoring serum copper concentration, blood count, and clinical symptoms and signs such as anemia and neuropathy, would help to mitigate the risks.

Copper Dose at 0.3 mg Maintains a Normal Serum Concentration: Supportive Evidence

Ishizuka 2011 (Ishizuka et al. 2011a) followed 46 surgical adult patients on TPN at Cu 0.3 mg per day. At baseline, two weeks, and four weeks, the serum copper concentration remained within normal level. Uzzan 2017 (Uzzan et al. 2017) studied 73 patients on stable PN for at least 1 month with copper at 0.31 mg per day. In 75% of patients, copper level was within normal limit;

25% has copper higher or lower. Akutsu 2012 (Akutsu et al. 2012) studied 28 patients with esophageal cancer on TPN with copper at 0.3 mg per day for 28 days in a nonrandomized controlled study. While the serum copper concentration was decreased in control group, it maintained within normal level in copper supplementation group (Table 19).

Table 19. Mean Serum Concentrations of Copper Over Time

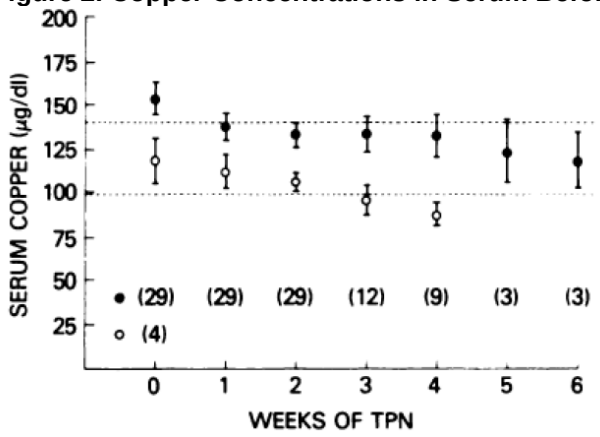
Trace Element (units)[a]	Day	Intervention (N=8)	Control (N=10)
Copper (µg/dL)	0	121.5	135.4
	14	114.4	122.1
	28	124.7	110.6*

Source: Akutsu 2012. A Units in mcg/dL; * p≤0.05 for change from day 0

Copper Serum Concentrations Maintained, Increased or Decreased in Response to a Wide Range of Copper Doses in Controlled Short-Term Studies (American Regent): Supportive Evidence

Many non-randomized or randomized controlled clinical trials tested different dose levels of copper in PN ranging from 0.3 mg to 3.7 mg vs. placebo or vehicle from 5 days to 28 days in patients under different medical conditions (burns, injuries, short bowel syndrome, tumor patients). In comparison with the placebo/vehicle group, the serum copper concentrations in most studies were increased or maintained. Only in rare occasion, the serum copper may decrease. There was no safety data in these trials. In a non-randomized controlled study of tumor-bearing patients receiving TPN (Lowry et al. 1981), followed 20 patients with trace elements supplemented with coper at 1.4 mg/mL for 22 days. Patients with copper supplementation maintained serum copper within the reference ranges as compared to progressive decline of concentration in the control group (n=4, Figure 2).

Figure 2. Copper Concentrations in Serum Before and During TPN



Source: Lowry 1981. Serum copper concentration before and during TPN in IV copper supplemented (filled circles) and unsupplemented (open circles) patients. Mean ± standard error, with total number of determinations at each time point denoted by (n). Dashed lines represent normal serum level.
Abbreviations: IV, intravenous; TPN, total parenteral nutrition

Conclusion

Shike 1981 remains the key balance study in TPN dependent-population and provides a reasonable basis for the parenteral dosing. The shortcomings of the study included (1) no control group with zero copper as there was an average of 0.25 mg /day copper contaminant in the PN of study patients; (2) small sample size; (3) short duration; (4) there is no second similar balance study to confirm the results. Nevertheless, there is an extensive evidence to support this dose: postmarketing experience with the dose appears safe for 30+ years; controlled studies with copper at the recommended dose showed the normal copper serum concentration; chronic supplementation well above 0.3 mg/day threshold resulted in significant hepatic copper accumulation and probable liver failure; chronic PN without copper resulted in deficiency manifestation such as pancytopenia; supplementation with copper resulted in the rise of serum copper concentration and correction of deficiency syndrome. In addition, the recommended dose is supported by an extrapolation from the oral recommended daily intake accepted by the FDA.

8.4. Review of Safety: Copper

This review for copper safety summarizes the clinically relevant safety issues regarding copper parenteral supplementation as identified in literature review. These safety concerns are conveyed through labeling (see Section 11.1).

Postmarketing Copper Exposure

There has been extensive postmarketing exposure with copper as single agent or within the multitrace products. An active product, cupric chloride manufactured by Hospira, was approved by the FDA on June 26, 1986 under NDA 018960. Another copper product, cupric sulfate manufactured by Abraxis Pharm, was approved on May 5, 1987, under NDA 19350 but discontinued on July 21, 2017. The Applicant has seven trace element injection-4 or injection-5 products containing copper that have been on the market unapproved for at least 3 decades. The multitrace products for adult, neonatal, pediatric formulations contain copper 0.1 mg or 0.3 mg or 0.4 mg or 1 mg (concentrated).

Of 39 published articles identified by the Applicant for parenteral copper use, n=1021 patients were exposed to copper. Among the 39 articles, five articles contain information on copper toxicity. Of the five studies, n=114 patients were exposed to copper PN. The duration of copper supplementation ranged from 3 weeks to 18 years. The daily doses of parenteral copper ranged from 0.25 mg to 2.7 mg (source: Applicant NDA submission: Summary of Clinical Safety for Trace Element Injection, Adult).

Reviewer's comments: *Most prospective and controlled studied identified by the Applicant regarding copper or other trace elements did not contain any safety information. The relevant safety data were mainly identified from case reports and case series. For postmarketing safety data through FDA Adverse Event Reporting System (FAERS), refer to Section 8.9 "Safety in the Postmarketing Setting" by the Division of Pharmacovigilance 1 (DPV-1).*

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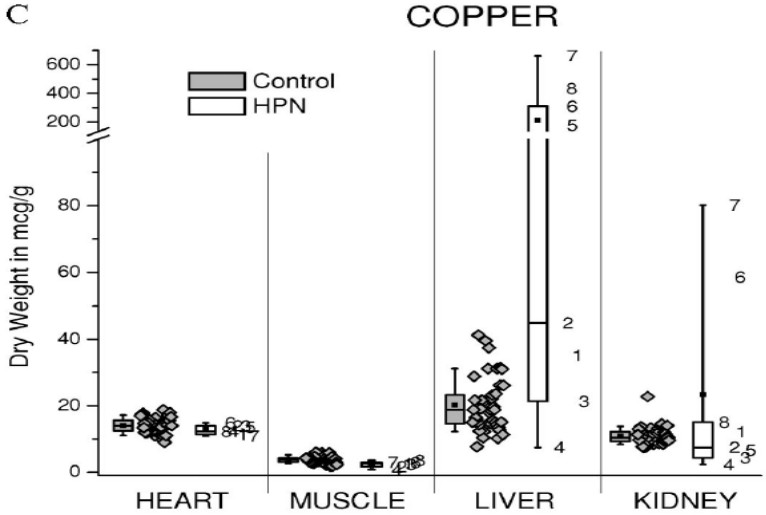
Hepatic Accumulation of Copper

The risk of hepatic copper accumulation in patients with liver cholestasis in long-term TPN use were studied through liver biopsy (Blaszyk et al. 2005) and autopsy (Howard et al. 2007). In Blaszyk paper, hepatic copper levels were compared between patients (n=28) with long-term TPN (0.3 years to 18 years) and patients with drug-induced cholestatic livers disease (n=10) without TPN. Results showed hepatic copper levels ranging from 11 to 2248 mcg/g in TPN patients vs. 37 to 350 mcg/g in control. Twenty-nine % TPN patients had level above the diagnostic threshold for Wilsons's disease (>250 mcg/g) vs. 10% in control. The hepatic copper levels were found to be correlated with aspartate aminotransferase (AST) and total bilirubin level, but not correlated with duration of the TPN or serum copper level. In Howard paper, copper level as well as other 5 trace elements in autopsy tissues of heart, muscle, liver & kidney were compared between patients (n=8) with short bowel syndrome on long-term TPN (2 years to 21 years) and patients (n=45) who died without GI disorder and not on TPN. The results showed significant elevation of hepatic copper (Figure 3 below) as well as hepatic manganese and chromium (data not shown). The eight TPN patients received 1.4 mg copper per day, which is greatly above the ASPEN recommended dose of 0.3 mg per day. Two patients who died of liver failure had liver copper levels comparable to Wilson disease (>250 mcg/g).

Figure 3. Copper Levels in Autopsy Tissues



Source: Howard 2007
Abbreviations: HPN, home parenteral nutrition

Reviewer's comments: *These two studies, in particular the Howard 2007 where the copper dose was given markedly above the recommended adult dose 0.3 to 0.5 mg per day concluded the following: (1) recommended dose should be much lower as the dose suggested by Shike 1981;(2) patients with liver abnormality are prone for accumulation of copper in the liver and may lead to liver failure; (3) discontinue copper in PN when transaminase and ALP levels elevated; (4) check copper serum level on the regular basis and monitor for anemia while holding copper in PN; (4) the risk of hepatic copper accumulation should be mitigated through labeling.*

Abnormalities of Copper Metabolism Due to Genetic Disease and Its Risk During PN

Patients with Wilson disease (Harris and Gitlin 1996; Bandmann et al. 2015) is especially sensitive to copper exposure due to genetic defect of copper export. Wilson disease is an autosomal recessive disease with mutation in gene ATP7B encoding a copper-transporting P-type ATPase. Accumulation of excessive copper in liver, brain, cornea leads to liver failure, neuropsychiatric disorders such as dystonia, ataxia, parkinsonian syndrome, personality changes, anxiety, depression as well as presence of Kayser-Fleischer rings in the cornea. Wilson disease is treated with copper chelators and/or zinc which interferes with intestinal uptake of copper.

Reviewer's comments: *Wilson disease illustrates how excessive accumulation of copper could lead to liver failure, cirrhosis with fatality if left untreated. Patients with Wilson disease as well as cholestasis, liver disease, liver cirrhosis should have regular monitoring of copper serum concentration, ceruloplasmin level, liver chemistry, and complete blood count. Risk of copper for patients with Wilson disease and other liver disease is conveyed through the labeling.*

Copper Hypersensitivity

Although there is no report of hypersensitivity reaction by using copper parenteral product, many cases of copper hypersensitivity reactions in women with copper IUD were identified during the literature review as summarized in Table 20 below (also see Section 8.9). The underlying mechanism may be delayed T-lymphocytes-induced immune reaction when copper is absorbed through the intrauterine mucous membrane and carried to the blood and lymphatics (Hostynek and Maibach 2004; Fage et al. 2014).

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Table 20. Case Reports of Hypersensitivity Cutaneous Reactions in Women With Copper IUD

Literature	Age (Years)	Clinical Manifestation	Onset From IUD	Diagnosis Test	Treatment & Response
(Rongioletti et al. 1985)	35	2 months of Itchy dermatitis on trunk & limbs; erythematous, papulovesicular eruption with excoriations in trunk, thighs, groins, vulva, vaginal discharge	A few weeks	Copper patch test: 3 (+)	Antihistamine local & systemic steroids: transient relief; IUD removal: complete resolution
(Barranco 1972)	26	1 month of pruritic dermatitis in arms; diffuse, erythematous, maculopapular eruption in arms and trunk with excoriations	2 weeks	Copper patch testing 4 (+)	Topical/systemic steroids, antihistamine: partial response; IUD removal: resolved within days
(Siliotti et al. 1987)	28	Eyelid and perioral erythema with itching, worsening erythema with wheals and vesicles in whole body with intense itching	2 months	Copper patch test markedly (+)	Antihistamine: not working; IUD removal: symptoms resolved
(Purello D'Ambrosio et al. 1996)	32	6 months of widespread urticaria with angioedema of eye lids and the labia majora & minora, vaginal discharge	6 months	Patch test positive; in vitro lymphocyte stimulating test (+). Skin Bx: T-cell, eosinophilic granulocytes infiltration	Antibiotics and anti-inflammatory: not working. Removal of IUD: complete remission.

Source: Generated from publications by Ronglioletter, Barranco, Siliotti, and D'Ambrosio
Abbreviations: (+) positive; Bx, biopsy; IUD, intrauterine device

Reviewer's comments: *Although this is a rare and potential risk due to other route of administration of copper with contact of intrauterine mucosa via IUD, the systemic nature of this delayed immune response leads to addition of copper hypersensitivity under Contraindication and language under Warnings and Precautions.*

Copper Deficiency

Many case reports/case series of copper deficiency in patients on chronic TPN were identified in the literature review. The Table 21 summarizes a sampling of five cases taken from 16 case reports identified by the Applicant and the reviewer.

Table 21. Case Reports of Copper Deficiency in Patients on Chronic Parenteral Nutrition (PN)

Source	Age, Gender	Time and Reason on PN	Clinical Manifestation	Blood Cu (mcg/dl)	Causes of Cu Deficiency	Treatment	Recovery
(Palm and Dotson 2015)	57 yo F	Years due to fistula	Moderate anemia	Before:24 After: 76	No Cu in PN for years	Daily copper 12.5 mg in PN x 97 days	Anemia resolved
(Imataki et al. 2008)	81 yo M	8 months due to gastrectomy	Pancytopenia with severe anemia; neuropathy	Before: 5 After: 71	No Cu in TPN	Daily copper 1.25 mg	Anemia & neuropathy resolved after one month of Cu
(Fuhrman et al. 2000)	39 yo F	19 months due to short bowel syndrome	Severe anemia; transfusion dependent	Before: 10	No Cu in PN x 1 yr due to cholestasis	1 mg/day added to PN x 1 months	Anemia improved by died due to complication of cirrhosis
(Spiegel and Willenbucher 1999)	32 yo M	8 weeks due to Crohn's disease	Pancytopenia	Before: 17 After: 102	No Cu in PN due to cholestasis x 8 weeks	1 mg/day	Pancytopenia improved 7 days after sCu but died due to cardiac tamponade
(Wasa et al. 1994)	69 yo F	10 months due to bowel surgery	Pancytopenia	Before: 10 After: 81	No Cu in PN x 10 months due to cholestasis	1.3 mg/day	Improved 2 weeks later

Source: Generated from Palm 2015; Imataki 2008; Fuhrman 2000; Spiegel 1999; Wasa 1995.
Abbreviations: Cu, copper; PN, parenteral nutrition; TPN: total parenteral nutrition

Reviewer's comments: *The case reports confirmed the importance and strong rationale for parenteral supplementation of copper for patients on chronic parenteral nutrition as shown in all the above cases. Holding copper due to reasons of cholestasis or liver function abnormality may lead to pancytopenia or neuropathy in these patients. Therefore, monitoring serum copper concentration, blood count,* (b) (4) *would help to mitigate the risks. These risk mitigation steps were conveyed in the labeling.*

Overdosing

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. Oldenquist and Salem (Oldenquist and Salem 1999) reported a case of copper overdose via intravenous and intramuscular routes in a 47-year-old man (Table 22). Patient injected himself with 50 mg copper sulfate IV and IM. He developed pancytopenia, renal failure, hepatic failure, hypotension, electrolyte abnormality, and rhabdomyolysis. He recovered after treatment with multiple copper chelators as well as hemodialysis for his renal failure.

Table 22. A Case Report of a 47-Year-Old Man With Copper Overdose Via Parenteral Route

Source	Overdose	Symptoms	Laboratory Tests	Treatment	Resolution
Oldenquist (1999)	Copper sulfate: 50 mg IV, IM	Nausea, vomiting, diarrhea, hematemesis, hematuria, anuric, diffuse abdominal pain, myalgia, jaundice, hypotension, & dyspnea	Hemoglobin: 5 g/dl Platelet: 94k CPK: 2528 Myoglobin (+), Na: 113 Total bilirubin: 14.6 Creatinine: 9.8 AST: 300 LDH: 13800 Serum copper: 180 (peak)	IV fluids, transfusion of packed red blood cells & fresh frozen plasma, penicillamine, dimercaprol, EDTA, hemodialysis	Cr =1.7 6 weeks later

Source: Generated from Oldenquist 1999
Abbreviations: AST, aspartate aminotransferase; CPK, creatine phosphokinase; Cr, creatinine; EDTA, ethylenediaminetetraacetic acid; IM, intramuscular; IV, intravenous; LDH, lactic acid dehydrogenase

Reviewer's comments*: most acute or chronic copper toxicity reports were identified as result of oral injection. One case of parenteral copper toxicity was identified with consequence of multi-organ failure. There were no reports of toxicity of copper when parenteral PN was used at the recommended copper dose.*

Zinc-Induced Copper Deficiency

Zinc competes with copper absorption in the intestine. Several case reports found that high level of supplemental zinc taken over extended periods of time may resulted in copper deficiency. Prasad et al. (Prasad et al. 2015) described a 65-year-old woman with Crohn's disease who have been on home parenteral nutrition for many years. She reported perioral paresthesia and burning sensation of her mouth. Her serum copper was low, and she had mild pancytopenia. Despite of increase in her copper in TPN, her anemia and her perioral sensation

did not change. After removing zinc from her dental adhesive, her copper level as well as pancytopenia were resolved with partial resolution of her oral paresthesia.

***Reviewer's comments**: There is a risk of zinc-induced copper deficiency especially when large amount and persistent source of zinc is added from enteral route. Enteral source of zinc competes with intestinal absorption of copper. In fact, zinc is used as medicine to decrease serum concentration of copper for Wilson disease patients. This risk of zinc-induced copper deficiency is described in the Warnings and Precautions section of the Prescribing Information for the approved zinc sulfate product. Since copper is a component of Tralement, the risk of copper deficiency in the presence of excessive zinc may be low. Therefore, this risk is not included in the Tralement label.*

PN Solution Contamination

Various amount trace elements were found in many parenteral solutions before the supplementation. Shike et al. (Shike et al. 1981) estimated the mean daily input of copper from TPN solution without supplementation was approximately 0.25 mg. The amount of copper in solution differ between manufacturers and event between batches from the same manufacturer.

***Reviewer's comments:** Supplementation with lower end of the recommended dose is reasonable given the uncounted amount of copper or other trace element contamination in PN products. In patients who have cholestasis, liver disease, or cirrhosis, the copper supplementation may need to be stopped for a while, and copper concentration and liver chemistry should be monitored periodically.*

Conclusion

Copper as a single agent or a component of multitrace products has been on market approved or unapproved for parenteral supplementation over 30 years to 40 years. The main issues identified from the literature review for copper safety include hepatic copper accumulation in cholestasis and liver disease; copper deficiency due to lack of supplementation, copper hypersensitivity. Monitoring the copper concentration, liver function, hematology, and chemistry are important for the safety of copper supplementation. The risks and risk mitigation plan are conveyed in the labeling.

8.5. Review of Efficacy: Manganese

The Applicant relied on published data on oral manganese RDI and bioavailability to justify the proposed parenteral manganese dose (Johnson et al. 1991; Finley et al. 1994; 2016). Essentially, based on a manganese adult RDI of approximately 2 mg/day and a bioavailability of 1% to 5%, the daily systemic assimilation of manganese in adults approximates 20 to 100 mcg/day, and the proposed 55 mcg/day parenteral dose of manganese falls within this calculated theoretical manganese assimilation range. Additionally, to justify the proposed manganese dose, the Applicant leans on position papers on parenteral MTE products issued by ASPEN in 2012 and

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2019 and by the European Society for Clinical Nutrition and Metabolism in 2016 (Vanek et al. 2012; Pironi et al. 2016; American Society for Parenteral and Enteral Nutrition 2019).

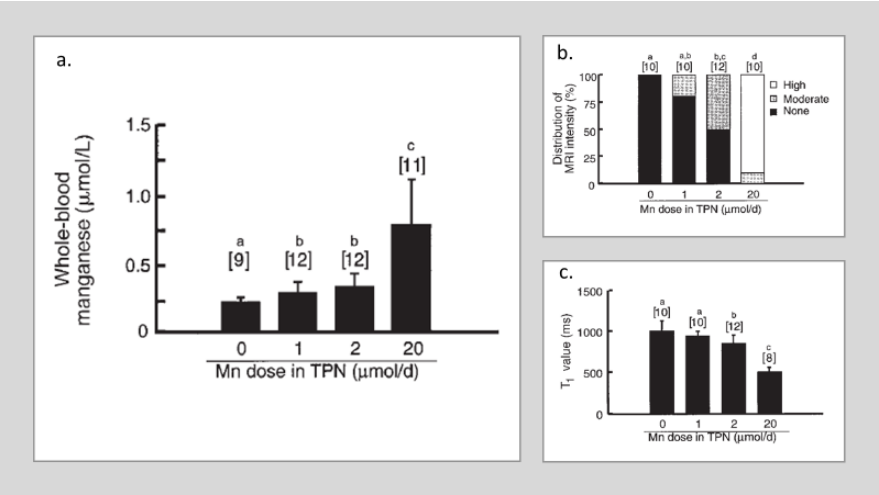
Two single-group controlled intervention studies are the best evidence supporting the proposed manganese dose and form (i.e., 55 mcg/day, as manganese sulfate) for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. These studies are outlined and critically reviewed below. In addition, the sections of the 2012 ASPEN position paper (Vanek et al. 2012) pertaining to manganese is critically reviewed below.

The remaining observational and case summaries are briefly summarized in Section 14.4.

Prospective Controlled Intervention Study (Takagi et al. 2002)

The study was single-center, prospective interventional, single-arm, and open-label. It included 12 patients on long-term standard home parenteral nutrition (HPN group; six men and six women; age range 17 years to 62 years), five patients on long term elemental diet (ED group) as normal cerebral MRI control group, and 49 healthy volunteers to establish normal blood manganese level (Control group). Intervention consisted of a preset sequence of four doses of parenteral manganese (1,100 mcg/day, 0 mcg/day, 110 mcg/day, and 55 mcg/day, as manganese chloride) in the HPN group only, each dose administered for at least 6 months. The variables of interest were the whole blood and serum manganese concentrations (measured monthly), the brain MRI T1-weighted signal intensity (measured every 2 months to 3 months) and routine clinical variables (measured every 2 months to 3 months). The primary endpoint was the intensity of the MRI T1-weighted signal in the globus pallidus, as a function of parenteral manganese exposure for 6 months. Secondary endpoint was the correlation of blood manganese levels and MRI signal intensity. The translational objective of the study was to define the optimal IV dose of manganese based on the above variables.

Figure 4. Effect of Long-Term Infusion With Mn 0, 1, 2, or 20 mcmol/day on (a) WB Mn Concentrations, (b) Intensity of MRI in the GP, and (c) T1-Weighted Magnetic Resonance Images in the GP of HPN Patients



Notes: Columns and error bars indicate mean (± SD). Different letters indicate statistically significant difference, P<0.05 (Tukey-Kramer multiple comparisons test). Number of patients in brackets. 1 mcmol =55 mcg, 2 mcmol =110 mcg, or 20 mcmol =1100 mcg.
Abbreviations: GP, globus pallidus; HPN, home parenteral nutrition; Mn, manganese; MRI, magnetic resonance imaging; WB, whole blood

Results

As shown in Figure 4 panel (a), the whole blood manganese concentration increased in a dose-dependent manner in the HPN patients. Concentrations were different between all dose pairs except between doses 55 and 110 mcg/day. Figure 4 panel (b) shows a manganese dose-dependent increase in the globus pallidus MRI T1-weighted signal intensity in the same patients. Signal intensity was normal (solid bar) in all patients exposed to 0 mcg/day of manganese, while it was moderately increased (dotted bar) in two patients infused with 55 mcg/day, in 6 patients infused with 110 mcg/day, and in one patient infused with 1100 mcg/day; and it was highly increased (open bar) in nine patients infused with 1100 mcg/day. Figure 4 panel (c) shows manganese dose-dependent decline in MRI T1 score, which is inversely related to manganese deposition. Differences in T1 score were significant between all manganese dose pairs except the 0 and 55 mcg/day doses. As shown in Figure 5, the whole-blood manganese concentrations was within the normal range (5.2 to 24.0 mcg/L) when the HPN patients were infused 0 and 55 mcg/d, but they were above the normal range in 19% of patients when infused 110 mcg/d and in 91% when infused 1100 mcg/d. Correlation analysis of whole-blood manganese concentration and T1-weighted MRI intensity, showed the blood concentration to correlate positively with MRI intensity (r =0.7728). The authors concluded that a parenteral manganese dose of 55 mcg/day is efficacious because (1) the whole-blood manganese concentration is on average higher with the 55 mcg/day than with the 0 mcg/day manganese dose, and (2) the MRI signal intensity in the basal ganglia is statistically equivalent in the HPN patients following exposure to either 0 or 55 mcg/day. In addition, the authors pointed out that the MRI-detected changes may be a more sensitive marker of in vivo manganese status than the clinical changes, since no patient showed neurologic or other clinical symptoms suggestive of manganese intoxication or deficiency during the trial.

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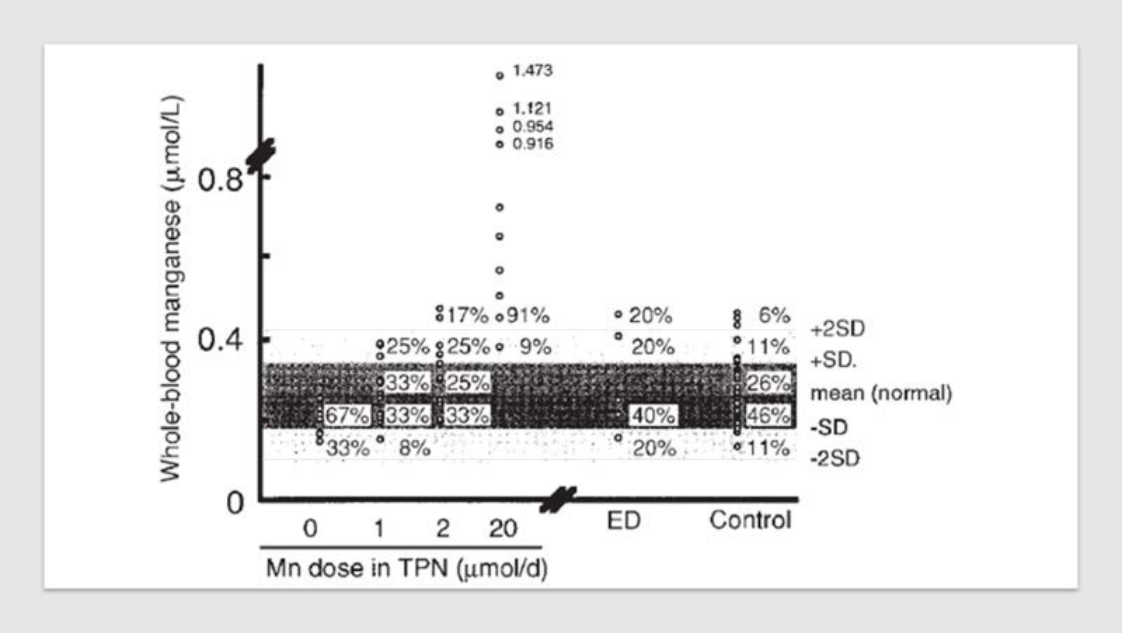
Figure 5. Distribution of WB Mn Concentrations in HPN Patients Who Received Parenteral Mn 0, 1, 2, or 20 mcmol/d Via TPN, in Patients Administered an Elemental Diet (ED) Daily for ≥1 Year and in Healthy Control Subjects



Note: 1 mcmol =55 mcg, 2 mcmol =110 mcg, or 20 mcmol =1100 mcg.
Abbreviations: ED, elemental diet; Mn, manganese; SD, standard deviation; TPN, total parenteral nutrition; WB, whole-blood

Reviewer's comments: *This study offers the best experimental evidence in support of the use of manganese 55 mcg/day in long-term PN. All subjects maintained the blood manganese concentration within the reference range during the 6 months of exposure to manganese 55 mcg/day, a period of observation that is sufficient to assure stability and reproducibility of the blood test (Takagi et al. 2001). In addition, no subject experienced clinical evidence of manganese deficiency. However, evaluation of effectiveness is limited primarily by the absence of interventions with a manganese dose lower than 55 mcg/day. In fact, although absence of infusion (i.e., manganese 0 mcg/day) resulted in statistically lower blood manganese concentrations than the infusion of 55 mcg/day, the blood manganese concentrations remained within the reference range throughout the 0 mcg/day period. The latter suggests that dosages between 0 and 55 mcg/day would have also been effective in maintaining the blood manganese concentrations within the reference range, while providing a wider safety margin for the prevention of manganese toxicity.*

Position Papers from Stakeholder Scientific Organizations (Vanek et al. 2012)

An experts work group reviewed the adult and pediatric literature with primary focus on publications originated from the 2009 ASPEN Research Workshop (Hardy 2009). Under the manganese subheading the experts work group supports a change in recommendation for manganese adult dosing from the previous 60 to 100 mcg/day (1998a) to 55 mcg/day, based on a brief discussion of the paper of Takagi, *et al*. (Takagi et al. 2002).

Reviewer's comments: *Emphasis on the Takagi, et al, paper is justified, this being the best original study to date on manganese supplementation in HPN patients. However, the position paper misrepresents the publication by Takagi, et al, on two important points. First the position*

paper states that Takagi, et al, had "tested manganese doses lower than 55 mcg/day," when the only lower alternative to manganese 55 mcg/day was absence of manganese (0 mcg/day). Second, the position paper states that the Takagi, et al paper demonstrated "lower whole blood manganese concentration with the 0 mcg/day versus 55 mcg/day manganese dose," while omitting to mention that the manganese concentration on 0 mcg/day was within the reference range and therefore normal. Notably, the position paper does not make recommendations on the monitoring of manganese levels and toxicity, or on the interpretation of manganese blood concentrations.

Conclusion

Since clinical efficacy is not a necessary outcome measure for the indication sought by the Applicant, the primary objective of this review was to critically assess clinical studies that measured blood manganese concentration in PN patients before and after parenteral manganese supplementation, or before and after discontinuation of the parenteral supplement, and that monitored clinical safety. Overall, the reviewed evidence supports long-term use of manganese 55 mcg/day to maintain manganese blood concentrations within the reference range.

8.6. Review of Safety: Manganese

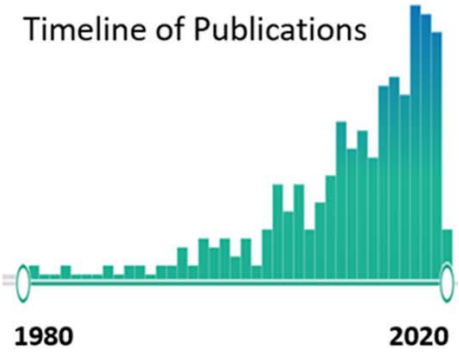
Prospective Controlled Intervention Study (Takagi et al. 2002)

This publication was described and reviewed for efficacy of parenteral manganese 55 mcg/day in Section 8.5. In this section, we address issues related to safety that emerge from detailed review of the paper.

Figure 6. Number of Original Publications of Basic Science on Manganese-Induced Oxidant Damage, Inflammation, Cell Transporter Dysregulation, and Metal Imbalance of Brain Cells

Time Period	Number of publications
No time limits	252
pre 2010	79
2010 to 2014	69
2015 to 2020	104

PubMed search (02-17-2020). Keywords: [manganese AND neurotoxicity AND (molecular OR biology) NOT review]



Reviewer's comments: *Four main criticisms emerge. (1) The publication shows that the average cerebral accumulation of manganese is not different after 6-month exposure to manganese 0 or 55 mcg/day, and it is significantly less than after exposure to 110 mcg/day. The authors interpret this finding to suggest that manganese 55 mcg/day is safe in terms of neurotoxicity [see Figure 4 panel (c)]. However, analysis of the MRI intensity [see Figure 4 panel (b)] shows that respectively 0%, 20% and 58% of the cases exposed to 0, 55, and 110 mcg/day had intermediate intensity, indicating that exposure to manganese 55 mcg/day carries a measurable*

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risk of neurotoxicity. Furthermore, since manganese accumulation depends on both dose and time of exposure, it is plausible that exposure to 55 mcg/day for longer than 6 months might result in further accumulation. (2) The 55 and 110 mcg/day manganese doses had quite different effects on brain accumulation, with respectively 20% and 58% subjects experiencing intermediate MRI intensity, suggesting that even relatively small increments in dose above the 55 mcg/day may result in substantially increased risk of manganese accumulation. Since standard adult and pediatric TPN products marketed in North America contain as much as 25 mcg/day of manganese contaminant (see Table 39 for data and references), it is plausible that U.S. patients prescribed manganese 55 mcg/day may instead receive up to 80 mcg/day, thus substantially increasing the risk of cerebral accumulation. Notably, manganese contamination of parenteral nutrition products in the Takagi study did not seem to cause as much of a problem since manganese contamination of Japanese products is less than 4.4 mcg/day (Isegawa et al. 1990; Takagi et al. 2002). (3) Brain accumulation of manganese was reversible in the study, as demonstrated by normalization of the MRI intensity after switch of the manganese dose from 1100 mcg/day to 0 mcg/day [see Figure 4 panel (b)]. However, concern lingers that even a temporary brain accumulation of manganese may cause irreversible subclinical cell injury that may declare itself clinically at a later date. This possibility is supported indirectly by an exponential growth of evidence from basic science about manganese-induced oxidant damage, inflammation, cell transporter dysregulation, and metal imbalance of brain cells (see Figure 6) (Miah et al. 2020). (4) In this study, despite normal whole blood levels in all samples collected during the period of exposure to 55 mcg/day manganese, 2 out of 10 patients accumulated manganese in the basal ganglia during the same period. In regression analysis, the R^2 for the whole-blood manganese levels and MRI findings was 0.59, indicating that approximately 41% of the MRI findings cannot be explained by the whole-blood manganese levels. Notably, out of the 10 publications reporting both whole-blood manganese levels and MRI findings in adult or pediatric HPN patients, seven concluded that blood manganese concentration at the individual level is an unreliable marker of cerebral manganese deposits; the remaining three publications found nearly perfect correlation between the two parameters, but only the patients with known elevated blood manganese levels were tested with an MRI in these studies, thus biasing results and interpretation (see Table 34 and Table 37 for data and references).

Prospective Controlled Intervention-Withdrawal Study (Bertinet et al. 2000)

The study was prospective interventional, single-arm, and open-label. It included 15 patients on long-term HPN (eight men and seven women; age range 32 years to 74 years), with median total bilirubin 0.5 mg/dL (range 0.4 to 2.5 mg/dL). Prior to study initiation, the patients had exposure to parenteral manganese as summarized in Table 23.

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Table 23. Parenteral Manganese Exposure Before Study Initiation

Parameter	Median (Range)
Manganese supplementation duration (years)	3.6 (2–10)
Manganese supplementation (mcg/bag)	198 (55–258)
Manganese supplementation (mcg/day)	110 (16–187)
Cumulative manganese dose (mg/HPN duration)	140 (30–980)
Manganese contaminant in PN (mcg/L)	5 (2–18)

Abbreviations: HPN, home parenteral nutrition; PN, parenteral nutrition

Intervention consisted of the discontinuation of parenteral manganese for 1 year. The study objectives were to test, first, for the presence of abnormalities in cerebral T1-weighted MRI signal intensity and, second, the relationship between whole-blood manganese levels and neuroradiologic abnormalities, at the beginning (baseline) and end (study-end) of 1 year discontinuation of parenteral manganese. The translational objective was to infer the appropriate manganese dose during long-term HPN. Results: At baseline, the MRI of 10 of 15 patients (67%) showed high T1-weighted signal intensity in the basal ganglia, consistent with manganese accumulation. At study-end, the same 10 patients showed a substantial but incomplete reduction in manganese accumulation. In all patients, the whole blood manganese concentrations dropped markedly from 24.7 mcg/L at baseline to 5 mcg/L at study-end ($p = 0.017$), which were respectively above ($p<0.001$) and below ($p = 0.003$) the reference range [8.5 mcg/L (3 to 19.6)]. At study-end, the manganese brain deposits and blood concentrations were significantly reduced and positively correlated. The authors pointed out that a wide majority of patients had brain manganese deposits at study baseline despite long exposure to relatively low parenteral manganese (median 110 mcg/day, range 15 to 187 mcg/day) and despite relatively modest levels of manganese contamination of other TPN components. In addition, the manganese blood levels 1 year after manganese discontinuation were significantly lower than the reference range. Notably, one of the five patients with a negative MRI at baseline had received HPN for 9.6 years with cumulative high exposure to manganese (0.96 g). No patient showed clinical evidence of psychosis or extrapyramidal syndrome (tremor, rigidity, or hypo/akinesis) prior to or at the start of the study, or clinical evidence of manganese deficiency at the end of the study.

Reviewer's comments: *The most relevant observation of this work is that the majority of patients had brain accumulation of manganese at baseline despite relatively low exposure prior to the study, i.e., dosages of 18 to 110 mcg/day in 50% of patients. Another important observation was that 1-year complete manganese withdrawal yielded subnormal blood manganese levels, suggesting that a certain amount of manganese supplementation must be maintained in these patients. Finally, one patient on TPN for 9.6 years and a cumulative exposure of 0.96 mg manganese, had a normal MRI, emphasizing that individual manganese accumulation varies in unpredictable manner among patients.*

Parenteral Manganese in Incipient and Established Liver Injury

Effect of Manganese on the Liver - Animal Studies

Two independent laboratories published 32 original studies on the acute toxic effect of manganese on liver and biliary function of experimental rats, between 1968 and 2004 (Ayotte

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and Plaa 1988). These studies are only marginally informative for the clinical condition of parenteral nutrition patients due to their basic experimental design that does not correspond to the clinical circumstances of PN patients, including the induction of anesthesia prior to starting the acute manganese exposure, the precise and closely-timed sequence of infusions necessary to cause cholestasis (i.e., acute infusions of manganese and bilirubin at 15 min interval), and the very high dose of manganese and bilirubin applied [i.e., 4.5 mg manganese/kg (4.5x103-fold the currently recommended 1 mcg/kg infusion rate in pediatric patients) and 25 mg bilirubin/kg]. Notably, none of these 32 studies attempted to reflect the experience of PN patients by administering magnesium chronically, or to apply their experimental design to non-rodent animal models that more closely reflect human biology.

Clinical Studies

In pediatric patients, Fok et al., conducted the most rigorous and informative study. In a hypothesis driven protocol, these authors compared prospectively the effect of parenteral manganese 55 mcg/kg x 41 days (Group 1; n=78) vs. manganese 1 mcg/kg x 40 days (Group 2; n=82) on cholestasis (defined as direct bilirubin >3 mg/dL) in preterm neonates (gestational age ~31 weeks). They failed, however, to demonstrate a difference in incident cholestasis between infants exposed to high and low manganese dose. Also, they found no difference in mortality (10% mortality in the high manganese dose vs 15% in the low manganese dose) or morbidity. The only significant difference was the median peak direct bilirubin, which was higher in the high than low manganese dose (Fok et al. 2001). In a letter to the editor, Beath et al, wrote about two groups of preterm infants (gestational age ~35 weeks) who, after receiving either manganese 44 mcg/kg (n=31) or 1 mcg/kg (n=16) for ~100 days, displayed no difference in the incidence of cholestasis (total bilirubin >4.1 mg/dL). (Beath et al. 1996) Three other papers are anecdotal case reports or series that do not inform about the causality of cholestasis (Hambidge et al. 1989; Reynolds et al. 1994; Fell et al. 1996). In adult patients, a letter to the editor by Forbes et al, describes 29 patients receiving manganese 3 mcg/kg/d (range 1.1 to 5.5) for ~48 months. These authors found normal liver function tests in 12 patients, stable mild cholestasis in 11, and liver function tests 2-fold higher than the upper limit of normal in 6; no correlation was found between whole blood manganese levels and cholestasis (Forbes and Forbes 1997). Reimund et al, described 21 patients infused with manganese 500 mcg/d for approximately 30 months who had serum manganese levels higher than healthy controls. The authors reported correlation between serum manganese and alkaline phosphatase levels that was statistically significant but of modest clinical significance (R2 0.26) (Reimund et al. 1999). Three other papers are case reports that do not allow to assess the cholestasis causality (Mehta and Reilly 1990; Alves et al. 1997; McKinney et al. 2004).

Effect of Biliary and Liver Failure on Manganese Retention and Accumulation

Patients on parenteral nutrition with either preexisting or incident liver disease and cholestasis (e.g., from hepatotoxic effects of parenteral lipids and, perhaps, manganese) are at high risk for hypermanganesemia, manganese accumulation in the basal ganglia, and associated Parkinson-like syndrome (Butterworth et al. 1995; Olanow 2004). This notion is supported by uncontrolled

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and anecdotal evidence in parenteral nutrition patients (Alves et al. 1997; Reimund et al. 1999), and by more structured evidence in patients with cirrhosis and cholestasis who were not on parenteral nutrition and were exposed to a spontaneous diet as the primary source of manganese (Burkhard et al. 2003).

Reviewer's comments: *The literature presents reasonably convincing evidence of a predisposing effect of either incident or preexisting liver disease and cholestasis on manganese blood levels and neurologic toxicity in parenteral nutrition patients. Conversely, the evidence of a possible toxic effect of manganese on the biliary tract in parenteral nutrition patients is limited and contradictory. None of the reviewed studies demonstrated convincingly such an effect and some of the studies refuted it. The animal studies support the existence of a hepatotoxic effect of manganese, but these studies used very high manganese dosages and strictly focused on acute experiments in rats. The latter limitations are important because of the recognized difficulty in reconciling acute and chronic toxicology studies and in extrapolating from animal to human toxicity.*

Manganese in Patients With Chronic Kidney Disease or End-Stage Renal Disease

Two case series reported on hemodialysis patients who, despite not having been exposed to PN, experienced increased cerebral manganese accumulation on MRI with concordant neurological signs and symptoms, but normal serum manganese concentration (da Silva et al. 2007; Akcan et al. 2018). An autopsy series had findings consistent with the above (Schabowski et al. 1994). Notably, one of the two case series also recruited pre-dialysis chronic kidney disease (CKD), peritoneal dialysis, and kidney transplant patients, and did not find cerebral accumulation of manganese in these patient groups. These observations single out chronic hemodialysis, versus pre-dialysis CKD, peritoneal dialysis and transplantation, as a condition predisposing to cerebral accumulation of manganese. A direct causal role of the hemodialysis procedure seems to be excluded by two studies in adults and children with acute kidney injury on continuous venous-venous hemodiafiltration, which reported undetectable manganese concentrations in the dialysis fluid (<1 mcg/L) and negligible loss of manganese through the dialysis membrane (<2% of the average standard oral intake) (Churchwell et al. 2007; Pasko et al. 2009).

Reviewer's comments: *Hemodialysis patients, but not patients treated with other modalities of chronic renal replacement, seem to be at risk of cerebral accumulation of manganese via unclear mechanisms. Hypothetically, this could be attributed to either inadvertent administration of contaminant manganese with oral or parenteral drugs and blood products that are frequently used in hemodialysis patients (e.g., albumin, packed red blood cells), supraphysiologic assimilation of dietary manganese due to uremic gastroenteropathy, or abnormally high transfer of manganese from plasma to brain tissues due to uremic disruption of the blood-brain barrier. Regarding the latter possibility, one ex vivo study comparing plasma from healthy versus uremic patients observed ~90% versus ~20% binding of manganese to plasma proteins, and 4-fold higher binding constant in the plasma from healthy subjects; lower affinity of plasma protein for manganese in uremic patients may favor translocation of the*

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metal across the blood-brain barrier thus favoring accumulation in brain tissue (Gidden et al. 1980).

Conclusion

The above evidence raises the concern that long-tern administration of manganese at a dosage of 55 mcg per day may carry a substantial risk of manganese deposition in the basal ganglia, which may foretell a risk of neurotoxicity. Some patients receiving dosages of manganese higher than 55 mcg per day experienced both deposition of this element in the basal ganglia and neuropsychiatric adverse reactions. This concern is even greater for those patients who, besides requiring parenteral nutrition, also suffer from advanced cirrhosis, cholestasis or end-stage renal disease requiring hemodialysis. These hepatic and renal conditions seem to carry an independent risk of manganese deposition in the basal ganglia that may compound with the risk intrinsic to infusion of manganese 55 mcg per day. The Division intends to address these concerns with the PMR of a prospective controlled study where brain manganese deposition will be compared in long-term parenteral nutrition patients will be randomly assigned to receive manganese 0 mcg per day, 55 mcg per day, (b) (4)

8.7. Review of Efficacy: Selenium

The following summarizes the efficacy of selenium as a source of PN from the excerpts of Multi-Discipline Review of Selenious Acid (Section 8.1 Review of Efficacy, NDA (b) (4)):

Selenium was not recognized as an essential trace element until 1984, when it was recommended as an additive to PN by the American Medical Association [17]. Literature in the 1980s to 1990s described case reports and observational studies of patients on long-term complete PN (TPN) or partial PN who presented with symptoms suggestive of selenium deficiency with baseline low plasma/serum Se levels that improved with selenium supplementation. However, it is important to note that not all patients with plasma Se levels below the reference range developed clinical symptoms. Also, selenium supplementation in PN and monitoring of selenium levels were not standard practice during that time and therefore such patients who were on long-term PN were likely to develop selenium deficiency as described in the literature. Since then, there has been increased awareness of the need to supplement patients, especially those on long-term PN who are at risk of developing selenium deficiency. Subsequent studies focused on dose exploration to correct underlying selenium deficiency using healthy controls as a reference. In recent years, clinical studies have focused on exploring the role of high-dose selenium as an anti-oxidant and its effects on improving clinical outcomes in patients who are critically ill as well as cancer therapy; results from such studies have been inconclusive.

A total of 47 publications submitted by the Applicant to support efficacy of intravenous selenious acid in adults were reviewed. Two publications by Lane et al. (1987) (Lane et al. 1987) and Sando et al. (1992) (Sando et al. 1992)were considered the most relevant to support use of parenteral selenium as a nutrient source in patients on PN based on the study objectives and enrollment population. Lane et al. (1987) conducted a controlled study that showed that

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parenteral selenium of 80 and 160 mcg/day increased selenium levels in seven adult patients with underlying malabsorption on long-term PN in a dose-dependent manner. Sando et al. (1992) showed in their controlled study that selenium levels fell with withdrawal of selenium supplementation of 200 mcg/day but rose back to within the referenced range in adult and six pediatric patients on long-term TPN. Additional supportive studies (primarily observational) in patients on PN reported a broad range of dosing (32 to 400 mcg/day) for parenteral selenium supplementation in adults on PN. In general, a dose range between 60 and 200 mcg/day was found to be sufficient to restore plasma Se levels to within the reference range.

Conclusion

Overall, the data supports the efficacy of 60 mcg/day in adults and 2 to 4 mcg/kg/day in pediatric patients weighing less than 7 kg and 2 mcg/kg/day in pediatric patients weighing 7 kg or greater. This dosage is anticipated to meet the nutritional requirements of most patients on PN. However, the dosage must be individualized accounting for the patient's clinical condition, nutritional requirements, and other sources of selenium intake either orally or enterally. Some patients will have higher clinical requirements, most notably those on chronic PN. Therefore, in these types of patients to avoid clinical deficiency, periodic monitoring of systemic selenium concentrations, along with clinical examination, should be considered.

8.8. Review of Safety: Selenium

The following summarizes the safety of selenium as a source of PN from the excerpts of Multi-Discipline Review of Selenious Acid (Section 8.2 Review of Safety, NDA (b) (4)):

Despite the paucity of safety information in published literature, it can be concluded that the margin of safety for dosing parenteral selenium as a source of nutritional TE requirements at the proposed dose of 60 mcg/day is wide based on the following observations:

- The Institute of Medicine established a tolerable upper intake level (UL) of 400 mcg/day, no-observed-adverse-effect level of 800 mcg/day, and the lowest-observed-adverse-effect level of 913 mcg/day for oral intake in adults based on chronic exposure to excessive levels of oral selenium.
- Unapproved but marketed parenteral selenium has been used in clinical practice for close to 30 years without reports of significant adverse events.
- No reports of significant adverse events in clinical studies attributed to parenteral selenium supplementation for up to 8 years at doses of up to 60 mcg/day, 129 months at doses up to 200 mcg/day, and 4 months at 400 mcg/day in adults.
- Studies and case summaries in pediatric patients on parenteral selenium supplementation between 14 days to 39 months reported no significant adverse events associated with parenteral selenium. The doses of selenium supplementation reported in these studies varied between 1.5 mg/kg/day to 7 mcg/kg/day.
- Reports of acute and chronic toxicities of oral selenium suggest that fatalities related to acute poisoning occur at doses greater than 5 grams while clinical signs and symptoms

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of chronic selenium toxicity have not been observed at oral ingestions below 800 mcg/day.

- The is no clear correlation between the amount of selenium ingested, severity of clinical presentation of toxicity and Se blood concentrations, although toxicity has not been observed in patients with plasma Se levels below 30 mcg/dL

Conclusion

The safety database includes information from clinical trials and post-marketing adverse event reports of intravenous selenious acid at and above the recommended clinical dosage (range of 32 mcg to 400 mcg/day). Despite some limitations to the safety information available from clinical studies, due to lack of rigorous data collection and reporting, there appears to be few, if any, adverse reactions within the recommended dosage range. Published case reports of acute toxicity reported with overdose of oral selenium and chronic selenosis also inform the safety of the recommended intravenous dosage. Signs and symptoms of toxicity have been reported with acute and chronic oral doses at least 100-fold above the proposed intravenous dosage. The safety margin in adults is further supported by the oral selenium UL of 400 mcg/day (approximately 280 mcg/day of intravenous selenious acid, based upon an oral bioavailability estimate of 70%).

8.9. Safety in the Postmarketing Setting

Safety Concerns Identified Through Postmarketing Experience

The DPV-I was consulted to conduct a pharmacovigilance review and provide an analysis of all adverse events associated with copper, manganese, selenium, and zinc products in the FDA Adverse Event Reporting System (FAERS), the Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS), and the medical literature. A summary of the review is discussed below. Refer to complete review by Drs. Jamie Ridley Klucken, Lisa Harinstein, and Eileen Wu for additional details.

Of note, DPV-I recently (2019) completed postmarketing reviews for selenious acid and zinc sulfate. Findings from searching the FAERS database, CAERS database, and medical literature included hypersensitivity events with zinc-containing products, cardiac failure with a fatal 1000-fold overdose[1] (January 2019) of zinc sulfate in an infant, and mild adverse events (e.g., gastrointestinal symptoms, paresthesia, alopecia, fingernail loss, signs of thyroid deficiency) with high doses of selenium that appeared to be reversible upon discontinuation.

[1] DPV-I calculated overdosages based on the maximum oral or parenteral daily dose recommended by the American Society for Parenteral and Enteral Nutrition (ASPEN).

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For this review, DPV-I performed a search of the FAERS database for all reports with 1) copper products through January 9, 2020; 2) manganese products through January 8, 2020; 3) selenium products from February 22, 2019,[2] through January 8, 2020; 4) zinc sulfate products from May 2, 2019,[3] through January 8, 2020; and 5) MTE products through January 9, 2020. DPV-I performed a search of the CAERS database for all reports with 1) copper products through February 17, 2020; 2) manganese products through February 18, 2020; 3) selenium products from February 26, 2019,[4] through February 24, 2020; 4) zinc sulfate products from May 6, 2016,[5] through February 24, 2020; and 5) MTE products through February 25, 2020. Additionally, DPV-I searched the medical literature for relevant case reports with copper, manganese, selenium, zinc, MTE products through February 2, 2020. The resulting 216 FAERS reports,[6] 61 CAERS reports,[7] and 32 medical literature case reports[8] were reviewed.

DPV-I did not identify any postmarketing reports of adverse events in patients receiving intravenously administered PN solutions containing copper, manganese, selenium, zinc sulfate, or MTE within the recommended dosage range. However, DPV-I identified multiple adverse events reported with different formulations or with unknown or higher than recommended doses of copper, selenium, and manganese products.

Copper

The medical literature search identified ten cases describing adverse events following ingestion of unknown (n=5) or higher than recommended doses (n=5, range 9- to 278-fold higher) of oral copper sulfate. The adverse events described include various gastrointestinal, hematologic, renal, hepatic, and respiratory complications as well as rhabdomyolysis, weakness/fatigue, and cardiac arrest. We also identified one case in the medical literature describing similar adverse events following parenteral administration of a 100-fold higher than recommended dose of copper sulfate.

DPV-I also identified 14 cases in the medical literature (n=8) and FAERS database (n=6) describing systemic hypersensitivity events such as rash, pruritis, urticaria, and angioedema following insertion of a copper IUD. Many cases described a positive dechallenge (n=11) and/or a positive scratch test to copper (n=7).

[2] Previous DPV-I review conducted a FAERS search through February 21, 2019, for selenium products.
[3] Previous DPV-I review conducted a FAERS search through May 1, 2019, for zinc sulfate products.
[4] Previous DPV-I review conducted a CAERS search through February 25, 2019, for selenium products.
[5] Previous DPV-I review conducted a CAERS search through May 5, 2019, for zinc sulfate products.
[6] The 216 FAERS reports included copper products (n=102), MTE products (n=74), manganese products (n=20), selenium products (n=15), and zinc sulfate products (n=5).
[7] The 61 CAERS reports included copper products (n=32), zinc sulfate products (n=16), manganese products (n=6), selenium products (n=6), and MTE products (n=1).
[8] The 32 medical literature case reports included copper products (n=19), manganese products (n=10), and selenium products (n=3).

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Manganese

The FAERS search identified two cases of manganese toxicity with parenteral administration of manganese. One case described Parkinson-like symptoms and positive imaging following administration of PN containing manganese at an unknown dose for an unknown duration. The second case described positive imaging following an 8000-fold overdose of manganese due to a compounding error; the patient did not display neurological symptoms despite magnetic resonance imaging (MRI) findings remaining positive for nearly 11 months.

The CAERS database search retrieved 3 cases describing neuropsychiatric adverse events (e.g., stuttering, slurring, headaches, agitation, anxiety, tremors, ataxia, sleep disruption) following ingestion of oral manganese supplementation at unknown (n=1) or 18- to 67-fold higher than recommended doses (n=2) over an average of 4.5 weeks (range 2.5 to 8 weeks).

The medical literature search identified 10 cases describing adverse events with parenteral administration of manganese at unknown (n=1) or 2.7- to 80-fold higher than recommended doses (n=9) administered over an average of 10 months (range 9 days to 4 years), of which a subset (n=7) had underlying hepatic dysfunction, biliary dysfunction, or both. The adverse events described include positive MRI findings (e.g., high-intensity signal on T1-weighted images of the globus pallidus) and neuropsychiatric complications (e.g., confusion, psychomotor retardation, gait disturbance, parkinsonism, and seizures). Notably, in patients reporting dechallenge information (n=9), most noted improvement or resolution of symptoms (7 of 9) and MRI lesions (4 of 5), following manganese discontinuation.

Selenium

DPV-I identified five additional cases of adverse events related to selenium supplementation in the updated search of the medical literature (n=3) and the CAERS database (n=2). Four cases described known adverse events associated with selenium toxicity (e.g., gastrointestinal symptoms, fatigue, alopecia, fingernail changes, and paresthesia) following ingestion of higher than recommended doses of oral selenium supplementation. The remaining single article described new adverse events associated with selenium toxicity such as leukoencephalopathy with progressive cognitive impairment and visual loss, reversible upon discontinuation. However, this case lacked typical adverse events associated with selenium toxicity and was unable to exclude the possibility of contaminants.

Zinc Sulfate

The updated FAERS, CAERS, and medical literature searches did not identify additional cases of adverse events related to zinc sulfate products.

MTE

The FAERS, CAERS, and medical literature searches did not identify cases of adverse events related to MTE products.

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Therefore, there does not appear to be any postmarketing safety signals or adverse events with any fixed-dose combination products or with individual parenteral supplementation of copper, manganese, selenium, zinc sulfate, or MTE at the proposed doses for approval after review of data retrieved in the FAERS database, CAERS database, and medical literature. DPV-I did identify post-marketing safety signals associated with non-parenteral administration of individual trace elements and/or at higher than recommended doses. These adverse events include: hypersensitivity with copper IUDs, copper toxicity, neuropsychiatric events and central nervous system deposition with manganese toxicity, and risk of manganese accumulation with hepatic/biliary dysfunction.

Expectations on Safety in the Postmarketing Setting

As presented above in the clinical review of manganese, patients on long-term PN can accumulate manganese in the basal ganglia. The available information does not allow to determine if doses lower than 55 mcg of manganese would provide adequate supplementation while reducing the risk of accumulation in the basal ganglia. The Applicant agreed to address this safety issue in a postmarketing safety trial requirement.

8.10. Integrated Assessment of Efficacy and Safety, Conclusions, and Recommendations

8.10.1. Efficacy

As Tralement is a nutritional source for patients on PN, the review of efficacy evaluates the effective dose for each trace element based on literature review. Efficacy conclusion is summarized as follows:

1. All four trace elements, zinc, copper, manganese, and selenium, are cofactors of various enzymes essential for body metabolism and biological function.
2. Patients dependent on long-term parenteral nutrition without supplement of any of four trace elements may cause specific and serious clinical abnormalities, which can be corrected with PN supplementation of the deficient trace element.
3. Established standards for dietary intake (RDA and RDI) provide an indirect reference for the parental trace element supplementation.
4. Evidence from the systemic review of literature generally supports the recommended doses by ASPEN position paper 2012 for each element for both adult and pediatric populations.
5. Tralement provides recommended doses for adult and children weighing at least 50 kg in a weight-based regimen.
6. Tralement may not provide the required daily amount for zinc, copper, and selenium to varied degrees for pediatric patient weighing 10 kg to 49 kg; therefore, single trace element product may be needed to add to Tralement.

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7. Tralement, a fixed-combination, provides safe and effective doses of zinc, copper, manganese, and selenium in a single administration but with potential inflexibility for dose adjustment of individual trace element.

8.10.2. Safety

The safety review evaluated more than four decades of marketing experience of single and multitrace products. Overall, the studies that used dosages of the individual four elements similar to the recommended doses did not identify safety signals. The following risks were identified:

1. Neurotoxicity of manganese: Although most reports of manganese accumulation in the basal ganglia and of consequent neuropsychiatric symptoms were in pediatric or adult long-term parenteral nutrition patients who had received manganese at higher than recommended dosages or in the setting of cholestatic liver disease, one prospective study and some case reports described toxicity in patients treated with lower doses. To resolve remaining uncertainties about the safety of the recommended manganese dose, the Applicant agreed to the postmarketing requirement (PMR) of conducting a prospective and controlled study of Tralement versus a trace element formulation without manganese but otherwise equal to Tralement, to test for possible manganese deposition in the basal ganglia and for manifestations of neurotoxicity. The Prescribing Information, Warning and Precautions for risk mitigation describes the risk of manganese neurotoxicity.
2. Hepatic Accumulation of Copper and Manganese: Both copper and manganese are primarily eliminated in the bile and their excretion is impaired in patients with cholestasis and/or cirrhosis. Liver biopsy and autopsy reports described hepatic accumulation of copper and manganese in patients exposed to long-term parenteral nutrition with unknown or higher than recommended dosages of copper and manganese. Furthermore, patients with cholestasis and/or cirrhosis who receive parenteral nutrition have increased risk of manganese brain deposition and neurotoxicity and increased risk of liver failure due to accumulation of copper in the liver. The Prescribing Information, Warning and Precautions for risk mitigation describes the risk of hepatic accumulation of copper and manganese.
3. Hypersensitivity reactions with zinc and copper: Hypersensitivity reactions to subcutaneously administered zinc-containing insulin products and copper-containing IUDs were identified in case reports. Although these hypersensitivity reactions occurred via routes of administration other than parenteral nutrition, these systemic reactions were described under Contraindications for risk mitigation.
4. Trace element overdosing: Overdosing information was identified from oral or parenteral routes in case reports of all four single trace elements up to 1000-fold higher than the recommended doses. The overdosing information was described under section 10 of the Prescribing Information for risk mitigation.
5. Trace element deficiency due to prolonged exclusion: copper deficiency was found in many case reports due to prolonged exclusion of copper in chronic parenteral nutrition

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in the setting of cholestasis. Therefore, periodic monitoring of blood concentration of each trace elements as well as other safety lab such as complete blood count and chemistry are important to minimize under- or over-dosing. This risk was addressed in the labeling.

6. Inflexibility of the fixed-dose combination: although Tralement provides the convenience of delivering safe and effective dosages of four trace elements in a single product, single trace element products should be used if one or more trace elements may need to be increased or decreased due to developmental need or medical conditions to minimize under- or over-dosing.
7. Other class adverse reactions that were identified in parenteral nutrition products may apply to Tralement, including pulmonary embolism, vein damage & thrombosis, and aluminum toxicity. These risks were all addressed in Tralement labeling.

8.10.3. Conclusion and Recommendation

The overall safety of Tralement is acceptable. The benefit of Tralement as a safe and effective source of four essential trace elements in adult and pediatric patients outweighs the identified risks. Potential risks as such were described in the Prescribing Information and patient counseling information for risk mitigation. Lingering uncertainties about safety of the manganese dosage will be addressed in the PMR to conduct a prospective and controlled study. Therefore, the review team recommends approval of Tralement.

9. Advisory Committee Meeting and Other External Consultations

9.1. Medical Policy & Program Review Council (MPPRC) (Feb. 27, 2019)

On Feb. 27, 2019, the Division sought the Council's comments and recommendations on the planned review approach for 505(b)2 applications regarding selenious acid (NDA 209379), zinc sulfate (NDA 209377), and multitrace elements (zinc sulfate, coper sulfate, manganese sulfate, and selenious acid, NDA 209376). The Division planned to approve the proposed TE parenteral additive products for the indication as a "source of" each respective element for PN in adult and pediatric patients based on collective evidence including clinical data on TE supplementation in PN, the known enteral nutritional requirements (RDA or RDI, etc.), relative bioavailability of oral vs. intravenous administration, current clinical PN guidelines, the available toxicity profile for each element, as well as the time and extent of use in clinical practice.

The Council agreed with the Division that there is substantial evidence that essential trace elements are required for health maintenance and recognized the challenges in identifying the optimal parenteral dose and the uncertainties of dosing in special populations. The Council agreed with DGIEP's approach to review and potentially approve the proposed fixed-dose combination product for the indication 'as a source of' for PN in adult and pediatric patients based on collective evidence including clinical data on individual trace element

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supplementation in PN patients, known enteral nutritional requirements, e.g., RDA, RDI, relative bioavailability of oral versus intravenous administration, current clinical PN guidelines, the available toxicity data, as well as the time and extent of use in clinical practice. In addition, the Council recommended the Division consider a post marketing requirement (PMR) study or studies to obtain additional data to support dosing in populations where the evidence is scarce and suggestive of differential dosing.

This NDA was not referred for an FDA Advisory Committee meeting because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

9.2. Evaluation of Systematic Review of Medical Literature (Office of Surveillance and Epidemiology)

To identify relevant literature, the Applicant commissioned a systematic literature review, conducted by (b) (4) DEPI previously validated the (b) (4) search in reviews completed for Selenious Acid Injection (NDA 209379) (July 2019b) and Zinc Sulfate Injection (NDA 209377) (July 2019a).

For this NDA review, the Division requested DEPI to identify study reports in medical literature that might support a dosing recommendation for copper (Cu) and manganese (Mn) in PN. DEPI used a systematic approach and identified 16 study reports in medical literature to support a dosing recommendation for Cu in PN for adult and pediatric population (Weissfeld 2019). DEPI's approach identified two types of studies, (1) pivotal studies of Cu balance in patients receiving Cu-supplemented PN and (2) supportive studies describing biochemical outcomes in patients receiving PN that contained well specified amounts of Cu. DEPI also identified six study reports in medical literature that support a dosing recommendation for manganese in PN for adult and pediatric population (Weissfeld 2020) In conclusion, all available information in the medical literature were used in the ascertainment of safety and effectiveness of Tralement.

10. Pediatrics

Multiple formulations of fixed-dose combinations of trace elements have been marketed unapproved for more than four decades in the United States for use in PN in both adults and pediatric patients, including neonates. These unapproved MTE formulations contain different proportional amounts of up to five essential trace elements per 1 mL of solution. See Table 7 in Section 2.2.1. None of the existing unapproved pediatric formulations contain an optimal amount of each trace element to meet the needs of the pediatric population, and clinicians are accustomed to supplementing pediatric patients who receive these formulations as a TPN additive with additional zinc, copper, and selenium. Additionally, the existing unapproved pediatric formulations contain variable amounts of manganese and chromium, precluding their use by some providers in the pediatric and neonatal populations due to concerns about manganese and chromium toxicity. See Table 24.

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Table 24. Individual Trace Element Composition of Unapproved Pediatric Formulations Marketed in the United States Compared to Tralement

	Trace Element Injection 4			
Element	**TE-4 Pediatric[9]**	**MTE-4 Pediatric C[10]**	**MTE-4 Neonatal[11]**	**Tralement**
Zn	500 mcg	1,000 mcg	1,500 mcg	3,000 mcg
Cu	100 mcg	100 mcg	100 mcg	300 mcg
Mn	30 mcg	25 mcg	25 mcg	55 mcg
Cr	1 mcg	1 mcg	0.85 mcg	0
Se	0	0	0	60 mcg

Source: Adapted from CMC reviewer Jane Chang.
Abbreviations: Cr, chromium; Cu, copper; Mn, manganese; MTE, multitrace element; Se, selenium; TE, trace element; Zn, zinc

The Applicant purports that Tralement is advantageous over the existing unapproved pediatric formulations because the product provides the lowest effective and highest safe dose of each trace element to achieve the optimal risk/benefit ratio. The product contains no chromium, less manganese, and higher amounts of both copper and selenium than current unapproved formulations to better meet the daily needs of pediatric patients. Approval of Tralement under an NDA will allow FDA to ensure product quality under the Current Good Manufacturing Practice regulations.

(b) (4)

Two of the four individual trace elements contained in Tralement were recently FDA approved as exclusively literature-based 505(b)(2) NDAs, and the Applicant is the holder of both approved marketing applications.

- On April 30, 2019, FDA approved NDA 209379 for Selenious Acid Injection in adults and pediatric patients as a source of selenium for PN. A Pediatric Research Equity Act (PREA) PMR was issued at the time of approval to develop an age-appropriate formulation to ensure accurate dosing volume for patients weighing less than 7 kg.
- On July 18, 2019, FDA approved NDA 209377 for Zinc Sulfate Injection (3 mg/mL and 5 mg/mL) in adults and pediatric patients as a source of zinc for PN. A PREA PMR was issued at the time of approval to develop an age-appropriate formulation to ensure accurate dosing by volume for pediatric patients weighing less than 12 kg.

The proposed pediatric doses of the selenious acid and zinc sulfate components in Tralement provide the same amounts of zinc and selenium as those approved for the two individual products. The FDA recommended dose of Selenious Acid Injection is 2 mcg/kg/day (up to 60 mcg/day) in pediatric patients weighing 7 kg and greater and 2 to 4 mcg/kg/day in pediatric

[9] NDC Code **0517-9310-25**; for use up to 11 years of age
[10] NDC Code **0517-9203-25**; for use up to 11 years of age
[11] NDC Code **0517-6202-25**; labeling is silent on age
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patients weighing less than 7 kg. The FDA recommended dose of Zinc Sulfate Injection is as follows:

- 50 mcg/kg/day (up to 3 mg/day) in patients weighing 10 kg and greater
- 100 mcg/kg in patients weighing 5 kg to less than 10 kg
- 250 mcg/kg in patients weighing 3 kg to less than 5 kg
- 400 mcg/kg in patients weighing less than 3 kg

Given these two recent FDA approvals for this Applicant, the review team for the Tralement NDA did not revisit the approved pediatric doses for the selenium and zinc components and focused instead on reviewing the literature in the NDA to identify a safe and effective pediatric dose for the copper and manganese components in Tralement. Refer to discipline-specific reviews in DARRTS under both NDAs for specific details about pediatric dosing considerations for both Selenious Acid Injection and Zinc Sulfate Injection.

Adult parenteral multivitamin drug products were reviewed for efficacy under the Drug Efficacy Study Implementation (DESI) program and, in the initial DESI notice of July 27, 1972, that addressed parenteral multivitamin preparations, FDA announced its conclusion that parenteral multivitamin preparations as then formulated lacked substantial evidence of effectiveness because they did not contain certain essential vitamins, or they contained certain vitamins in doses that were too high or too low (37 FR 15027).

The Nutrition Advisory Group of the American Medical Association (NAG-AMA) attempted to address the need for more appropriate commercially available formulations by convening an expert panel in 1977 to review parenteral trace element requirements and published guidelines in 1979 for parenteral multivitamins (1979a). The NAG-AMA suggested parenteral copper intake of 20 mcg/kg/day in pediatric patients. This recommendation was informed by expert opinion, clinical experience, and results from nutritional balance studies.

The Committee on Clinical Practice Issues of the American Society for Clinical Nutrition (ASCN) reevaluated existing data to determine if revisions were needed for pediatric parenteral trace element requirements and published its findings in 1988 (Greene et al. 1988). Unlike the NAG-AMA, the ASCN Committee focused on projected intravenous needs of individual trace elements, wherever possible based on amounts needed for growth and to replace endogenous losses (aka metabolic requirements). Additional factors which the Committee considered included supportive data from human milk, plasma concentrations, and clinical evidence of deficiency. The ASCN Committee also incorporated input from the National Institute of Health-National Institute of Child Health and Development. The ASCN Committee recommended intravenous intake of trace elements other than zinc only when TPN is provided for 4 or more weeks. Within this context, the ASCN Committee recommended 20 mcg/kg/day of copper in pediatric patients, including preterm and term neonates, with a maximum daily dose of 300 mcg/day but recognized that copper requirements may increase by 10 to 15 mcg Cu/kg in pediatric patients with jejunostomies or exterior biliary drainage. The ASCN Committee recommended against copper provision to pediatric patients with obstructive jaundice and recommended caution with copper provision to pediatric patients with impaired biliary excretion, including those with TPN cholestasis. The ASCN Committee also noted that PN

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solutions contain variable amounts of copper contamination that, in some cases, may exceed calculated copper needs for pediatric patients.

ASPEN subsequently published its initial guidelines in 1998 for PN practices and included recommendations for copper and manganese supplementation in pediatric patients receiving PN (1998b). ASPEN convened a task force in 2009 to provide evidence-based recommendations for changes in vitamin and trace element products marketed in the United States. ASPEN's updated recommendations considered the following for pediatric patients: (Vanek et al. 2012).

- The need to greatly reduce the copper and manganese content of available MTE products due to reports of manganese toxicity and excessive organ accumulation of both trace elements in patients who had received long-term TPN
  - Decrease manganese content to provide 1 mcg/kg/day in neonates
- Develop pediatric formulations containing no chromium
- Add selenium 2 mcg/kg/day in all pediatric and neonatal formulations
- Use an MTE formulation in neonates and pediatric patients that does not include added chromium

Given the time and extent of use of unapproved MTE products, FDA agreed the Applicant could provide published data in pediatric patients to support dosing, safety, and efficacy for the proposed indication (Division of Gastroenterology and Inborn Errors Products 2018). The Applicant relied on recommendations from ASPEN as the basis for the proposed pediatric dosing for each of the trace elements in Tralement. The 2019 ASPEN recommendations on appropriate PN dosing for neonatal and pediatric patients recommend the following daily doses for copper and manganese:

- 20 mcg/kg/day of elemental copper for patients weighing up to 40 kg (maximum dose of 500 mcg/day), including preterm and term neonates, and recommends 200 to 500 mcg/day for adolescents weighing greater than 40 kg
- 1 mcg/kg/day of manganese for pediatric patients weighing up to 40 kg (maximum dose of 55 mcg/day), including preterm and term neonates, and recommends 40 to 100 mcg/day for adolescents weighing greater than 40 kg

The Applicant commissioned (b) (4) to conduct a literature review of Medline, Excerpta Medica database, Cochrane Library, and Cumulative Index to Nursing and Allied Health Literature to identify reports which evaluated the nutritional need of each of the trace elements as an additive to PN in the pediatric population to further support its proposed pediatric dosing.

Contamination of PN solutions during the manufacturing process with trace elements found in MTE formulations was first described in the late 1970s. Potential chromium toxicity as a result of such contamination that led to PN-associated nephrotoxicity in humans was first described in the early 1990s (Moukarzel et al. 1992) followed by reports in the late 1990s (Fell et al. 1996; Reynolds et al. 1998) of neurotoxicity from excess manganese exposure in pediatric patients. Manufacturing processes have evolved in the last 50 years but the extent to which trace elements continue to contaminate PN solutions is unknown and difficult to predict without routine and widespread testing.

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When determining the most appropriate daily parenteral copper and manganese doses to meet metabolic requirements in the pediatric population for the proposed indication, the team considered the following factors:

- ASPEN guidelines
- Supportive published data identified by both the Applicant and the review team
- The possibility of copper and manganese contamination in PN administered to the target pediatric population
- The risk of deficiency against the risk of overdosage for both trace elements

The review team reviewed the following publications which the team identified as containing the most relevant information to inform pediatric copper dosing for Tralement:

- A French publication that described normal plasma copper concentrations observed in six patients, including at least four "infants" of unspecified age who were receiving TPN containing copper 20 mcg/kg/day. The authors recommended this dose for children (Ricour et al. 1977).
- A prospective trial in 20 cancer patients, ages 10 years to 69 years, who underwent evaluation of urinary excretion (n=8) and measurement of trace element serum levels after 29 courses of TPN (mean duration of TPN 22±2 days) supplemented with copper sulfate (total range 923 to 3,850 mcg/day; 21 to 105 mcg/kg/day) compared with un-supplemented patients (n=4; 14 to 30 years of age) (Lowry et al. 1981). Supplementation raised serum copper levels and un-supplemented patients had progressive decrease in serum copper levels during the fourth week of study. Supplementation of 60 to 65 mcg/kg/day maintained copper levels within the normal range. No evidence of copper deficiency or toxicity was noted at a wide range of daily copper intake. The authors did not specify the age distribution of the patients studied, including how many patients were less than 18 years of age.
- A prospective 3-week, randomized crossover trial evaluating copper metabolism and requirements in 24 patients, ages 15 years to 73 years receiving TPN (Shike et al. 1981). This trial included one pediatric patient, a 15-year-old (40 kg) with Crohn's disease receiving TPN due to bowel rest in the first phase of the study. Patients in the first phase (n=24) were divided into three groups and randomly assigned to one of the following regimens of copper chloride supplementation: A- 0 mg; B- 0.8 mg and C- 1.6 mg. However due to copper contamination of the TPN solutions, mean daily input of copper from these solutions, before supplementation was approximately 0.25 mg. Therefore, the total copper infused in each group was: A- 0.25 mg, B- 1.05 mg, and C- 1.85 mg. Each group remained on each regimen for 1 week. Stool, gastrointestinal drainage, and urine were collected and analyzed for copper. Results showed that patients achieved neutral copper balance through an assumed total copper exposure of 250 mcg/day from the copper contamination in PN solution; no additional copper in the PN solution was required. The authors concluded from these results that 300 mcg/day is the amount of copper needed to achieve balance in adults maintained on TPN.

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- A single-center retrospective review (March 2007-April 2013) of medical records from hospitalized pediatric patients from birth to 24 years of age receiving PN either supplemented with 20 mcg/kg/day of copper or not supplemented with copper (Johnsen et al. 2017). In total, 751 supplemented pediatric patients and 90 pediatric patients not supplemented had serum copper levels measured at a mean of 20 days of PN (range 1 day to 119 days). The authors found a 1.25-fold higher mean serum copper concentration in supplemented patients than those who received no copper supplementation.

The ASCN Committee noted that copper deficiency was reported in adults and pediatric patients who received PN and that the risk of deficiency appears to be greater in those with losses due to copper-containing biliary secretions. Early features of copper deficiency typically consist of osteoporosis followed by neutropenia and an iron-resistant microcytic anemia. Later, more severe skeletal defects can develop. Other features in preterm infants may include neurological abnormalities, anorexia, failure to thrive, and hepatomegaly. The greatest concern with copper overdose is the possibility of liver damage.

The review team evaluated the following publications which the team identified as containing the most relevant information to inform pediatric manganese dosing for Tralement:

- A randomized controlled trial comparing whole blood manganese levels in 244 neonates (mean gestational age of 32.8 weeks and mean birth weight of 1.84 kg) who were admitted to the neonatal intensive care unit and expected to require a minimum of two weeks of TPN (Fok et al. 2001). Patients were randomly assigned to receive low (n=123; 1 mcg/kg/day) or high (n=121; 55 mcg/kg/day) dose manganese. A subgroup analysis on Day 14 of TPN showed a significantly lower median peak in whole blood manganese level in the low dose than the high dose group, but the authors concluded that the neonatal manganese requirement was unknown.
- A retrospective cohort analysis (November 2011 through March 2015) of 36 hospitalized patients from birth to less than 18 years of age receiving TPN (mean ± SD duration, 108±104.2 days) supplemented with 1 mcg/kg/day of manganese (Greene et al. 2016). Twenty-five percent (9/36) had a measured whole blood manganese level above the normal range (4.0 to 17.9 mcg/L).
- A retrospective review (March 2007 through April 2013) comparing levels of selenium, manganese, and iodine in 597 hospitalized patients, ranging from “preterm infants to teenagers”, who received 1 mcg/kg/day manganese supplementation (those weighing less than 25 kg) or 100 mcg/day (for those weighing 25 kg or more) and who received no manganese supplementation (n=36). Whole blood manganese levels were measured after patients had been on TPN for a mean of 3 weeks, and results showed high whole blood manganese levels in patients both receiving and not receiving manganese supplementation. Based on these data, the institution discontinued routine supplementation of manganese (Johnsen et al. 2017).

When determining the most appropriate daily manganese dose to meet metabolic requirements in the pediatric population, the review team weighed the risk of manganese

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deficiency against the risk of manganese overdosage. Manganese deficiency in animal species results in impaired skeletal development and ataxia, but there is no published clinical evidence of manganese deficiency in pediatric patients.

Iatrogenic manganese toxicity due to manganese exposure via TPN has been described in both adults and pediatric patients, but this safety signal is not well-characterized in either population. Modifiable factors which may impact hypermagnesemia-induced toxicity include the parenteral manganese dose, the duration of manganese supplementation, and the presence of underlying co-morbidities which may predispose patients to developing hypermanganesemia. Published reports of manganese toxicity are generally described in adults receiving greater than 500 mcg/day of manganese and pediatric patients receiving greater than 40 mcg/kg/day. Several publications suggest there is an association between long-term TPN, increased whole blood manganese levels, and brain manganese deposition in the basal ganglia as detected by T1-weighted MRI. MRI findings of manganese deposition in the basal ganglia have been associated with neuropsychiatric adverse reactions in patients but not all patients are symptomatic, so the clinical implications of central nervous system deposition are not clear. Because manganese is primarily excreted through bile, hypermagnesemia can occur in the presence of liver disease and decreased biliary excretion. Patients on long-term TPN are particularly susceptible to development of biliary stasis or obstructive jaundice and may develop excess tissue manganese accumulation as a result.

The ASCN Committee recommended a manganese dose of 1 mcg/kg/day, including for preterm and term neonates, with a maximum daily dose of 50 mcg/day and noted at the time that amounts 10-fold higher have been administered without toxicity. The ASCN Committee recommended against manganese supplementation in the presence of cholestatic liver disease and obstructive jaundice. Similar to copper contamination, manganese contamination in PN solutions can also be large enough to meet calculated needs even without supplementation. Iatrogenic manganese toxicity due to excessive manganese exposure via TPN has been described in pediatric patients. Publications evaluated by the review team to inform the scope of manganese toxicity reported in pediatric patients include the following:

- A 1-year cross-sectional study of the prevalence of hypermagnesemia in 57 children (median [range] age 9 months [1 month to 162 months]) receiving TPN for more than 2 weeks (median [range] duration of 1.25 months [0.5 months to 17 months]) (Fell et al. 1996). Children weighing less than 10 kg received manganese supplementation at a dose of 1 mcmol/kg/day (55mcg/kg/day) and children weighing 10 kg or more received 0.8 mcmol/kg/day (44 mcg/kg/day). Study results showed that 79% (45/57) had whole blood (WB) manganese concentrations above the reference range of 72 to 210 nmol/L. The highest WB manganese levels were found in the youngest children. There was a significant correlation between WB manganese concentration and AST concentration ($r = 0.64$; $p<0.001$). The authors further analyzed a subset of 11 children with elevated WB manganese concentration (median [range] concentration of 1,303 nmol/L [615 to 1,840 nmol/L]) and cholestatic liver disease and noted that seven of the 11 children had a decrease in plasma bilirubin level and decreased AST by 8 months after decreasing or discontinuing manganese supplementation. Seven patients in the overall cohort

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received TPN for more than 2 years while receiving manganese supplementation at a dose of 0.1 to 0.6 mcmol/kg/day (5.5 to 33 mcg/kg/day); basal ganglia abnormality on T1-weighted MRI scans were observed in more than 50% (4/7) of these patients. Patients with basal ganglia deposition did not have any signs of neurologic abnormalities. The authors concluded that central nervous system deposition of manganese can occur within 8 months of manganese supplementation and that the long-term effect of this deposition on the developing brain is unclear.

- A case report and case series of hypermagnesemia in pediatric patients with cholestatic liver disease who were receiving long-term TPN (Reynolds et al. 1994). The case report describes a 5-year-old girl, born at 35 weeks gestational age with intrauterine growth retardation, who began TPN after undergoing a laparotomy for intestinal resection and restoration of intestinal continuity due to jejunal atresia. She was diagnosed with cholestatic liver disease 3 months after starting TPN and 4 months later was diagnosed with developmental delay, abnormal dystonic movements of both arms, and microcephaly. An MRI obtained at age 12 months showed basal ganglia changes. Her WB manganese concentration at age 17 months was 1,740 nmol/L. The period of time between onset of neurologic symptoms and MRI scan was not specified in the publication. The authors also did not describe results of WB manganese concentrations prior to 17 months of age. The authors further analyzed WB manganese concentrations in a larger cohort of 53 children who had received TPN for more than 6 weeks and noted that WB manganese concentrations were greater than 360 nmol/L in two-thirds (35/53).
- A case report of basal ganglia deposition associated with hypermagnesemia and neurological symptoms in a 5-year-old Japanese boy who had received TPN supplemented with 10 mcmol/day (550 mcg/day) of manganese for 2 years starting at age 10 months (Ono et al. 1995). He underwent a T1-weighted MRI at 4.5 years of age that showed bilateral symmetrical hyperintense lesions in the basal ganglia. Five months after manganese was removed from his TPN, his WB manganese level decreased from 135 mcg/L to 20 mcg/L (normal range 14.6$\pm$4.7 mcg/L). A second MRI showed improvement in the hyperintense lesion. He had been experiencing severe headaches and amnesia which disappeared before the manganese was discontinued.
- A case report of basal ganglia deposition associated with hypermagnesemia and neurological symptoms in a 2-year-old who had received TPN supplemented with 83 mcg/kg/day of manganese for 14 months starting at age 8 months (Komaki et al. 1999). The child began developing a tremor and generalized tonic-clonic seizures 14 months after starting TPN that were increasing in frequency. Mild psychomotor retardation, hyperactivity, and frequent static and intention tremor were also described. T1-weighted MRI showed symmetrical areas of hyperintensity and the WB manganese concentration was 9.7 mcg/L. Three months after discontinuation of manganese, the WB manganese concentration normalized and the seizures, tremor, and MRI abnormalities resolved.
- A case report of basal ganglia deposition associated with hypermagnesemia and neurological symptoms in a 10-year-old girl who had received TPN supplemented with

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8 mcg/kg/day of manganese for 3 months for short bowel syndrome (Hsieh et al. 2007). She presented with tonic clonic seizures, decreased level of consciousness, and fever. A brain MRI showed symmetric high intensity signal on T1 weighted image in the basal ganglia. The WB manganese level was 3.7 mcg/dL (reference range 0.4 to 1.4 mcg/dL).

Collectively, these publications describe manganese toxicity in children 5 years of age and younger who had been receiving manganese supplementation ranging from 8 to 82 mcg/kg/day. Four of these publications described neurological signs and symptoms associated with hypermagnesemia in pediatric patients who had received TPN for a duration of 3 months to up to 24 months. WB manganese was used to monitor manganese exposure in all the publications.

Based on review of available published data as described above, Division of Hepatology and Nutrition (DHN) recommends approval of Tralement in pediatric patients weighing 10 kg and greater provided labeling conveys to prescribers that additional supplementation with the individual trace elements may be needed. DHN plans to recommend pediatric dosages of 0.2 mL to 0.8 mL to patients in four weight strata. See Table 25.

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Table 25. Amount of Individual TEs Provided by Tralement Per Recommended Pediatric Dosage of Tralement for Proposed Indication

		Weight of Pediatric Patients (in kg)*			
Individual TEs	**Recommended Dosage of TE**	**10–19**	**20–29**	**30–39**	**40–49**
Zinc[a]	50 mcg/kg/day (up to 3,000 mcg/day)	32–60	41–60	46–60	49–60
Copper[b]	20 mcg/kg/day (up to 300 mcg/day)	3.2–6	4.1–6	4.6–6	4.9–6
Manganese[c]	1 mcg/kg/day (up to 55 mcg/day)	0.6–1.1	0.8–1.1	0.8–1.1	0.9–1.1
Selenium[d]	2 mcg/kg/day (up to 60 mcg/day)	0.6–1.2	0.8–1.2	0.9–1.2	1–1.2

Source: Developed by Tralement review team
All values are expressed as mcg/kg/day unless indicated otherwise.
* The recommended dosages of Tralement are 0.2 mL, 0.4 mL, 0.6 mL, and 0.8 mL for pediatric patients weighing 10–19 kg, 20-29 kg, 30–39 kg, and 40–49 kg, respectively.
[an] Additional supplementation with a single-ingredient **zinc** product is recommended for heavier patients in some of the weight bands.
[b] Additional supplementation with a single-ingredient **copper** trace element product is recommended.
[c] Accumulation of **manganese** in the brain can occur with long-term administration at doses higher than recommended *[see Warnings and Precautions (5.3)]*
[d] Additional supplementation with a single-ingredient **selenium** trace element product is recommended.
Abbreviations: TE, trace element

The recommended weight-based pediatric doses and corresponding volumes are anticipated to be added to the PN solution using an automated compounding device (ACD) or manually via a syringe at institutions which do not have ACD capabilities. The Applicant notes that, once primed and ready to deliver an individual patient's components to the PN solution bag, the ACD can accurately deliver a volume as low as 0.2 mL, which is the lowest recommended volume.[13]

This NDA included an agreed iPSP containing the Applicant's plan to provide a pediatric assessment with no planned requests for waiver or deferral of pediatric study requirements under the PREA. This application is subject to PREA study requirements because Tralement contains a novel fixed-dose combination of MTE that represents a new active ingredient, and the assessment will be considered complete in pediatric patients weighing 10 kg and greater. Tralement volumes less than 1 mL (0.1 mL, 0.25 mL, 0.5 mL) would not provide adequate copper, zinc, or selenium but would still provide an excess of manganese to patients weighing less than 10 kg. This information will be conveyed to prescribers in subsection 8.4 of Tralement labeling. DHN plans to issue a PMR under PREA for the Applicant to develop an age-appropriate and weight-appropriate formulation suitable for administration to patients weighing less than 10 kg for the same indication. (b) (4)

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

Table 26 summarizes major changes (addition, deletions, or modifications) made by the FDA to the proposed Prescribing Information by the Applicant. The rationale for the FDA recommendation is provided in the table based on the evidence from the literature and interactive review with the Applicant. Refer to Section 8 for specific information.

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Table 26. FDA Recommendations to the Prescribing Information (PI)

Section	Section Title	FDA Recommendation	Rationale
1	Indications and Usage	• Specify Tralement as a "combination of trace elements" in Highlights • Specify indicated population as "adult and pediatric patients weighing at least 10 kg"	• Emphasize the fixed combination and add the Established Pharmacologic Class • Clarify the approved patient population (see also Pediatric Use)
2	Dosage and Administration	• Add "interactions between cupric ion and ascorbic acid" • Modify dosage (1) adult and pediatric patients ≥50 kg, 1 mL per day; (2) pediatric patients 10 kg to 49 kg: weight-based dosage from 0.2 mL to 0.8 mL. Additional single element product of zinc, copper or selenium may be needed • Add normal range of blood concentrations for four elements	• Risk mitigation • Provide recommended dose, delivered dose, & needed single element for pediatric populations • Provide lower and upper thresholds for trace element blood concentration
4	Contraindications	• Add copper hypersensitivity • Move "pre-existing copper storage disease or hepatic copper overload" to Warnings and Precautions	• Evidence from literature • This is not an absolute contraindication given the patient population requiring TPN
5	Warnings and Precautions	• Add "neurologic toxicity with manganese" • Add "hepatic accumulation of copper and manganese" • Modify exposure to aluminum from Tralement • Delete (b) (4)	• Evidence from literature review • Risk mitigation • Quantitate aluminum exposure for Tralement • (b) (4)
6	Adverse Reactions	• Add "neurologic toxicity with manganese" • Add "hepatic accumulation of copper and manganese" • Add "hypersensitivity reaction with copper" • Delete " (b) (4)	• Evidence from the literature review • Risk mitigation • Evidence from literature • (b) (4)
8	Use in Specific Population	• Revise text for Pediatric Use to indicate Tralement is not approved for use in pediatric patients <10 kg because the product does not meet the needs of this subpopulation • Add "hepatic impairment" for copper and manganese	Risk mitigation
10	Overdosage	• Modify acute and chronic toxicity for all four elements	• High level summary and risk mitigation
11	Description	• Add structural formula and molecular weight for each element	• Useful information for trace element

Section	Section Title	FDA Recommendation	Rationale
12	Clinical Pharmacology	• Modify mechanism of action for each element • Revise the statement that pharmacodynamics is unknown for each element • Modify ADME information for copper and manganese in Section 12.3	• High level summary at molecular level • No information • Evidence from literature
16	How supplied/Storage and Handing	• Add “store admixed solution” information	• Useful information for users
17	Patient Counseling Information	• Add “neurologic toxicity with manganese” • Add “hepatic accumulation of copper and manganese” • Add “hypersensitivity reactions with copper”	• Risk mitigation

Source: The table is generated with reference from the original PI (version September 4, 2019) and the final PI (6/29/2020)
Abbreviations: TPN, total parenteral nutrition

12. Postmarketing Requirements and Commitment

Safety information in the literature (Takagi et al. 2002; Chalela et al. 2011; Jin et al. 2018; Amin and Shawkat 2019) shows that the administration of manganese at a dosage of 55 mcg per day and higher is associated with deposition of manganese in the basal ganglia, a finding on MRI scans of the brain. MRI findings of manganese deposition in the basal ganglia have been associated with neuropsychiatric adverse reactions in patients. While we are including this information in section 5 Warning and Precautions, this safety signal should be further evaluated by conducting a postmarketing study under section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act for postmarketing requirements (PMR). As an example of a potential regulatory outcome of this PMR, the results of this study could support a safe (and effective) dosage of less than 55 mcg per day as a source of manganese for parenteral nutrition when oral or enteral nutrition is not possible, insufficient or contraindicated.

The aim of this PMR is to find out if doses of manganese lower than 55 mcg per day might be sufficient for replacement and have fewer associated adverse reactions. The proposed trial will be prospective, (b) (4) randomized, and controlled (b) (4)

Therefore, based on appropriate scientific data, American Regent, Inc. agreed to conduct the following trials:

3877-01 Conduct a randomized controlled trial of Tralement versus a fixed-dose manganese-free combination trace element product to evaluate manganese in patients receiving long-term parenteral nutrition.

The timetable was submitted on June 5, 2020, which stated that the Applicant will conduct this trial according to the following schedule:

Draft Protocol Submission: September 2020

Final Protocol Submission: March 2021

Study Completion: March 2024

Final Report Submission: December 2024

Under the Pediatric Research Equity Act (PREA) (21 U.S.C.355c), the Applicant is required to provide a pediatric assessment for this product, including an age-appropriate and weight-appropriate formulation for use in the full pediatric population. Therefore, a PREA PMR will be issued to the Applicant to provide an age-appropriate and weight-appropriate formulation to ensure accurate dosing volumes of Tralement Injection for pediatric patients weighing less than 10 kg. The Applicant has agreed to the following PMR:

3877-02 Develop an weight-appropriate formulation for pediatric patients weighing less than 10 kg

The timetable was submitted on July 1, 2020, which states that the Applicant will provide the formulation according to the following schedule:

Final Report Submission: December 2020

13. Division Director Comments

This NDA review documents the evidence for the safe and effective use of Tralement for the indications of 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. The review teams identified the relevant publications in the literature and other scientific data, the so-called “totality of evidence”, that support the safe and effective dosing recommendations for each of the four trace elements contained in Tralement under the 505(b)(2) approval path. The review by the pediatrics team provides for a clear assessment of Tralement administration and why it’s important to have Tralement approved in the pediatric population greater than 10 kg. The risk of overdose of zinc, copper, and selenium in the pediatric population is balanced by Tralement dosing, or rather underdosing, and the labeling recommendations to supplement pediatric patients with individual trace elements provide for the safe and effective administration of Tralement in the

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pediatric population weighing greater than 10 kg. Safety concerns were identified by the review team and are appropriately conveyed in labeling, under Warnings and Precautions. One safety issue that was identified for postmarketing evaluation was manganese deposition in the basal ganglia of the brain with its associated potential for neurological toxicities. Although Warnings and Precautions also describe this safety issue appropriately, it has not been fully evaluated with the 55 mcg daily dose of manganese administered chronically. The Applicant agreed to conduct a 505 (o) safety PMR to further evaluate manganese deposition in the basal ganglia following chronic administration of Tralement. I concur with the review and approval action for this 505(b)(2) NDA. The applicant also agreed to continue their development of a new formulation of Tralement that would allow for safe and effective dosing in the pediatric population less than 10 kg. this will be issued under a Pediatric Research Equity Act (PREA) PMR.

14. Appendices

14.1. Financial Disclosure

Not applicable.

14.2. Systemic Review Framework

Briefly (in a few paragraphs) summarize the prevailing rationale for adding each individual TE to standard parenteral nutrition formulations:

- Include the best available evidence that this element is essential (animals/humans), mechanism of action, etc.
- It is anticipated that some of this information may come from textbooks (and constitute general medical knowledge); therefore, it does not need to be extensively written/supported
- This information can be used to write section 12.1 Mechanism of Action of the label.

Summarize the current ASPEN dosing recommendations in adults/pediatrics for each TE in relation to the proposed dosing for each TE:

- In a paragraph or two summarize the rationale and basis for the current ASPEN recommendations (2015) supported by primary literature references.
- Discuss any changes to the ASPEN recommendations over time and include the primary literature references to support the more recent changes in the recommendations.
- The recommendations for some of the elements (e.g., zinc) have not changed substantially since 1979. For zinc, provide more complete details as to etiology of the original recommendations.
- If societal guidelines are available, other than ASPEN, provide a discussion on any points of uncertainty or controversy between the guidelines with regards to best practices.

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Summarize the evidence to support the proposed dosing for each TE in parenteral nutrition:

- One table for adults and a separate table for pediatrics. These tables would be in addition to the tables numbered 1 through 4 found in your systematic literature reviews.
- Study design should focus on randomized controlled trials that look at each TE separately. However, other trials with multitrace elements can be grouped by type and assessed accordingly.
- Focus on studies that used TE measurement which is widely approved as accurate description of TE content, given that all TE content measurement are not accurate.
- The unit of doses should be the same across studies to allow for easier interpretation and comparability of studies. For example, micromolar units may be used, but the preferred units are mg or mcg.
- When providing the concentration of TE in whole blood/serum/plasma, specify the biologic matrix, provide units reported in the article and provide a conversion to the units used by U.S. laboratories, if different. For example, selenium is measured in serum and whole blood. Units include mcg/dL and mcmol/L. Report concentration in mcg/dL. Include reference ranges, when available.
- Include mention of whether patients were receiving total parenteral nutrition (TPN) only, TPN plus oral feeds, or TPN with TE supplementation.
- The data presented in this table should allow the reviewer to understand all the relevant aspects of the publication, sufficient to permit an understanding of the study results/conclusions without rereading the entire publication.
- Use the tables to summarize information on intravenous (IV) administration of TE in TPN (i.e., from the systematic review);
- Supplement the SR data using evidence from other patient populations/routes of administration (e.g., oral) using the best available data and supported by primary literature references.
- Integrate the data in the tables with the other available evidence in a narrative for each TE that considers the totality of the evidence (max of 3-5 pages).
- As part of the summary, describe the quality of the efficacy data, strengths and weaknesses, how persuasive, what are the limitations? What are the uncertainties in the available evidence to support the proposed dosing regimen?

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Table 27. Summary of Publications in Adults of Trace Element – According to the Efficacy Outcome Studied (i.e., Prevention of Deficiency (Maintenance), Development of Deficiency With Suboptimal Supplementation, or Deficiency That Responded to Supplementation)

Author/Year of Pub/ Ref #	Study Design[1]	Study Population[2]	Dose(s) Duration of Trt Reason for TE Supplementation Other Coadministered TEs	Efficacy Outcome Include Descriptive and/or Quantitative Information for Any of the Outcomes Provided Specify Clinical, Laboratory[3] and/or Radiological Outcomes	Comments[4]

[1] Study design to include design (RCT or other), number of patients on treatment, number on placebo (if applicable), primary disease.
[2] Study population to include demographics (age [mean ± SD], race, gender, country) and baseline characteristics (other comorbidities, pregnancy/lactation, renal impairment, hepatic impairment, elderly, etc.). Baseline TE concentrations (if available). Number of patients who discontinued.
[3] Laboratory includes both standard chemistries as well as the concentrations of TE in biologic fluids (blood, serum, etc.) measured during and at the end of study.
[4] The Comments column is a free text column to capture any other relevant information included in the publication.
Abbreviations: pub, publication; ref, reference; TE, trace element; trt, treatment

Additional TE specific comments:

Copper

- Copper can be added as various salts. Specify the salt form in the table (e.g., copper chloride vs copper gluconate).

Identify clinical conditions, medical settings, or population subgroups that may require higher or lower doses of each TE for parenteral nutrition.

- Briefly summarize what is known about the TE in Renal Impairment, Hepatic Impairment, Geriatric Use, and Pregnancy. This may involve integrating data from routes of administration other than IV.

Describe toxicities or adverse events associated with each TE, when used for parenteral nutrition.

- One table for adults and a separate table for pediatrics.
- See comments pertaining to Efficacy table above.
- Integrate the data in the tables with the other available evidence in a narrative for each TE that considers the totality of the evidence (max of 3-5 pages).
- As part of the summary, describe the quality of the safety data, strengths and weaknesses, how persuasive, what are the limitations? What are the uncertainties in the available evidence to support the proposed dosing regimen?

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Table 28. Summary of Publications of Trace Element – According to Safety or Toxicity Outcome Reported

Author/ Year of Pub/Ref #	Study Design[1]	Study Population[2]	Dose(s) Duration of Treatment Reason for TE Supplementation Other Coadministered TEs	Safety Outcome Include Descriptive and/or Quantitative Information for Any of the Outcomes Provided Specify Clinical, Laboratory[3] and/or Radiological Outcomes	Comments[4]

[1] Study design to include design (RCT or other), number of patients on treatment, number on placebo (if applicable), primary disease.
[2] Study population to include demographics (age [mean ± SD], race, gender, country) and baseline characteristics (other comorbidities, pregnancy/lactation, renal impairment, hepatic impairment, elderly, etc.). Baseline TE concentrations (if available). Number of patients who discontinued.
[3] Laboratory includes both standard chemistries as well as the concentrations of TE in biologic fluids (blood, serum, etc.) measured during and at the end of study.
[4] The Comments column is a free text column to capture any other relevant information included in the publication.

Overall risk/benefit assessment:

- Using the available evidence and any uncertainties about the quality/strength of the evidence presented above, do the data support adding the trace element to total parenteral nutrition to support the adult/pediatric indication of "maintaining serum levels" of each TE?
- Consider the risk of deficiency versus toxicity for each TE. Which drives the overall assessment?

14.3. Summary Recommendations on Daily Nutritional Trace Element Supplement From Consensus Groups and Guidelines

Table 29. Recommendations on Daily Nutritional Zinc Supplement

Age Group	IOM RDA[1] (Enteral)	IOM UL[1] (Enteral)	21 CFR 101[2] RDI	ASPEN (2012)[3] (Parenteral)	ASPEN (2019)[4] (Parenteral)	ESPGHAN/ESPEN/ ESPR/CSPEN[5] (Parenteral)
Preterm	NA	NA	NA	450–500 mcg/kg	400 mcg/kg	400–500 mcg/kg
0–6 months	0.2 mg (AI)	4 mg	3 mg	<3 mo: 250 mcg/kg >3 mo: 50 mcg/kg (max 5,000 mcg)	250 mcg/kg (3–10 kg)	<3 mo: 250 mcg/kg >3 mo: 100 mcg/kg (max 5,000 mcg)
7–12 months	3 mg	5 mg			50 mcg/kg (10–40 kg) (max 5000 mcg)	
1–3 years	3 mg	7 mg	3 mg	50 mcg/kg (max 5,000 mcg)		50 mcg/kg (max 5,000 mcg)
4–8 years	5 mg	12 mg	11 mg			
9–13 years	8 mg	23 mg				
14–18 years	M: 11 mg, F: 9 mg	34 mg			Adolescents >40 kg: 2–5 mg	
>18 years	M: 11 mg, F: 8 mg	40 mg		M: 11 mg, F: 8 mg	3–5 mg	3–5 mg
Lactation	14–18 yo: 13 mg 19–50 yo: 12 mg	14–18 yo: 34 mg 19–50 yo: 40 mg	13 mg	12 mg		
Pregnancy	14–18 yo: 10 mg 19–50 yo: 9.5 mg	14–18 yo: 34 mg 19–50 yo: 40 mg		11 mg		

[1] Institute of Medicine (US) Panel on Micronutrients (2000). Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington (DC), National Academies Press (US).
[2] Office of the Federal Register. Code of Federal Regulations Title 21 - FDA. In: FDA" US, editor.: Government Publishing Office; 2016. p. 33.
[3] Vanek VW, Borum P, Buchman A, Fessler TA, Howard L, Jeejeebhoy K, et al. ASPEN position paper: recommendations for changes in commercially available parenteral multivitamin and multitrace element products. Nutrition in clinical practice: official publication of the American Society for Parenteral and Enteral Nutrition. 2012;27(4):440–91.
[4] American Society Parenteral and Enteral Nutrition (2019, 12-20-2019). "Appropriate Dosing for Parenteral Nutrition: ASPEN Recommendations." from http://www.nutritioncare.org/uploadedFiles/Documents/Guidelines_and_Clinical_Resources/PN%20Dosing%201-Sheet-FINAL.pdf.
[5] Domellöf M, Szitanyi P, Simchowitz V, Franz A, Mimouni F, Braegger C, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals. Clinical Nutrition. 2018;37(6):2354-9.
Abbreviations: AI, adequate intake; ASPEN, American Society for Parenteral and Enteral Nutrition; CSPEN, Chinese Society of Parenteral and Enteral Nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition; ESPR, European Society for Pediatric Research; F, female; IOM, Institute of Medicine; M, male; NA, not applicable; RDA, recommended dietary allowance; RDI, reference daily intake; UL, tolerable upper intake level; yo = year-old

Table 30. Recommendations on Daily Nutritional Copper Supplement

Age Group	IOM RDA[1] (Enteral)	IOM UL[1] (Enteral)	21 CFR 101[2] RDI	ASPEN (2015)[3] (Parenteral)	ASPEN (2019)[4] (Parenteral)	ESPGHAN/ESPEN/ ESPR/CSPEN[5] (Parenteral)
Preterm				20 mcg/kg	20 mcg/kg	20 mcg/kg
0–6 months	200 mcg (AI)	ND	200 mcg	20 mcg/kg	20 mcg/kg	20 mcg/kg
7–12 months	220 mcg (AI)	ND				
1–3 years	340 mcg	1,000 mcg	300 mcg	20 mcg/kg	20 mcg/kg	20 mcg/kg
4–8 years	440 mcg	3,000 mcg	900 mcg	(max 500 mcg)	(max 500 mcg)	(max 500 mcg)
9–13 years	700 mcg	5,000 mcg				
14–18 years	890 mcg	8,000 mcg			200–500 mcg	
>18 years	900 mcg	10,000 mcg		300–500 mcg	300–500 mcg	300–500 mcg
Lactation	14–18 yo: 1,300 mcg 19–50 yo: 1,300 mcg	8,000 mcg 10,000 mcg	1,300 mcg			
Pregnancy	14–18 yo: 1,000 mcg 19–50 yo: 1,000 mcg	8,000 mcg 10,000 mcg				

[1] Institute of Medicine (US) Panel on Micronutrients (2000). Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington (DC), National Academies Press (US).
[2] Office of the Federal Register. Code of Federal Regulations Title 21 - FDA. In: FDA" US, editor.: Government Publishing Office; 2016. p. 33.
[3] Vanek VW, Borum P, Buchman A, Fessler TA, Howard L, Jeejeebhoy K, et al. ASPEN position paper: recommendations for changes in commercially available parenteral multivitamin and multitrace element products. Nutrition in clinical practice: official publication of the American Society for Parenteral and Enteral Nutrition. 2012;27(4):440–91.
[4] American Society Parenteral and Enteral Nutrition (2019, 12-20-2019). "Appropriate Dosing for Parenteral Nutrition: ASPEN Recommendations." from http://www.nutritioncare.org/uploadedFiles/Documents/Guidelines_and_Clinical_Resources/PN%20Dosing%201-Sheet-FINAL.pdf.
[5] Domellöf M, Szitanyi P, Simchowitz V, Franz A, Mimouni F, Braegger C, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals. Clinical Nutrition. 2018;37(6):2354–9.
Abbreviations: AI, adequate intake; ASPEN, American Society for Parenteral and Enteral Nutrition; CSPEN, Chinese Society of Parenteral and Enteral Nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition; ESPR, European Society for Pediatric Research; IOM, Institute of Medicine; RDA, recommended dietary allowance; RDI, reference daily intake; UL, tolerable upper intake level; yo, year-old

Table 31. Recommendations on Daily Nutritional Manganese Supplement

Age Group	IOM AI[1] (Enteral)	IOM UL[1] (Enteral)	21 CFR 101[2] RDI	ASPEN (2012)[3] (Parenteral)	ASPEN (2019)[4] (Parenteral)	ESPGHAN/ESPEN/ ESPR/CSPEN[5] (Parenteral)
Preterm	NA	NA	NA	1 mcg/kg	1 mcg/kg	≤1 mcg/kg
0–6 months	3 mcg	NA	0.6 mg	1 mcg/kg (max 50 mcg/d)	Term neonates: 1 mcg/kg	≤1 mcg/kg
7–12 months	600 mcg	NA			Children 10–40 kg: 1 mcg/kg (max 55 mcg)	≤1 mcg/kg
1–3 years	1.2 mg	2 mg	1.2 mg			≤1 mcg/kg (max 50 mcg)
4–8 years	1.5 mg	3 mg	2.4 mg			
9–13 years	M: 1.9 mg F: 1.6 mg	6 mg				
14–18 years	M: 2.2 mg F: 1.6 mg	9 mg			Adolescents >40 kg: 40–100 mcg	
>18 years	M: 2.3 mg F: 1.8 mg	9 mg		60–100 mcg	55 mcg	≤1 mcg/kg (max 50 mcg)
Lactation	2.6 mg	14–18 yo: 9 mg 19–50 yo: 11 mg	2.6 mg			
Pregnancy	2.0 mg	14–18 yo: 9 mg 19–50 yo: 11 mg				

[1] Institute of Medicine (US) Panel on Micronutrients (2000). Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington (DC), National Academies Press (US).
[2] Office of the Federal Register. Code of Federal Regulations Title 21 - FDA. In: FDA" US, editor.: Government Publishing Office; 2016. p. 33.
[3] Vanek VW, Borum P, Buchman A, Fessler TA, Howard L, Jeejeebhoy K, et al. ASPEN position paper: recommendations for changes in commercially available parenteral multivitamin and multitrace element products. Nutrition in clinical practice: official publication of the American Society for Parenteral and Enteral Nutrition. 2012;27(4):440–91.
[4] American Society Parenteral and Enteral Nutrition (2019, 12-20-2019). "Appropriate Dosing for Parenteral Nutrition: ASPEN Recommendations." from http://www.nutritioncare.org/uploadedFiles/Documents/Guidelines_and_Clinical_Resources/PN%20Dosing%201-Sheet-FINAL.pdf.
[5] Domellöf M, Szitanyi P, Simchowitz V, Franz A, Mimouni F, Braegger C, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals. Clinical Nutrition. 2018;37(6):2354–9.
Abbreviations: AI, adequate intake; ASPEN, American Society for Parenteral and Enteral Nutrition; CSPEN, Chinese Society of Parenteral and Enteral Nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition; ESPR, European Society for Pediatric Research; F, female; IOM, Institute of Medicine; M, male; RDA, recommended dietary allowance; RDI, reference daily intake; UL, tolerable upper intake level; yo, year(s) old

Table 32. Recommendations on Daily Nutritional Selenium Supplement

Age Group	IOM RDA[1] (Enteral)	IOM UL[1] (Enteral)	21 CFR 101[2] RDI	ASPEN[3, 4] (1998. 2004) (Parenteral)	ASPEN (2012)[5] (Parenteral)	ESPGHAN/ESPEN/ESPR/CSPEN[6] (Parenteral)
Preterm				Preterm neonates: 1.5–4 mcg/kg/day Term neonates: 2 mcg/kg/day Premature infants: 2–3 mcg/kg/day Infants: 1–3 mcg/kg/day (Max 100 mcg/day)	2 mcg/kg/day	7 mcg/kg/day 2–3 mcg/kg/day (max 100 mcg/day)
0–1 month	15 mcg/day	45 mcg/day	20 mcg/day			
1–6 months						
7–12 months	20 mcg/day	60 mcg/day				
1–3 years	20 mcg/day	90 mcg/day		1–3 mcg/kg/day (max 100 mcg/day)		
4–8 years	30 mcg/day	150 mcg/day	55 mcg/day			
9–13 years	40 mcg/day	280 mcg/day				
14–18 years	55 mcg/day	400 mcg/day		20–60 mcg/day		
>18 years					60–100 mcg/day	
Lactation	60 mcg/day		70 mcg/day			
Pregnancy	70 mcg/day					

[1] Institute of Medicine (U.S.) Panel on Dietary Antioxidants and Related Compounds. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academies Press; 2000.
[2] Office of the Federal Register. Code of Federal Regulations Title 21 - FDA. In: FDA" US, editor.: Government Publishing Office; 2016. p. 33.
[3] Greene HL, Hambidge KM, Schanler R, Tsang RC. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. Am J Clin Nutr. 1988;48(5):1324–42.
[4] Mirtallo J, Canada T, Johnson D, Kumpf V, Petersen C, Sacks G, et al. Safe practices for parenteral nutrition. JPEN Journal of parenteral and enteral nutrition. 2004;28(6):S39–70.
[5] Vanek VW, Borum P, Buchman A, Fessler TA, Howard L, Jeejeebhoy K, et al. ASPEN position paper: recommendations for changes in commercially available parenteral multivitamin and multitrace element products. Nutrition in clinical practice: official publication of the American Society for Parenteral and Enteral Nutrition. 2012;27(4):440–91.
[6] Domellöf M, Szitanyi P, Simchowitz V, Franz A, Mimouni F, Braegger C, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals. Clinical Nutrition. 2018;37(6):2354–9.
Abbreviations: ASPEN, American Society for Parenteral and Enteral Nutrition; CSPEN, Chinese Society of Parenteral and Enteral Nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition; ESPR, European Society for Pediatric Research; IOM, Institute of Medicine; RDA, recommended dietary allowance; RDI, reference daily intake; UL, tolerable upper intake level

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Table 33. Range of Concentrations of Manganese in Various Biomatrices From Health Subjects Reported in Literature

Biomatrix	Laboratory	Method	Reference Range (mcg/L)	n	Comments
Whole blood	(ARUP Laboratories 2019)	ICP-MS	4.2–16.5	n/a	- Reflects intra and extracellular Mn
	(Scottish Trace Element and Micronutrient Diagnostic and Research Laboratory 2020)	ICP-MS	3.8–15.4	n/a	- Reflect Mn intake over xx months - Slower responses to changes in dietary intake thus not commonly reported in studies
	(Dastych et al. 2016b)	GF-AAS	6.15–8.53	20	
	(Hardy 2009)		7.7–12.1	n/a	- Range may vary depending on geographical location and age
	(Takagi et al. 2002)	GF-AAS	5.2–24.0	46	
Serum/plasma	(Mayo Clinic Laboratories 2020)	ICP-MS	<2.4	n/a	Responds rapidly (within days to 1 week) to changes in Mn intake thus often used for supplementation studies Lower values in acute inflammatory state
	(Hardy 2009)		0.38–1.1	n/a	
	(Takagi et al. 2002)	GF-AAS	1.9–5.8	46	
	(Bertinet et al. 2000)	GF-AAS	0.6–5.5	30	
Erythrocytes	(Mayo Clinic Laboratories 2020)	ICP-MS	11–20.3	n/a	
	(Bertinet et al. 2000)	GF-AAS	5–41	30	
	(Fitzgerald et al. 1999)	GF-AAS	11–23	n/a	

Source: Reviewer generated based on literature review
Abbreviations: GF-AAS, graphite-furnace atomic absorption spectrometry; ICP-MS, inductively coupled plasma mass spectrometry; Mn, manganese; n/a, not applicable

14.4. Parenteral Dose and Blood Concentration of Manganese in Adult

Table 34. Daily Dose and Whole Blood Concentration of Manganese in Adults

Source	Design	# Pts	Daily IV Dose	Duration	$[Mn]_{WB}$ (mcg/L)	Reference Range (mcg/L)	Reliability of $[Mn]_{WB}$ as Marker of Mn Tissue Stores
(Wardle et al. 1999)	INT, CS, UNC	30	~3.3 mcg/kg [2.75–5.5 mcg/kg]	43 m [3–168 m]	19 subjects: 11.5–19.8 7 subjects: >19.8	4.0–11.5	N/A
(Bertinet et al. 2000)	INT, PROSP. CONTR	15	16.5–187 mcg → 0 mcg	12 m	24.7 (16.8–39) → 5.0 (2.0–15.5)	3–19.6	Poor
(Orimo and Ozawa 2001)	INT, CS, UNC	13	1,100 mcg	46±43 d (7–175)	58.8±24.7 (range 30.8–100.1)	8.2–25.3	Good [Mn] tested exclusively in Pts w/ (+) MRI

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Source	Design	# Pts	Daily IV Dose	Duration	$[Mn]_{WB}$ (mcg/L)	Reference Range (mcg/L)	Reliability of $[Mn]_{WB}$ as Marker of Mn Tissue Stores
(Takagi et al. 2001)	INT, PROSP. CONTR	11	1,100 mcg	99 m [13–225 m]	32±10	5.2–24.0	Poor $[Mn]_{WB}$ ∴ MRI R^2 0.59 i.e., 41% of (+) MRI was unexplained by $[Mn]_{WB}$
		11	→ 0 mcg	10 m [5–17 m]	32±10 → 12±2		
		11	→ 1,100 mcg	9 m [4–14 m]	10±2 → 45±20		
		11	→ 0 mcg	13 m [5–16 m]	45±12 → 10±2		
(Takagi et al. 2002)	INT, PROSP. CONTR	12	1,100 mcg	4–14 m	44±22	8–25	Poor $[Mn]_{WB}$ ∴ MRI R^2 0.59 i.e., 41% of (+) MRI was unexplained by $[Mn]_{WB}$
		10	→ 0 mcg	13–16 m	14±3		
(Iwase et al. 2002)	INT, PROSP. CONTR	32	1,100 mcg	0.5–0.75 m	Baseline 1–20 → After PN 15–50		Poor "monitoring of $[Mn]_{WB}$ cannot predict the early stage of brain Mn deposition during PN" "MRI is more useful than $[Mn]_{WB}$ for avoiding excessive Mn infusion in PN in the clinical setting"
(Papageorgiou et al. 2002) United States	INT, PROSP, UNC	40	300 mcg	3 d	Before surgery: 2.1±5.0 Day 1 postop: 1.8±1.0 Day 3 postop: 1.4±0.4	2.6±0.2 ($\bar{m}$±SE)	N/A
(Abdalian et al. 2013b) Canada	INT, CS, UNC	16	400±53 mcg	9.43±2.12 y	21.9±1.4	4.3–15.9	Poor 4/6 w/ normal $[Mn]_{WB}$ had (+) MRI
(Dastych et al. 2016a) Czechia	INT, CS, UNC	16	80–470 mcg	4–96 m	16.2 (12.9–20.4) [MED (range)]	7.4 [6.4–8.4] (Med [range])	Good MRI tested exclusively in Pts w/ high [Mn]

Reference ID: 4635033

Source	Design	# Pts	Daily IV Dose	Duration	$[Mn]_{WB}$ (mcg/L)	Reference Range (mcg/L)	Reliability of $[Mn]_{WB}$ as Marker of Mn Tissue Stores
(Jin et al. 2018) Canada	INT, PROSP, CONTR	11	400±53 mcg → 0 mcg	60 m	17.7 [6.0–75.1] → 10.8 [5.4–35.4]	4.3–15.9	Poor 3/8 cases w/ (+) MRI had normal $[Mn]_{WB}$

Source: Data Generated by the Reviewer Based on Published Literature. The reviewer converted molar quantities and concentrations into the respective mass to harmonize the presentation of data.
Abbreviations: CONTR, controlled; CS, cross-sectional; d, day; INT, interventional; IV, intravenous; m, month; $[Mn]_{WB}$, whole-blood manganese concentration; MRI, magnetic resonance imaging; PROSP. prospective, pts, patients; RETRO, retrospective; UNC, uncontrolled; y, year

Table 35. Daily Dose and Plasma or Serum Concentration of Manganese in Adults

Source	Design	# Pts	Daily IV Dose	Duration	$[Mn]_S$ (mcg/L)	Reference Range (mcg/L)	Reliability of $[Mn]_{WB}$ as Marker of Mn Tissue Stores
(Phillips and Garnys 1981)	INT, PROSP. CONTR	8	100–300 mcg	7 d	Not given	Not reported	N/A
(Shenkin et al. 1986)	INT, CS, INC	56	<1,100 mcg	3–48 m	0.5–2.2	0.38–1.48	N/A
			1,100 mcg		0.5–3.8		
			2,200 mcg		0.5–19.2		
(Falbe et al. 1987)	INT, PROSP. CONTR	25	300 mcg	28 d	<Range 0.71±0.40 (n=11); In range 2.5±0.86 (N=14)	15–35	N/A
(Shenkin et al. 1987)	INT, PROSP, CONTR	21	275 mcg	21 d	Before surgery: 1.2±0.6 ($\bar{m}$±SD) 21 days post-op: 1.8±1.7	0.38–1.6	N/A
(Malone 1989)	INT, PROSP. CONTR	24	2,200 mcg → 275 mcg	5±2.7 m [1–9 m]	Pre 66.3±37.2 → Post 25.9±15.6	0.4–1.4	N/A
(Forbes and Forbes 1997)	INT, CS, UNC	49	110 mcg	64 m (1–175 m)	0.55–2.36	0.27–0.82	N/A
(Reynolds et al. 1998)	INT, PROSP. UNC	3	230 mcg → 0 mcg	28–63 m	5.3 → 1.6	0.38–1.48	Good MRI tested exclusively in Pts w/ high [Mn]
		6	120–230 mcg	9–76 m	1.2–2.7		
(Wardle et al. 1999)	INT, CS, UNC	30	~3.3 mcg/kg [2.75–5.5 mcg/kg]	43 m [3–168 m]		Not reported	N/A
(Reimund et al. 2000)	INT, CS, UNC	27	?	?	1.97±0.9 (0 low, 2 normal, 25 high)	0.9±0.5	N/A

Source	Design	# Pts	Daily IV Dose	Duration	$[Mn]_S$ (mcg/L)	Reference Range (mcg/L)	Reliability of $[Mn]_{WB}$ as Marker of Mn Tissue Stores
(Bertinet et al. 2000)	INT, PROSP. CONTR	15	16.5–187 mcg → 0 mcg	12 m	3.4 (1.8–4.6) → 1.1 (0.4–2.4)	0.6–5.5	Poor
(Reimund et al. 2000)	INT, CS, UNC	21	~500 mcg	30.5 m [3±132 m]	1.96±1.1	0.81±0.4	Good MRI tested exclusively in Pts w/ high [Mn]
(Takagi et al. 2001)	INT, PROSP. CONTR	11	1100 mcg	99 m [13–225 m]	4±0.9	5.2–24 mcg/L	Poor
			0	10 m [5–17 m]	4.0±0.9 → 2.0±0.5		
			1100 mcg	9 m [4–14 m]	2.0±0.7 → 3±1.0		
			0	13 m [5–16 m]	2.1±0.2 → 1.8±0.2		
(Takagi et al. 2002)	INT, PROSP. CONTR	12	1100 mcg	4–14 m	28±24	5.2–24 mcg/L	Poor
			0 mcg	13–16 m	14±3		
(Siepler et al. 2003)	INT, RETRO, CONTR	67		~60 m	44/67 (70.1%) subjects > ref range	Not reported	N/A
(Hardy et al. 2008)	INT, PROSP, CONTR	6	275 mcg (1–6 d/w)	1–25 m	0.22–60.5	0.3–1.8	"There is no reliable biomarker of whole body Mn status. $[Mn\}_S$ is very variable and generally not a good indicator of body stores. $[Mn\}_{WB}$ or $[Mn\}_{RBC}$ are more accurate and reproducible."
(Btaiche et al. 2011)	INT, CS, UNC	26	470±100 mcg	≥12 m	1.69±0.4	0.4–0.8	N/A
(Ishizuka et al. 2011b)	INT, PROSP, UNC	46	55 mcg	28 d	Before 14±7 After 28 days: 16±5	8–25	N/A
(Akutsu et al. 2012)	INT, PROSP. CONTR	18	55 mcg/day vs. 0 mcg	1 m	0.97–1.07 vs. 1.34–1.20	Not reported	N/A

Source: Data Generated by the Reviewer Based on Published Literature. The reviewer converted molar quantities and concentrations into the respective mass to harmonize the presentation of data.
Abbreviations: CONTR, controlled; CS, cross-sectional; d, days; d/w, days per week; INT, interventional; IV, intravenous; m, month; $[Mn]_{RBC}$, red blood cell manganese concentration; $[Mn]_S$, plasma or serum manganese concentration; $[Mn]_{WB}$, whole blood manganese concentration; MRI, magnetic resonance imaging; N/A, not applicable; PROSP. prospective; pts, patients; RETRO, retrospective; UNC, uncontrolled

Table 36. Daily Dose and Erythrocyte Concentration of Manganese in Adults

Source	Design	# Pts	Daily IV Dose	Duration	$[Mn]_{RBC}$ (mcg/L)	Reference Range (mcg/L)	Reliability of $[Mn]_{WB}$ as Marker of Mn Tissue Stores
(Fitzgerald et al. 1999)	INT, CS, CONTR	21	500 mcg	1–167 m	5.6–43 [15 subjects > Reference Range]	11–23	Good MRI tested exclusively in Pts w/ high [Mn]
(Bertinet et al. 2000)	INT, PROSP. CONTR	15	16.5–187 mcg → 0 mcg	12 m	0.07 → 0.03	0.04 (0.01–0.12)	Poor

Source: Data Generated by the Reviewer Based on Published Literature. The reviewer converted molar quantities and concentrations into the respective mass to harmonize the presentation of data.
Abbreviations: CONTR, controlled, CS, cross-sectional, INT, interventional, IV, intravenous; $[Mn]_{RBC}$, red blood cell manganese concentration; $[Mn]_{WB}$, whole blood manganese concentration; PROSP. prospective, pts, patients; RETRO, retrospective; UNC, uncontrolled

14.5. Parenteral Dose and Blood Concentration of Manganese in Children

Table 37. Daily Dose and Whole Blood Concentration of Manganese in Children

Source	# Pts	Age	Daily IV Dose	Duration	$[Mn]_{WB}$ (mcg/L)	Reference Range (mcg/L)	Reliability of $[Mn]_{WB}$ as Marker of Mn Tissue Stores
(Fell et al. 1996)	57 (Survey)	MED =9 m [1–162m]	55 mcg/kg (<10 kg) - 44 mcg/kg (>10 kg)	1–25 m (0.5–17 m)	34 (59%): 11.5–33.8 11 (19%): 33.8–101	4.0–11.5	Good MRI tested exclusively in Pts w/ high [Mn]
	11 TBili ≥6 mg/dL, (Nl <.7 mg/dL)	MED =7 m [4–17 m]	44 mcg/kg (before) → 0 mcg/kg	2–9 m 4 died w/in 2 m	33–101 (before) → 14–60		
	6 (>24 m PN)	MED =66 m [27–121m]	5.5–33 mcg/kg	>24 m	13.7–28.4		
(Quaghebeur et al. 1996)	4	$\bar{m}$=42 m [6–121m]	Mn 1.0 mcmol/kg (<10 kg BW) or 0.8 mcmol/kg (>10 kg).	TPN for 3–108 months.	46.1–101.2	<13.2	N/A

Source	# Pts	Age	Daily IV Dose	Duration	$[Mn]_{WB}$ (mcg/L)	Reference Range (mcg/L)	Reliability of $[Mn]_{WB}$ as Marker of Mn Tissue Stores
(McMillan et al. 2008)	54	MED Wt ~3 kg [0.76-65.2 kg]	n=49 $\bar{c}$ BW <25 kg → Mn 5 mcg/kg. n=5 $\bar{c}$ BW >25 kg → Mn 150 mcg	Nor given	20 $\bar{c}$ CBili >2 mg/dL; 21 $\bar{c}$ Mn >17 Cholestasis not associated $\bar{c}$ high Mn	4.2–16.5	N/A
(Aschner et al. 2015)	58	n=39: gestational age 27 wks. At MRI: 13 wks	Total Mn exposure: MED 415 mcg (IQR 312–760)	13 wks	13.2 (IQR: 9.7–17.0)	8–12	Poor "No significant associations were observed between $[Mn]_{WB}$ and MRI"
		n=19: gestational age 37 wks. At MRI: 2 wks	Total Mn exposure: MED 5 mcg (IQR 0–101)	2 wks			
(Johnsen et al. 2017)	561	<5 kg: n=315 $\bar{m}$=2.4±1.2 kg	1 mcg/kg	~4 w	29% >16.5	4.2–16.5	N/A
		≥5 kg: n=246 $\bar{m}$=21.7±18.2 kg			10% >16.5		
	36	<5 kg: n=22, $\bar{m}$=2.09±1.0 kg	None	~4 w	41% >16.5		
		≥5 kg: n=14 $\bar{m}$=19.3±18.8 kg.			36% >16.5		

Source: Data Generated by the Reviewer Based on Published Literature. The reviewer converted molar quantities and concentrations into the respective mass to harmonize the presentation of data.
Abbreviations: BW, body weight; CONTR, controlled; CS, cross-sectional, INT, interventional; IQR, interquartile range; IV, intravenous; Mn, manganese; $[Mn]_{WB}$, whole-blood manganese concentration; MRI, magnetic resonance imaging; PROSP. prospective, pts, patients; RETRO, retrospective; UNC, uncontrolled,

Table 38. Daily Dose and Plasma Concentration of Manganese in Children

Source	# Pts	Age	Daily IV Dose	Duration	$[Mn]_S$ (mcg/L)	Reference Range	Reliability of $[Mn]_S$ as Marker of Mn Tissue Stores
(Hambidge et al. 1989)	9	MED 14m [1–210m]	~>10 mcg/L	1 d–17 m	0.79±0.18	0.89±0.18	N/A
	5	MED 7m [3–169m]		3 w–14 m	3.06±2.07		

Source: Data Generated by the Reviewer Based on Published Literature. The reviewer converted molar quantities and concentrations into the respective mass to harmonize the presentation of data.
Abbreviations: CONTR, controlled; CS, cross-sectional; d, day(s); INT, interventional; IV, intravenous; m, month(s); $[Mn]_S$, plasma or serum manganese concentration; PROS, prospective; RETRO, retrospective; UNC, uncontrolled

14.6. Manganese Contamination of Parenteral Products

Table 39. Manganese Contamination Analysis

Source	Synopsys
(Kurkus et al. 1984) United States	19 products tested. Aminosyn 10% amino acid solution: Mn 5.2–17.0 mcg/L. Veinamine 8%, FreAmine II, 8.5%, Travasol 10%, and Nephramine: all < Mn 6.7 mcg/L. Dextrose 50%: Mn 0.64–2.5 mcg/L. Potassium phosphate: 280 mcg/L, magnesium sulfate 50% up to 225 mcg/L, and Berocca C 245.8 mcg/L (actual contributions to daily TPN <3.3 mcg /day). Calculated Mn content in TPN with varying source materials ranged 8.1–21.7 mcg/day.
(Hambidge et al. 1989) United States	"Analysis of different lots of MVI Pediatric (Armour) and of Aminosyn (Abbott) (used in children) indicated that the Mn "contamination" level in some final infusates could exceed 10 mcg/L.
(Isegawa et al. 1990) Japan	Mn in lipid solutions in Japan <1.5 mcg/L Mn in vitamin, insulin, and heparin preparations <0.1 mcg/vial.
(Bertinet et al. 2000) Italy	Mn contaminant per TPN bag: 5 mcg/L (1.5 18.2 mcg/L) Median (range)
(Buchman et al. 2001) United States	4 TPN solutions (1 renal, 2 standard adult, and 1 standard pediatric formula) were analyzed with ICP-MS.
(Malecki et al. 1995) United States	TPN solutions containing no added Mn with by analysis 6.6 mcg/kg rat/d. Commercial TPN solutions of amino acids (FreAmine III, McGaw Inc, Irvine, CA), dextrose, lipid emulsion (Intralipid, Kabi-Vitrum, Alameda, CA), electrolytes, vitamins, choline, iodide, selenium, zinc, copper, chromium, and manganese.
(Pluhator-Murton et al. 1999) Canada	8 products tested (3 lots each) Mn common contaminant, present in 5 of the tested products Amount of Mn contaminant in a 2L bag: ~38 mcg (expected 560, measured 598 mcg/2L)
(Takagi et al. 2002) Japan	Mn (2–4 mcg/L) in the glucose and electrolyte solutions and <0.5 mcg/L) in the amino acid solutions. Thus, the Mn contaminants (1200 mL glucose and electrolyte solution +600 mL amino acid solution each day) was 3–6 mcg/d. Mn eluted from bags, infusion devices, catheters, and filters <1 mcg/L (J Isegawa, Ajinomoto Co, Inc, unpublished observations, 2001).
(Olson et al. 2019) United States	65 products (32 unique components) tested Mn common contaminant, present in ~ half of all tested products. Adult PN formulation predicted to contain Mn 5.5 to 25.2 mcg. Pediatric PN formulation predicted to contain Mn 9.9 mcg Neonatal PN formulation predicted to contain Mn 1.4 mcg
(Kirk et al. 2019) United Kingdom	Mn levels in 6 unused "Mn-free" HPN bags was 4.4 mcg/L.

Abbreviations: HPN, home parenteral nutrition; Mn, manganese; PN, parenteral nutrition; TPN, total parenteral nutrition

Reference ID: 4635033

14.7. Synopsis of Studies Evaluating Parenteral Manganese

Table 40. Synopsis of Studies Evaluating Parenteral Manganese in Adults

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose Duration	Reported Findings	Comments
(Mirowitz et al. 1991) United States	To determine if changes in MRI signal intensity are present in patients on TPN therapy and to investigate the cause and potential clinical significance.	9 patients 2 men and 7 women, 51–74 y/o (mean, 58.9 years).	3–4 ml of 5-E MTE (Zn, Cr, Cu, Mn, and Se). Duration: 5 m to 11 y (mean, 5.3 y).	No blood tests In all 9 patients, globus pallidus markedly HI on Tl-weighted images. (+) neurologic questionnaire in 5 pts: 2 w/ memory loss, weakness, and fatigue. 1 (CVA during TPN) w/ difficulty in initiating movements and walking, generalized weakness, and slowing of responses. 2 w/ memory loss, episodes of confusion, slowing of response time, imbalance, seizures, weakness, fatigue, and spasms.	Prospective single arm Suspected role of Mn
(Forbes and Jawhari 1996) United Kingdom	Letter to the Editor To examine the prevalence of high $[Mn]_{WB}$ and cholestasis Design: PROS INT, UNC	29 adults on HPN	Dose: $\bar{m}$ 3 mcg/kg/d (range 1.1–5.5) Duration: 48 mo (range 3 mo- 14 yr)	High $[Mn]_{WB}$: n=25 (86%) ($\bar{m}$ 16.4 mcg/L, range 7.3–35.6 mcg/L) Toxic $[Mn]_{WB}$: n=7 (24%) (>19.8 mcg/L) No patient w/ neurologic signs (reference range $[Mn]_{WB}$ <11.5 mcg/L). Normal LFTs: n=12 Mild intrahepatic cholestasis (stable); n=11 AlkPhos 165 U/L (69–539) GGT 121 U/L (13–837) No correlation $[Mn]_{WB}$ ∴ cholestasis	
(Forbes and Forbes 1997) United Kingdom	To document the $[Mn]_S$ within the HPN program. Design: INT, UNC	49 patients 17 M, 32 F 46 y/o (range 24–66 y).	Mn 110 mcg/day Duration: 64 mo (range 1–175 mo)	$[Mn]_S$ 550–2.36 mcg/L 1 patient in in the normal range 48 patients above the normal Reference range $[Mn]_S$ 0.27–0.82 mcg/L	

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose Duration	Reported Findings	Comments
(Wardle et al. 1999) United Kingdom	To investigate the incidence of high $[Mn]_{WB}$ in adult patients on long-term PN (HPN group) and in patients with chronic liver disease (CLD group). Design: INT, CS, UNC	HPN group – n=30 on long-term HPN (9 M, 21 F) Age range: 24–66 y/o. Dx: resected Crohn's (n=15), functional intestinal failure (n=2), miscellaneous causes of resection (n=13).	HPN group Dose: Mn: $\bar{m}$ ~3.3 mcg/kg (range 2.7–5.5 mcg/kg) Duration: $\bar{m}$ 43 mo (range 3–168).	HPN group $[Mn]_{WB}$ In 4 subjects: <11.5 mcg/L In 19 subjects: 11.5–19.8 mcg/L In 7 subjects >19.8 mcg/L	Cross sectional
		CLD group – n=10 $\bar{c}$ chronic liver disease (CLD) & cholestasis (4 M, 6 F); Age range: 39–74 y/o Dx: alcoholic liver disease (n=7), cirrhosis (NOS n=1), and primary biliary cirrhosis (n=2).	CLD group No IV Mn	CLD group $[Mn]_{WB}$ <11.5 mcg/L in all 10 subjects (reference range $[Mn]_{WB}$ 4.0–11.5 mcg/L). No correlation of $[Mn]_{WB}$ with markers of cholestasis, Mg intake, or Mg duration	
(Reimund et al. 2000) France	To examine the association of $[Mn]_S$ with hepatic enzymes, markers of inflammation and immunity, and PN dose in HPN patients.	HPN (all >3 mo, $\bar{x}$ 30.5+36.7 mo) n=21 (6 F, 15 M) Age 54.6+14.2 y/o Healthy controls n=10	Dose: ~500 mcg Duration: 30.5 m [3–132 m]	**Test** **HPN Pts** **Vs.** **Controls** $[Mn]_S$ 1.96±1.1 Vs. 0.81±0.4 mcg/L p<0.001 AlkPhos 323+279 Vs. 79+18 IU/L p<0.001 g-GT 200+211 Vs. 27+10 IU/L p<0.01 AST 44+42 Vs. 23+8 IU/L p<0.05 TBili 9.9+10.9 Vs. 10.5+4.4 mcmol/L $[Mn]S \therefore$ AlkPhos r^2=0.26 p<0.0001	

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose Duration	Reported Findings	Comments
(Bertinet et al. 2000) Italy	To evaluate the effect of long term IV Mn on: (1) the cerebral MRI in HPN patients w/o neurologic signs or cholestasis; (2) the relationship between $[Mn]_S$, $[Mn]_{WB}$, and $[Mn]_{RBC}$ and neuroradiologic abnormalities. Design**:** INT, PROS, CONTR	15 patients 8 men and 7 women; median 54 y/o. WB-Mn, plasma -Mn, RBC-Mn, and brain MRI at start (time 0, t0) and after 1 year w/o IV Mn	Before study: Mn 110 mcg per day [range: 16.5-187 mcg per day] Duration: $\bar{m}$ 3.6 years (2–10 years) During 1-year study: Mn 0 mcg per day	Before: $[Mn]_{WB}$ 24.7 (16.8–39) mcg/L. [median (range)]. 10 of 15 patients (67%) w/ MRI accumulation in globus pallidus. After 1 year: $[Mn]_{WB}$ 5 (2–15.5) mcg/L (reference range $[Mn]_{WB}$ 3–19.6 mcg/L). Reduction in Mn accumulation confirmed by a marked reduction in globus pallidus signal, but regression was incomplete.	Single arm, Prospective

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose Duration	Reported Findings	Comments
(Takagi et al. 2001) Japan	To determine the temporal relationships between the MRI intensity and the whole-blood and plasma Mn with the aim of elucidating the potential of the MRI intensity to serve as an index of the *in vivo* manganese level. Design**:** INT, PROS, CONTR	11 patients (7 men, 4 women; 31-64 y/o) Diagnoses: short bowel syndrome (n=3), Crohn's disease (n=4), idiopathic intestinal pseudo-obstruction syndrome (n=2), and NOS diseases (n=2).	First period Mn 1,100 mcg for 99 months (range 13–225 months), then Second period Mn 0 mcg for 10 months (range 6–12 months), then Third Period Mn 1,100 mcg for 9.3 months (range 5–13 months), then Fourth period Mn 0 mcg for 13 months (range 5–16 months)	First period $[Mn]_{WB}$ Mn: 34±10 mcg/L, MRI (+): High 10, intermediate 1, absent 0 Second period $[Mn]_{WB}$ from 32±10 mcg/L to 12±2 mcg/L MRI (+): High 1, intermediate 1, absent 10 Third Period $[Mn]_{WB}$ from 10±2 mcg/L to 45±20 mcg/L MRI (+): High 10, intermediate 1, absent 0 Fourth period $[Mn]_{WB}$ from 45±12 mcg/L to 10±2 mcg/L MRI (+): High 0, intermediate 0, absent 11 (reference range $[Mn]_{WB}$ 5.2–24.0 mcg/L)	Single arm prospective. None of the patients showed any clinical symptoms of manganese intoxication (e.g., Parkinsonian-like neurologic abnormalities) or deficiency (e.g., abnormalities in lipid metabolism) that could be attributed to manganese administration.
(Orimo and Ozawa 2001) Japan	To report WB Mn and brain MRI in patients on HPN Design**:** INT, CS, UNC	13 Pts (5 males, 8 females, 70±19 yo)	Dose**:** Mn 1,100 mcg Duration**:** 46±43 d; range 7–175 d	$[Mn]_{WB}$ 58.8±24.7 mcg/L (range 30.8–100.1 mcg/L) MRI**:** 6 (+), 8 (-) for globus pallidus Mn accumulation	Neuro exam not different between before and after Mn IV infusion

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose Duration	Reported Findings	Comments
(Takagi et al. 2002) Japan	To investigate (1) the MRI intensity and T1 values in the globus pallidus of patients on home TPN, (2) the relations between blood Mn and the MRI variables, and (3) the optimal IV dose of Mn based on these variables. Design**:** INT, PROS, CONTR	12 patients (6 females, 6 males) on long term HPN. Mean age 43.5 y/o. (range 17 62 y/o)	First period 1100 mcg Mn for 9.4 months (range 4–14 months) Second period 0 mcg Mn for 14.6 months (range 13–16 months) Third period 110 mcg Mn for 15 months (range 13–19 months) Fourth period 55 mcg Mn for 17 months (range 11–19 months).	First period (1,100 mcg/d) $[Mn]_{WB}$: 44 mcg/L MRI c̄ high intensity (HI) findings: Present 9, intermediate 1, absent 0 Second period (0 mcg/d) $[Mn]_{WB}$ 13.7 mcg/L, MRI c̄ HI findings: Present 0, intermediate 0, absent 10 Third period (110 mcg/d) $[Mn]_{WB}$ 19.2 mcg/L MRI c̄ HI findings: Present 0, intermediate 6, absent 6 Fourth period (55 mcg/d) $[Mn]_{WB}$ 16.5 mcg/L MRI c̄ HI findings Present 0, intermediate 2, absent 8 (reference range $[Mn]_{WB}$ 5.2–24.0 mcg/L)	In each period, analyses were done during month 6 of intervention. 2 out of 10 patients had intermediate MRI after 6 months on Mn 55 mcg/d.

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose Duration	Reported Findings	Comments
(Iwase et al. 2002) Japan	To investigate the serial changes in $[Mn]_{WB}$ and brain MRI following perioperative PN therapy for gastrointestinal surgeries. Design**:** INT, PROS, CONTR	Intervention: pancreatoduodenectomy (PD) (n=6), esophagectomy (TE) (n=6), gastrectomy (TG) (n=18), colectomy (CR) (n=20) from 1988 to 1997. Controls: PD-control (n=5), TE-control (n=4), TG-control (n=9), CR-control (n=11) from 1998 to 1999.	Intervention: Mn 1,100 mcg per day. PD: 30±13 days TE: 33±13 days TG: 21±5 days CR: 24±7 days Controls: No Mn	Intervention group: MRI HI lesion of basal ganglia and $[Mn]_{WB}$ > ref range: PD: MRI (+) 4 out of 6; $[Mn]_{WB}$ (>ref range) 4 out of 6 TE: MRI (+) 3 out of 4 $[Mn]_{WB}$ (>ref range) 3 out of 4 TG: MRI (+) 4 out of 18 $[Mn]_{WB}$ (>ref range) 1 out of 18 CR: MRI (+) 5 out of 20. $[Mn]_{WB}$ (>ref range) 2 out of 20 Control group: No MRI HI lesions or $[Mn]_{WB}$ > ref range (reference range $[Mn]_{WB}$ 8.0–25.0 mcg/L).	Two-arm prospective, unblinded distribution
(Ishizuka et al. 2011b) Japan	To evaluate prospectively if PN patients receiving 55 mcg Mn show alterations of the $[Mn]_S$ levels of the TE. Design**:** INT, PROS, UNC	46 patients colorectal CA (n=20), small bowel obstr (n=11), complications after colorectal Sx (n=10) IBD (n=2) others (n=3).	55 mcg Mn per day Duration**:** 28 days	Baseline $[Mn]_S$: 14±7 mcg/L After 14 days $[Mn]_S$: 14±6 mcg/L After 28 days $[Mn]_S$: 16±5 mcg/L. Reference range**:** 8–25 mcg/L	Short study $[Mn]_S$ not as reliable as $[Mn]_{WB}$ No MRI

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose Duration	Reported Findings	Comments
(Akutsu et al. 2012) Japan	To assess $[Mn]_S$ fluctuation in esophageal Ca patients on cisplatin-Rx and on TPN with or without Mn supplementation. Design: INT, PROS, CONTR	18 patients Group 1: 10 subjects on PN w/o Mn for one month. Group 2: 8 patients on PN w/Mn for one month	Group 1: 0 Mn Group 2: 55 mcg Mn Duration: 1 month	Group 1: Baseline $[Mn]_S$: 1.34 mcg/L After 1 month $[Mn]_S$: 1.20 mcg/L Group 2: Baseline $[Mn]_S$: 0.97 mcg/L After 1 month $[Mn]_S$: 1.07 mcg/L Reference range: not given	Only available study with Mn dosing at 55 mcg per day. Two arms prospective One-month duration of intervention Serum (not WB) [Mn] No MRI No ref range for Mn plasma levels
(Abdalian et al. 2013a) Canada	to survey a population sample receiving long-term PN to assess the effect of Mn supplementation from a commercial multi-TE supplement.	16 patients on HPN for >3 months Age $\bar{x}$ 48.63±5.25 y/o Sex: 6M/10F	Dose: 400±53 mcg per day. Duration: 9.43±2.12 years with 4.75±0.38 days per week.	$[Mn]_{WB}$ 21.9±1.4 mcg/L MRI HI (+) signal of basal ganglia, 13 out of 16 patients. 2 patients with positive MRIs (15%) had a clinical diagnosis of Parkinson disease. (reference range $[Mn]_{WB}$ 4.3–15.9 mcg/L)	Single arm prospective.

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose Duration	Reported Findings	Comments
(Dastych et al. 2016a) Czechia	to determine the $[Mn]_{WB}$ of patients with long-term HPN as compared to healthy volunteers. Additionally, to compare $[Mn]_{WB}$ in patients with and without cholestasis.	68 subjects Sex: 16M/52F; Age 28–68 y/o.	Dose: Median Mn 236 mcg/d (IQR 196–275 mcg/d). Duration: From 4 to 96 months.	$[Mn]_{WB}$ 18.6 (14.0–24.8) mcg/L. Ref range $[Mn]_{WB}$ median 6.9 mcg/L (IQR 6.15–8.35 mcg/L)	Single-arm prospective (or retrospective??)
(Jin et al. 2018) Canada	to assess the effect of removing Mn from HPN on $[Mn]_{WB}$ over a 5-year period.	11 subjects Sex: 4M, 7F Age: $\bar{x}$ 62 y/o (range 24–84).	400±53 mcg (BSL) → 0 mcg (observation period) Duration: 60 months	$[Mn]_{WB}$ from 17.7 [6.0–75.1] mcg/L (BSL) to 10.8 [5.4–35.4] mcg/L. (reference range $[Mn]_{WB}$ 4.3–15.9 mcg/L) Repeated MRI in 8 patients 6 out of 8 $\bar{c}$ resolved basal ganglia deposits, 1 out of 8 $\bar{c}$ improved deposits, 1 out of 8 $\bar{c}$ unchanged deposits	Single-arm prospective.

Source: Data Generated by the Reviewer Based on Published Literature. The reviewer converted molar quantities and concentrations into the respective mass to harmonize the presentation of data.
Abbreviations: AlkPhos; alkaline phosphatase; CONTR, controlled; Cr, chromium; CS, cross-sectional; Cu, copper; CVA, cerebrovascular accident; Dx, diagnosis; g-GT, gamma-glutamyl transferase; HI, high intensity; HPN, home parenteral nutrition; INT, interventional; IQR, interquartile range; IV, intravenous; LFT, liver function test; m, month(s); Mn, manganese; $[Mn]_{WB}$, whole-blood manganese concentration; MRI, magnetic resonance imaging; MTE, multitrace element; NOS, not otherwise specified; PN, parenteral nutrition; PROS, prospective; RETRO, retrospective; Se, selenium; TPN, total parenteral nutrition; UNC, uncontrolled; y, year(s); y/o, year(s) old; Zn, zinc

Table 41. Synopsis of Studies Evaluating Parenteral Manganese in Children

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose, Duration	Reported Findings	Comments
(Hambidge et al. 1989) United States	To determine (1) if cholestasis caused by PN is associated with elevation of $[Mn]_P$, (2) if elevated $[Mn]_P$ is corrected by withholding Mn supplements, and (3) to determine the Mn content of the PN solutions.	Group (1) Normal TBili (0.4±0.2 mg/dL) n=9 Age: 1–18 months (n=6) 95–210 months (n=3)	Group (1) ~>10 mcg/L Duration: 1 d–17 m	Group (1): $[Mn]_P$ 0.79±0.18 mcg/L (range 0.4-1.0 mcg/L)	n=4>10 kg BW (3 $\bar{s}$ cholestasis 1 $\bar{c}$ cholestasis)
		Group (2) High TBili (6.3±6.0 mg/dL) n=5 Age: 3–16 months (n=4) 169 months (n=1)	Group (2) ~>10 mcg/L Duration: 3 w–14 m	Group (2): $[Mn]_P$ 3.06±2.07 mcg/L (range 0.6-5.8 mcg/L). p<0.01 vs. group 1.	
(Fell et al. 1996) United Kingdom	To examine (1) the effect of withdrawing Mn in children with gross hyper[Mn]emia and cholestatic liver disease; and (2) the CNS in children on very long PN with a lower Mn dose.	Group (1) $\bar{c}$ cholestasis (TBili 1.5–23 mg/dL) n=11 Sex: 8 M, 3 F. Age 4–17 months (4 died w/in 2 months)	Group (1) before: Mn 55 mcg/kg if <10 kg Mn 44 mcg/kg if >10 kg Duration: 2–16 m	Group (1): $[Mn]_{WB}$ m 71.6 mcg/L (range 33.8-101) TBili (in the 7 survivors) 1.5–8.5 mg/dL Neurological: 2 children $\bar{c}$ BSL dystonic movements: 1 died and one improved by 8 months. MRI (+) HI signal in 2 of 3 children with top $[Mn]_{WB}$.	Single-arm prospective. n=7>10 kg BW ($\bar{s}$ cholestasis)
			Group (1) during follow-up: Mn 0 mcg/kg Duration: 8 m	Then $[Mn]_{WB}$ m 12.7 mcg/L (range 4.3-23.6 mcg/L) TBili 0.3–3.3 mg/dL	
		Group (2) $\bar{s}$ cholestasis n=7 Sex: 4 M, 3 F. Age 27–121 months	Group (2) Mn 5.5–33 mcg/kg Duration: >24 m	Group (2): $[Mn]_{WB}$ 13.7-28.4 mcg/L (range) TBili <0.7 mg/dL MRI (+)in 4 out of 7 Reference range $[Mn]_{WB}$ 4.0–11.5 mcg/L	

Reference ID: 4635033

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose, Duration	Reported Findings	Comments
(Quaghebeur et al. 1996) United Kingdom	Not given	n=13 (8 M, 5 F) Age range 6–121 m/o	Group 1: (n=4) Mn 55 mcg/kg if <10 kg Mn 44 mcg/kg if >10 kg. Duration: 4 months	Group 1: $[Mn]_{WB}$ 46.1-101.2 mcg/L (range) MRI (+) in 3 out of 4 Clinical toxicity in 2 (seizure in 1 and dystonia in 1) Cholestasis in 4 out of 4	n= ? >10 kg BW
			Group 2 (n=9) Mn 5.5-33.3 mcg/kg Duration: >24 months	Group 2: $[Mn]_{WB}$ not given MRI (+) in 4 ($\bar{c}$ 4 highest $[Mn]_{WB}$ levels) out of 9 Clinical toxicity in 0 out of 9 Cholestasis in 0 out of 9 Reference range $[Mn]_{WB}$ <13.2 mcg/L	
(Beath et al. 1996) United Kingdom	Frequency of cholestasis in neonates on high Mn TPN vs. neonates on low Mn TPN	Group 1: TPN between Jan-92 and Jun-94 (n=31) Age: <6 months (gestational age 35±2.6)	Dose: 44 mcg/kg Duration: >28 days ($\bar{x}$ 79±55)	TBili >70 mcmol/L n=12 (42%)	Letter to the Editor
		Group 2: TPN between Jul-94 and Jun-96 (n=18) Age <6 months (gestational age 35±3.2)	Dose: Mn 1 mcg/kg Duration: >28 days ($\bar{x}$ 102±106)	TBili >70 mcmol/L n=10 (55%)	
(Fok et al. 2001) Hong Kong	To investigate the causal relationship between PN Mn intake and cholestasis (DBili 3 mg/dL) in pre-term infants Design: RAND, PROS, INT, CONTR.	Group 1: 78 infants Gestation: 31 wk Weight: 1347 g	Group 1: Mn 55 mcg/kg (Ped-El) Duration: >14 days	Group 1: $[Mn]_{WB}$ 41 mcg/L (27.4–66.6 mcg/L) Med (IQR) Peak DBii >3 mg/dL: 58 Peak DBii >6 mg/dL: 32 Mortality: 8	
		Group 2: 82 infants Gestation: 32 wk Weight: 1395 g	Group 2: Mn 1 mcg/kg (Peditrace) Duration: >14 days	Group 2: $[Mn]_{WB}$ 32 mcg/L (24–45 mcg/L) Med (IQR) Peak DBii >3 mg/dL: 49 Peak DBii >6 mg/dL: 20 Mortality: 12	

Reference ID: 4635033

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose, Duration	Reported Findings	Comments
(Iinuma et al. 2003) Japan	To evaluate if $[Mn]_{WB}$ in children receiving long-term HPN is a clinically useful indicator of Mn accumulation in brain.	7 children 3 M and 2 F Age $\bar{x}$ 125 mo (range 41–249)	<10 kg: Mn 275 mcg/d 10–20 kg: 550-825 mcg/d >30 kg: 1,100 mcg/d	MRI: (+) in all 7 patients $[Mn]_{WB}$ elevated in 4 out of 7 (31–51 mcg/L), while $[Mn]_{WB}$ normal in 3 out of 7 (18–24 mcg/L).	n=7>10 kg BW
(McMillan et al. 2008) United States	To investigate the relationships among cholestasis and WB Mn levels in pediatric patients receiving PN.	n=54 Age: <24 months (n=43) >24 months (n=11)			Prospective observational n=11>10 kg BW
(Pasko et al. 2009) United States	To determine the transmembrane clearance of Mn and quantify the daily CRRT loss in relation to Mn in PN in children on CRRT.	5 children $\bar{c}$ AKI on CRRT 2–15 y/o 3 males and 2 females	<30 kg: Mn 5 mcg/kg/d. >30 kg: MN 500 mcg/d.	$[Mn]_S$ 2.83±1.34 mcg/L (reference range $[Mn]_S$ 4-11 mcg/L) Mn CRRT clearance**:** 2.48 mL/1.73m^2/min	n=5>10 kg BW

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose, Duration	Reported Findings	Comments
(Aschner et al. 2015) United States	Hypothesis that infants with > parenteral Mn exposure have > brain Mn deposition in the basal ganglia than do infants with < parenteral Mn exposure. Secondary goals to examine the associations between T1R and $[Mn]_{WB}$, enteral Mn exposure, and conjugated bilirubin concentrations.	58 infants $\bar{c}$ high-quality MRI. Group (1) (high-exposure) n=39 Gestational Age (GA) median 27 wks, IQR 25–35 wks Group (2) (low-exposure) n=19. GA median 37 wks, IQR 35–39 wks Postmenstrual age (GA + chronological age): similar in the 2 groups.	Mn (total dose) from birth to MRI: High-exposure group (~13 wks): $\bar{m}$ 415 mcg (IQR 312–760) Low-exposure group (~2 wks): $\bar{m}$ 5 mcg (IQR 0–101)	MRI T1 Relaxation time (T1R) High-exposure gr median: 1109; IQR: 1046–1260. Low-exposure gr median: 1075; IQR: 1015–1199. Regression analysis: >Parenteral Mn associated $\bar{c}$ <T1R (P =0.02). For every 100 mcg intake in parenteral Mn, T1R decreased by 14 ms (95% CI: 227, 21.6). No association of $[Mn]_{WB}$ $\bar{c}$ T1R. Neuro exam: Severely abnormal at hospital discharge in one high-exposure infant (preterm $\bar{c}$ short bowel syndrome) and MRI short T1R but otherwise normal brain.	Prospective observational
(Greene et al. 2016) United Kingdom		36 children	Mn 1 mcg/kg/d (max 10 mcg) Duration: NR	9 out of 36 (25%) with $[Mn]_{WB}$ >17.9 mcg/L. Ref. range $[Mn]_{WB}$: 4.0-17.9 mcg/L.	Letter to the Editor n >10 kg BW = unknown
(Johnsen et al. 2017)	To test if children on PN not supplemented with MN have lower $[Mn]_{WB}$, than the historically supplemented comparison group	Group 1 (n=561): 315<5 kg, $\bar{m}$=2.4±1.2 kg	Mn 1 mcg/kg Duration: ~4 w	29% (n=91) $[Mn]_{WB}$ >16.5 mcg/L	Retrospective no difference between the groups. Supports notion that Mn should be withheld from MTE and from PN
		246≥5 kg, $\bar{m}$=21.7±18.2 kg		10% (n=56) $[Mn]_{WB}$ >16.5 mcg/L	
		Group 2 (n=36): 21<5 kg, $\bar{m}$=2.09±1.0 kg	Mn none Duration: ~4 w	41% (n=9) $[Mn]_{WB}$ >16.5 mcg/L	
		14≥5 kg, $\bar{m}$=19.3±18.8 kg.		36% (n=5) $[Mn]_{WB}$ >16.5 mcg/L Ref. range $[Mn]_{WB}$: 4.2–16.5 mcg/	

Source: Data Generated by the Reviewer Based on Published Literature. The reviewer converted molar quantities and concentrations into the respective mass to harmonize the presentation of data.
Abbreviations: BW, body weight; CNS, central nervous system; CONTR, controlled; F, female; GA, gestation age; INT, interventional; IQR, interquartile range; M, male; Mn, manganese; $[Mn]_{WB}$, whole-blood manganese concentration; MRI, magnetic resonance imaging; MTE, multitrace element; NR, not reported; PN, parenteral nutrition; PROS, prospective; RAND, randomized; TPN, total parenteral nutrition; BSL baseline; CRRT, continuous renal replacement therapy

Table 42. Synopsis of Studies and Case Reports Addressing Parenteral Manganese and Liver Disease

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose Duration	Reported Findings
(Hambidge et al. 1989) United States	PEDIATRIC To determine if cholestasis caused by PN is associated with high $[Mn]_S$, and if high $[Mn]_S$ is corrected by stopping IV Mn. Also, to determine the [Mn] of the PN solutions.	14 children (8 M, 6 F) on PN		log $[Mn]_S$ ∴log TBili (all subjects) r =0.874, p<0.001.
		Group 1**:** n=9 $\bar{c}$ normal TBili TBili 0.35±0.16 mg/dL Age $\bar{m}$ 14 m/o (range 1–210)	Dose: ≈18 mcg/L (includes contaminants) Duration: 1 d–17 m	$[Mn]_S$ 0.79±0.18 mcg/L (0.40–1.00 mcg/L). (reference range 0.89±0.18 mcg/L)
		Group 2: n=5 $\bar{c}$ high TBili TBili 6.3±6.0 mg/dL Age $\bar{m}$ 7 m/o (range 3–169)	Dose: ≈18 mcg/L (includes contaminants) Duration**:** 3 w–14 m	$[Mn]_S$ 3.06±2.07 mcg/L (0.60-5.80 mcg/L) Pt 1: no Δ IV Mn→ Somewhat lower $[Mn]_S$ and TBili. Pt 2: stop IV Mn→ Normalized $[Mn]_S$ and TBili. Pt 3: stop IV Mn→ Normalized $[Mn]_S$ and TBili. Pt 4: stop IV Mn→ Normalized $[Mn]_S$. TBili high no Δ. Pt 5: no sequential sampling.
(Mehta and Reilly 1990) United States	ADULTS Case report	32-year-old female s/p total colectomy for IBD	Dose: Mn 300 mcg. Duration**:** 4 months, then stop	Enterectomy for volvulus. Start PN w/ Mn. After 3 m, TBili 16.2 mg/dL; liver Bx c/w early biliary cirrhosis. New extrapyramidal signs w/ tremors, slowed speech, mask-face, and micrographia. $[Mn]_{WB}$ 50 mcg/L (reference range 4–14 mcg/L). Stop Mn→ w/rapid neuro resolution. 2 months later, $[Mn]_{WB}$ 18.2 mcg/L. Awaiting multiorgan Tx.
(Reynolds et al. 1994) United Kingdom	PEDIATRIC Case Report	18-month-old girl, born prematurely (35 weeks), hospitalized since 5 days old.	Mn dose: ~50 mcg/kg (44–55) Duration: 7 m	At age: <1 month-old, start PN $\bar{c}$ Mn. 3 m/o, cholestatic liver disease 7 m/o, first dystonic movements. 12 m/o, (+) MRI 17 m/o, $[Mn]_{WB}$ 95.7 mcg/L. (reference range 4–11.5 mcg/L) 18 m/o, died

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose Duration	Reported Findings
(Beath et al. 1996) United Kingdom	PEDIATRIC Letter to the Editor Frequency of cholestasis in neonates on high vs. low Mn TPN	Group 1: TPN between Jan-92 and Jun-94 (n=31) Age: <6 months (gestational age 35±2.6)	Dose: 44 mcg/kg Duration: >28 days ($\bar{x}$ 79±55)	TBili >4.1 mg/dL: n=12 (42%)
		Group 2: TPN between Jul-94 and Jun-96 (n=18) Age <6 months (gestational age 35±3.2)	Dose: Mn 1 mcg/kg Duration: >28 days ($\bar{x}$ 102±106)	TBili >4.1 mg/dL: n=10 (55%)
(Forbes and Jawhari 1996) United Kingdom	ADULTS Letter to the Editor To examine the prevalence of high $[Mn]_{WB}$ and cholestasis Design: PROS INT, UNC	29 adults on HPN	Dose: $\bar{m}$ 3 mcg/kg/d (range 1.1–5.5) Duration: 48 mo (range 3 mo–14 yr)	High $[Mn]_{WB}$: n=25 (86%) ($\bar{m}$ 16.4 mcg/L, range 7.3-35.6 mcg/L) Toxic $[Mn]_{WB}$: n=7 (24%) (>19.8 mcg/L) No patient w/ neurologic signs (reference range $[Mn]_{WB}$ <11.5 mcg/L). Normal LFTs: n=12 Mild intrahepatic cholestasis (stable): n=11 >2x ULN: n=6 AlkPhos 165 U/L (69–539) gGT 121 U/L (13–837) No correlation $[Mn]_{WB}$ ∴ cholestasis

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose Duration	Reported Findings
(Fell et al. 1996) United Kingdom	PEDIATRIC to examine (1) the effect of withdrawing Mn in children with gross hyper[Mn]emia and cholestatic liver disease; and (2) the CNS in children on very long PN with a lower Mn dose.	Group (1) $\bar{c}$ cholestasis (TBili 1.5–23 mg/dL) n=11 (8 M, 3 F), Age range 4–17 m/o (4 died w/in 2 months)	Group (1) Before study: Mn 55 mcg/kg if <10 kg; Mn 44 mcg/kg if >10 kg Duration: 2–16 m	Group (1): Start of study: $[Mn]_{WB}$ $\bar{m}$ 71.6 mcg/L (range 33.8–101) TBili (in the 7 survivors) 1.5–8.5 mg/dL Neurological: 2 children $\bar{c}$ BSL dystonic movements: 1 died and one improved by 8 months. MRI (+) HI signal in 2 of 3 children with top $[Mn]_{WB}$.
			During study: Mn 0 mcg/kg Duration**:** 8 m	end of study: $[Mn]_{WB}$ $\bar{m}$ 12.7 mcg/L (range 4.3-23.6) TBili 0.3–3.3 mg/dL
		Group (2) $\bar{s}$ cholestasis n=7 (4 M, 3 F), age range 27–121 m/o	Group (2) Mn 5.5-33 mcg/kg Duration: >24 m	Group (2): $[Mn]_{WB}$ 13.7–28.4 mcg/L (range) TBili <0.7 mg/dL MRI $\bar{c}$ (+) HI in 4 out of 7 Reference Range $[Mn]_{WB}$ 4.0–11.5 mcg/L
(Alves et al. 1997) France	ADULTS Case Report	63-y/o woman	Mn dose: 990 mcg Duration: 17 m	s/p total bowel resection for carcinoid and GI bleed TBili 5.8 mg/dL. Start PN with Mn 990 mcg/day. After 17 m, hospitalized w/ abulia, echolalia and palilalia, altered gait, falls w/ change of posture, dystonia of limbs w/o hypermetria. TBili 11 mg/dL. (+) Brain MRI. $[Mn]_S$ ~6.05 mcg/L (reference range 0.55–2.2 mcg/L)**.** Stop IV Mn After 6 m, significantly improved neuro, TBili 15 mg/dL, $[Mn]_S$ ~1.65 mcg/L. After another 4 m, modestly improved MRI. TBili 4 mg/dL.

Reference ID: 4635033

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose Duration	Reported Findings
(Wardle et al. 1999) United Kingdom	ADULTS To investigate the incidence of high $[Mn]_{WB}$ in adult patients on long-term PN (HPN group) and in patients with chronic liver disease (CLD group). DESIGN: INT, CS, UNC	HPN group – n=30 on long-term HPN (9 M, 21 F) Age range 24-66 y/o. Dx: resected Crohn's (n=15), functional intestinal failure (n=2), miscellaneous causes of resection (n=13).	HPN group Dose: Mn: $\bar{m}$ ~3.3 mcg/kg (range 2.7–5.5 mcg/kg) Duration: $\bar{m}$ 43 mo (range 3–168).	HPN group $[Mn]_{WB}$ In 4 subjects: <11.5 mcg/L In 19 subjects: 11.5–19.8 mcg/L In 7 subjects >19.8 mcg/L
		CLD group – n=10 $\bar{c}$ chronic liver disease (CLD) & cholestasis (4 M, 6 F); Age range: 39-74 y/o Dx: alcoholic liver disease (n=7), cirrhosis (NOS n=1), and primary biliary cirrhosis (n=2).	CLD group No IV Mn or PN	CLD group [Mn]WB <11.5 mcg/L in all 10 subjects (reference range $[Mn]_{WB}$ 4.0–11.5 mcg/L). No correlation of $[Mn]_{WB}$ with markers of cholestasis, Mg intake, or Mg duration
(Reimund et al. 2000) France	ADULTS To examine the association of $[Mn]_S$ with hepatic enzymes, markers of inflammation and immunity, and PN dose in HPN patients.	HPN (all >3 mo, $\bar{x}$ 30.5+36.7 mo) n=21 (6 F, 15 M) Age 54.6+14.2 y/o Healthy controls n=10	Dose: ~500 mcg Duration: 30.5 m [3–132 m]	**Test** / **HPN Pts** / **Vs.** / **Controls** $[Mn]_S$ 1.96±1.1 Vs. 0.81±0.4 mcg/L p<0.001 AlkPhos 323+279 Vs. 79+18 IU/L p<0.001 g-GT 200+211 Vs. 27+10 IU/L p<0.01 AST 44+42 Vs. 23+8 IU/L p<0.05 TBili 9.9+10.9 Vs. 10.5+4.4 mcmol/L [Mn]S ∴ AlkPhos r^2=0.26 p<0.0001

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Daily Dose Duration	Reported Findings
(Fok et al. 2001) Hong Kong	PEDIATRIC To investigate the causal relationship between PN Mn intake and cholestasis (DBili 3 mg/dL) in pre-term infants DESIGN: RAND, PROS, INT, CONTR.	Group 1: n=78 $\bar{c}$ >14 days PN Gestation: 31 wk Weight: 1347 g	Group 1: Mn 55 mcg/kg (Ped-El) Duration: 41 days	Group 1: $[Mn]_{WB}$ $\bar{m}$ 41 mcg/L (IQR 27.4-66.6 mcg/L) Peak DBili $\bar{m}$ 84.0 (IQR 28.0, 170.0) mg/dL Peak DBili >3 mg/dL: n=58 (74%) Peak DBili >6 mg/dL: n=32 (41%) Mortality: 8 (10%)
		Group 2: n=82 $\bar{c}$ >14 days PN Gestation: 32 wk Weight: 1395 g	Group 2: Mn 1 mcg/kg (Peditrace) Duration: 40 days	Group 2: $[Mn]_{WB}$ $\bar{m}$ 32 mcg/L (IQR 24-45 mcg/L) Peak DBili $\bar{m}$ 25.5 (IQR 9.0, 117.0) mg/dL Peak DBili >3 mg/dL: n=49 (59%) Peak DBili >6 mg/dL: n=20 (24%) Mortality: 12 (15%)
(McKinney et al. 2004) United States	ADULTS Case report	64 y/o female	Mn dose: (1/3 TE dose). Duration: ?	s/p liver tx (3 weeks earlier) for porphyria, on immune-suppression, and TPN x3 weeks w/ intermittent tube feeds, intubated and sedated. Hospitalized w/ TBili 11.1–27 mg/dL, fever and abnormal CXR, decreased mental status, and hypotonia. (+) MRI in globi pallidi. Aspergillosis with pulmonary infiltrate and liver infarctions. Death on post-Tx day 26. At autopsy, $[Mn]_S$ 195 mcg/L (Ref range <8 mcg/L), globus pallidus histopathology c/w manganese toxicity.

Abbreviations: AlkPhos; alkaline phosphatase; CS, cross-sectional; CXR chest X-ray; Dx, diagnosis; F, female; g-GT, gamma-glutamyl transferase; GI, gastrointestinal; HPN, home parenteral nutrition; IBD, inflammatory bowel disease; INT, interventional; IV, intravenous; LFT, liver function test; M, male; Mn, manganese; $[Mn]_s$, plasma or serum manganese concentration; $[Mn]_{WB}$, whole-blood manganese concentration; MRI, magnetic resonance imaging; PN, parenteral nutrition; PROS, prospective; TPN, total parenteral nutrition; tx, treatment; ULN, upper limit of normal; UNC, uncontrolled

14.8. Synopsis of Studies Addressing Manganese Deficiency

Table 43. Synopsis of Studies Addressing Manganese Deficiency in Adults

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Information	Brief Narrative	Comments
(Hoekstra et al. 1974) United States	Long-term chemically defined diet to address vitamin K deficiency in man. Accidental omission of Mn from the trace-element supplement.	1 male subject, undefined age.	Placed for 6.5 months on a chemically defined vitamin K deficient diet. Mn accidentally omitted from the diet after the initial 3 months	Delayed clotting response during the experimental diet period with failure of the suppressed clotting proteins to rise in response to IV and IM vit K_1. However, return of the Prothrombin time to normal within 3 weeks of restoration to the normal diet. Other changes noted during the 6.5 months were decreases serum cholesterol from 206 to 80 mg/dL. paralleling the trough of the blood-clotting proteins, discolored (reddened) black hair, slowed growth of hair and nails, and scaly dermatitis.	This atypical response to K_1 suggested the possibility of coincident deficiency in another essential nutrient. Retrospective analyses of all records and minutes finally revealed that MnS04 had been accidentally omitted from the trace-element supplement after the first 3 months, the deficiency being continued until normal diet was fed 3.5 months later.
(Friedman et al. 1987) United States	To determine the effects of Mn-deficient and -adequate diets on manganese balance in males, aged 19–22 yr	7 male subjects 19–21 y/o.	Baseline diet $\bar{c}$ 2.59 mg Mn/d and 135 mg cholesterol for 21 d. Then, formula diet $\bar{c}$ 0.11 mg of Mn/d for 39 days.	The minimum Mn requirement for 19–22 y/o males was 0.74 mg/d or 10.8 mcg/kg. Miliaria cristallina at the end of the depletion period.	The skin rash appeared at the end of a 54-hr integumental collection period during which most areas of the skin were covered by collection garments. These garments may have produced an occlusive environment for the epidermis, but no dermatitis was observed during collections conducted prior to depletion and during repletion.

Abbreviations: IM, intramuscular; IV, intravenous; Mn, manganese; yr, year(s)

Table 44. Synopsis of Studies Addressing Manganese Deficiency in Pregnancy

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Information	Brief Narrative	Comments
(Spencer 1999) Australia	To monitor WB Mn during pregnancy and in the neonate in initial post-partum period. Design: INT, PROS, CONTR	34 pregnant women at weeks 10, 20 and 34. 34 newborn infants.	None	WB Mn in gestating women: 10 wk: 8.3±2.9 mcg/L 20–25 wk: 9.4±3.3 mcg/L. 34 wk 12.6±3.7 mcg/L. WB Mn in newborn infants: 40.6±11.5 mcg/L (Ref range: 4.4±13.2 mcg/L)	Prospective single arm. Not on TPN.
(Zota et al. 2009) United States	To examine the relationship between in utero manganese exposure and birth weight. Hypothesized that the relationship between fetal manganese exposure and infant birth weight would be in the form of an inverse U-shaped curve appropriately modeled with nonlinear models.	470 mother-infant pairs born at term (≥37 weeks gestation).	Maternal blood Mn 2.4±0.95 mcg/dL and cord blood Mn 4.2±1.6 mcg/dL.	Nonlinear relationship of maternal Mn with birth weight after adjusting for confounders. Birth weight increased with Mn up to 3.1 mcg/L, then it slightly declined. Compared with the 3.1 mcg/L point of inflection, birth weight estimates were -160 g (95% confidence interval = -286 to -33) at the 5th Mn percentile (Mn 1.3 mcg/L) and -46 g (-38 to 131) at the 95th Mn percentile (4.0 mcg/L).	Conducted in a population living near a lead and zinc mining site in northeastern Oklahoma, U.S.A., with a potential environmental metal exposure.
(Chen et al. 2014) China	To examine the association between Mn concentration and birth weight. Hypothesis that lower and higher Mn exposures would be associated with lower birth weights.	Cohort of 172 mother–infant pairs born in Shanghai, China,	Mn in maternal and cord blood from two hospitals.	In maternal blood: Mn 66±47 mcg/L. In cord blood Mn 85±46 mcg/L. The birth weight increased with Mn concentrations up to 41.8 mcg/L, while the weight decreased slight at higher concentrations	Mn is very high relative to other studies (methodology problem?).

Reference ID: 4635033

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Information	Brief Narrative	Comments
(Eum et al. 2014) Korea	To assess the association between maternal blood Mn concentrations during pregnancy and birth weight in the general population without a prominent source of Mn exposure	352 pregnant women consecutively recruited from 7/2007 to 12/2009 from three centers.	Whole blood Mn level was measured by graphite furnace	Maternal Mn concentration 22.5±7.2 mcg/L, range 8.5-58.6 mcg/L. Borderline quadratic association of maternal Mn with newborn weight (p 0.054). Odds ratio (OR) of newborn <3,000 g were higher in the highest Mn quintile (Mn >26.9 mcg/L; OR 2.60; p 0.098) and lowest (Mn <16.9 mcg/L; OR 2.77; p 0.079) (borderline significance).	

Abbreviations: CONTR, controlled; INT, interventional; Mn, manganese; OR, odds ratio; PROS, prospective; TPN, total parenteral nutrition; WB, whole blood

Table 45. Synopsis of Studies Addressing Manganese Deficiency in Children

First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Information	Brief Narrative	Comments
(Claus Henn et al. 2010) United States	Prospective study to examine if early-life Mn exposure is associated with neurodevelopmental effects among children between ages 1 and 3 years.	448 mother-infant pairs were enrolled either during pregnancy or 1 month postpartum	None	At age 12 m/o: Mean (SD) WB Mn 24.3 (4.5) mcg/L (median 23.7 mcg/L) Mental Development Index (MDI) 97.7 points (highest) with Mn 24.4 mcg/L. MDI 93.9 points with Mn 18.1 mcg/L (5th percentile) MDI 94.2 points with Mn 32.5 mcg/L (95th percentile). At age 24 m/o: Mean WB Mn 21.1 (6.2) mcg/L (median 20.3 mcg/L). MDI – WB Mn association not as strong but still apparent.	

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First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Information	Brief Narrative	Comments
(Rodríguez-Rodríguez et al. 2011) Spain	To study the relationship between the adequacy of the intake of Mn and glucose levels, insulin and existence of insulin resistance in healthy school children in the Madrid's community.	573 school-children between 8 and 13 years old	3-day dietary record	Boys: no differences in glucose, insulin and insulin resistance (HOMA), as a function of adequate (≥100%) or inadequate (<100%) Mn Intakes. Girls: with inadequate Mn intake had higher insulin and HOMA that girls with adequate intake (100%). Higher % of girls with high HOMA when Mn intake was inadequate. Boys/Girls: No correlation between Mn intake and glucose or insulin after correcting for the confounders intake of energy carbohydrates and lipids, BMI, and age). Girls: inverse association of Mn intake with HOMA (but not in boys) after correcting for the above confounders (R =0.2499; p<0.001; ß=-0.018±0.0008; p =0.025).	

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First Author, Year, Location	Study Objective and Study Design	Patient Population	Trace Element Information	Brief Narrative	Comments
(Bhang et al. 2013) Korea	Use a nationwide cross-sectional design study to address association between manganese extreme blood levels and academic and attention function-development among school aged children.	Secondary objective of 'Effects of pollution on neurobehavioral development […]', funded by the Korean Ministry of Environment's Eco-Technopia 21 Project. 1005 out of 1712 eligible 8–11 y/o children participated and had Mn levels. 571 (52.4%) males and 518 (47.6%) females.	Low WB Mn: ≤5th percentile. Normal WB Mn: 5th - 95th percentile High WB Mn: ≥95th percentile. Assessment of attention, behavior, emotion, and learning via questionnaires.	Mean Mn 14.4±4.1 mcg/L (range 4.25–31.5 mcg/L.). In unadjusted test, the low WB Mn was associated with lower color score of the Stroop test (*B* = −3.18, p 0.05), compared with the middle Mn group. In multiple regression models, the low WB Mn group had lower color scores on the Stroop test (B = −3.43, p =0.029 for Model 1; B=−3.27, p =0.038 for Model 2; B=−3.24, p=0.040 for Model 3).	Prospective observational. Recruitment bias (several subjects with mental problems elected not to participate) Little evidence of an association between low Mn and altered mental function. Much stronger association of high than low Mn levels with mental function.

Source: Data Generated by the Reviewer Based on Published Literature. The reviewer converted molar quantities and concentrations into the respective mass to harmonize the presentation of data.
Abbreviations: BMI, body mass index; HOMA, homeostatic model assessment; m/o, months old; MDI, mental development index; Mn, manganese; SD, standard deviation; WB, whole blood; y/o, year(s)/old

14.9. Case Reports on Parenteral Manganese Toxicity

Table 46. Case Reports of Parenteral Manganese Toxicity in Adults

First Author, Year, Location	Patient Characteristics	Trace Element Daily Dose Duration	Reported Findings
(Taylor and Price 1982) Canada	48-year-old female on chronic HD	Dialysis bath contamination	Nausea, severe vomiting, epigastric pain radiated to her chest 10 minutes after the start of dialysis. Drowsy, perioral numbness 4 hours after starting dialysis. The next day, severe abdominal pain and acute pancreatitis, amylase 565 IU/L. Slow recovery.

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First Author, Year, Location	Patient Characteristics	Trace Element Daily Dose Duration	Reported Findings
(Mehta and Reilly 1990) United States	32-year-old female s/p total colectomy for IBD	Dose: Mn 300 mcg. Duration: 4 months, then stop	Enterectomy for volvulus. Start PN w/ Mn. 3 months later, TBili 16.2 mg/dL; liver biopsy c/w early biliary cirrhosis. New extrapyramidal signs w/ tremors, slowed speech, mask-face, and micrographia. $[Mn]_{WB}$ 50 mcg/L (ref range 4–14 mcg/L). Stop Mn, w/rapid neuro resolution. 2 months later, $[Mn]_{WB}$ 18.2 mcg/L. Awaiting multiorgan Tx. **Comments:** Case report.
(Ejima et al. 1992) Japan	62-y/o man, s/p massive bowel resection for SMA occlusion.	Mn dose: 2,200 mcg Duration: 31 m	Hospitalized w/ parkinsonism, dysarthria, mild rigidity, hypokinesia with masked face, a halting gait, and severely impaired postural reflexes, slowly worsening over 16 months Alert and oriented. MRI w/ symmetrical HI signal on T1- in basal ganglia (globus pallidus, tectum, and tegmentum of midbrain and pons). $[Mn]_{WB}$ 30–56 mcg/L (ref range 4–20 mcg/L). Stop Mn supplement. 4 month later, $[Mn]_{WB}$ 5 mcg/L and MRI improved. After another 2 months, MRI further improved but not normal. **Comments:** Case report.
(Taylor and Manara 1994) United Kingdom	44-y/o woman subjected to Whipple's procedure.	Mn dose: 2200 mcg Duration: 9 days	Hospitalized after Whipple's procedure and started on PN w/ Mn 2200 mcg/day. Progressive onset of confusion, aggression, and choreoathetoid movements. On HD #9, obstructive jaundice w/ TBili 179 mcmol/L, $[Mn]_{WB}$ 26 mcg/L (ref range <10 mcg/L). IV Mn reduced to 6 mcg. Choledochojejunostomy w/>50% drop TBili by HD #14. Now, oriented w/ occasional confusion. On HD #16, back to PO intake and $[Mn]_{WB}$ 22 mcg/L. **Comments:** Case report.
(Fredstrom et al. 1995) United States	A 51-year-old woman underwent allogeneic BMT for CML.	Mn dose: 300 mcg Duration: 58 days	Complications during the hospitalization: neutropenia, A Fib/Flutter $\bar{c}$ cardioversion, CHF, cholestasis $\bar{c}$ TBili 14.2 (day 11), mechanical ventilation (day 19), CMV viremia and acute GVHD (skin & GI). Extubated and alert on day 40. On day 55, stop TPN, start oral intake. On day 56, Parkinson-like syndrome $\bar{c}$ masked facies, slow movement without rigidity, UE& LE fine tremor, and retropulsive gait. Brain MRI $\bar{c}$ bilateral symmetrical increased T1 signal of globus pallidus and associated white matter. $[Mn]_{S}$ 2.5 mcg/L (normal 4–8.5 mcg/L). Start Sinemet $\bar{c}$ marked improvement after 2 days, including fluidity of movement and a decrease in tremor. Continued improvement with near resolution of masked facies and bradykinesia, and normalization of gait at the time of hospital discharge on day +66. **Comments:** Case report.

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First Author, Year, Location	Patient Characteristics	Trace Element Daily Dose Duration	Reported Findings
(Alves et al. 1997) France	63-y/o woman	Mn Dose: 990 mcg Duration: 17 m	Hospitalized w/ severe UGI bleeding 2/2 carcinoid tumor of small intestine, requiring total small bowel resection. Start PN with Mn 0.99 mg/day. After 17 months, hospitalized w/ abulia, echolalia and palilalia, altered gait, falls w/ change of posture responsible for bone fractures, dystonic movements of the limbs without hypermetria. Brain MRI w/ HI signal of basal ganglia on T1 images. $[Mn]_S$ ~6.05 mcg/L (ref range 0.55–2.2 mcg/L)**.** Stop Mn supplementation. After 6 months, the neuro symptoms had significantly improved and $[Mn]_S$ ~1.65 mcg/L. After another 4 months MRI showed only modestly improved HI signal lesions. **Comments:** Case report.
(Nagatomo et al. 1999) Japan	68 y/o woman with UC, on TPN x3 m	Mn Dose: 1100 mcg Duration: 3 m	Hospitalized w/ confusion and Parkinsonism (dysarthria, marked rigidity, hypokinesia with masked facies, supranuclear vertical gaze palsy). Normal LFTs, $[Mn]_S$ 42 mg/L (ref range 4–20 mg/L). MRI w/ symmetrical high-intensity signal in the basal ganglia especially globus pallidus. Stop Mn and treatment with 1 g Ca–EDTA daily, then symptoms abated gradually.
	70 y/o man	(Nagatomo et al. 1999)	Hospitalized for aorto-femoral bypass, complicated by aspiration pneumonia, and then on TPN w/ Mn x4 m. After 2 m, gait disturbance and confusion, $[Mn]_S$ 51 mcg/L, marked rigidity, masked facies, hypokinesia, and slight resting finger tremor. Brain MRI w/ symmetrical HI signal in the basal ganglia especially globus pallidus. Stop Mn treatment with 1 g Ca–EDTA daily, then gradual improvement in Parkinsonism and $[Mn]_S$ down to 34 mcg/L, and improvement of MRI.
(Kondoh et al. 1999) Japan	73 y/o man s/p radical esophagectomy for cancer.	Mn Dose: 1100 mcg Duration: 28 d	On postop day 5, maximum TBili 5.1 mg/dL, with DBili 3.5 mg/dL, then slowly improved and normal TBili on postop day 22. Parenteral Mn stopped on postop day 21. No neurologic symptoms. On postop day 32, brain MRI w/ bilateral symmetrical HI lesions in basal ganglia, especially globus pallidus, and $[Mn]_{WB}$ 4.9 mcg /L (ref range 0.8–2.5 mcg /L). Discharged on postop day 43. On postop day 67, MRI w/ gradual improvement, and $[Mn]_{WB}$ 4.6 mcg /L. On postop day 99, MRI w/ further gradual improvement, and $[Mn]_{WB}$ 1.8 mcg /L. On postop day 158, normal MRI.
(Mirowitz et al. 1991) United States	61-y-o woman w/ severe GI dyskinesia, on TPN x3 years.	Mn Dose: 400 mcg Duration: 3 y	Screened with MRI for research study. BSL MRI w/ prominent increased signal intensity within the globi pallidi bilaterally. Stop Mn supplement. and 1-year later, repeat MRI: signal intensity in basal ganglia and the globi pallidi had normalized, with normal appearance. **Comments:** Case report. No blood tests

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First Author, Year, Location	Patient Characteristics	Trace Element Daily Dose Duration	Reported Findings
(McKinney et al. 2004) United States	64 y/o female.	Mn dose: (1/3 TE dose). Duration: ?	s/p liver tx (3 weeks earlier) for porphyria, on immune-suppression, and TPN x3 weeks w/ intermittent tube feeds, intubated and sedated. Hospitalized w/ TBili 11.1-27 mg/dL, fever and abnormal CXR, decreased mental status, and hypotonia. (+) MRI in globi pallidi. Aspergillosis with pulmonary infiltrate and liver infarctions. Death on post-tx day 26. At autopsy, $[Mn]_S$ 195 mcg/L (ref range <8 mcg/L), globus pallidus histopathology c/w manganese toxicity. **Comments:** Case report.
(Chalela et al. 2011) United States	A 22-y/o female	Mn dose: Not given Pt also received IV magnesium for eclampsia Duration: 2 weeks	Hospitalized w/eclampsia and seizures, given IV magnesium and phenytoin. On day, 4 new ileus, hyperamylasemia, and imaging c/w necrotizing pancreatitis. Complicated by acute respiratory distress syndrome, acute renal failure, and pulmonary sepsis. The patient required TPN and approximately 2 weeks later developed encephalopathy, not waking up during pharm sedation withdrawals. The patient had to be stimulated frequently to follow simple commands and she weakly followed commands with all extremities. Motor examination revealed antigravity strength in all limbs, diffuse hyperreflexia, ankle clonus, and down going toes. Arm myoclonic jerks were noticed intermittently. Diffuse paratonia was noted. Normal EEG, spinal fluid, and general blood chemistry. A brain MRI revealed symmetrical, abnormal signal in the thalamo- capsular region bilaterally. The lesions were hyperintense on FLAIR images and ADC maps and did not show restricted diffusion on DWI imaging. After 10 days, $[Mn]_S$ 11.5 mcg/L (reference range <2.0). The patient was diagnosed with manganese toxicity. The patient recovered well except for mild bilateral visual impairment.
(Gil et al. 2012) Korea	65 y/o man	Prochloraz-manganese poisoning	Hospitalized 5.5 h after ingesting prochloraz-manganese complex, w/ CV shock, and coma requiring mechanical ventilation. Started on norepinephrine and hemoperfusion, hemodialysis and continuous venovenous hemodiafiltration. Blood manganese levels were 34.1 mcg/L on day 1, 23.6 mcg/L on day 2, and 12.5 mcg/L on day 4. Recovered from the CV shock within 7 days. Full consciousness after 4 weeks. CONCLUSION: Comment that dialysis was effective

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First Author, Year, Location	Patient Characteristics	Trace Element Daily Dose Duration	Reported Findings
(Walter et al. 2016) United Kingdom	62 y/o man	270 mcg of Mn per day Duration: 2.5 months	h/o acute pancreatitis and intestinal insufficiency, on PN x6 months with Mn 270 mcg/day, while in ICU. After 2 ½ months, intermittent 15–30 s episodes of bilateral tremor, initially distal limbs then centripetal spread. Normal non-contrast brain CT scan. Metallic headwear prevented an MRI. $[Mn]_{WB}$ 23.6 mcg/L (reference range 4–12 mcg/L). Mn was discontinued immediately, but high levels and symptoms persisted four months later. AlkPhos high during admission.
(Hines et al. 2016) United States	52 y/o female	800 mg x 1 infusion	h/o Hashimoto's thyroiditis, suspected heavy metal toxicity on outpatient IV chelation, (baseline sCr 0.8 mg/dL; Lead 3.0 mcg/dL, the IV solution erroneously included Mn 800 mg x1 infusion. Patient experienced flushing after the first infusion, asymptomatic, normal vital signs, unrevealing physical examination. She underwent two, four-hour hemodialysis sessions at 7 and 21 h following exposure. Following hemodialysis, she received five consecutive days of calcium disodium EDTA (1 g/m2 over eight hours). $[Mn]_{WB}$ 120 mcg/L (by ICPMS) 6 hours after exposure and prior to any treatment (reference range $[Mn]_{WB}$ <5 mcg/L). Following hemodialysis, $[Mn]_{WB}$ 20 mcg/L. Despite the fall in the patient's $[Mn]_{WB}$, the dialysate from the 1st hemodialysis revealed a total elimination of only 604 mcg (~1.4% of Mn burden). An MRI on day-2 revealed T1 HI in bilateral globus pallidi, c/w Mn exposure. On day-5, discharged with $[Mn]_{WB}$ 2.2 mcg/L. One month later, her MRI was unchanged. Asymptomatic after 9 months, with stable MRI findings at 11 months.

First Author, Year, Location	Patient Characteristics	Trace Element Daily Dose Duration	Reported Findings
(Amin and Shawkat 2019) United States	38 y/o female	No Mn	h/o bariatric Roux-en-Y surgery complicated with malnutrition and anastomotic leak requiring HPN. Admitted to ICU with new onset encephalopathy, including extrapyramidal symptoms such as tremors, gait imbalance, multiple falls, as well as mood swings over the past few months. Somnolent, bilateral horizontal nystagmus and myoclonus. AlkPhos 160 and transaminase normal. Negative encephalopathy workup, except for MRI showing T1 hyperintensities in bilateral globus pallidi, c/w manganese or copper deposition, and $[Mn]_S$ 4 mcg/L (reference range <2.5 mcg/L), whereas copper level was normal. Parenteral nutrition was transiently held, and this led to an improvement in patient's symptoms. The case is unique because the patient was not receiving additional manganese through parenteral nutrition. **Comments:** Case report.

Abbreviations: ADC, apparent diffusion coefficient; BSL, brainstem lesion; CHF, congestive heart failure; CMV, cytomegalovirus; CT, computerized tomography; CV, cardiovascular; CXR, chest X-ray; DWI, diffusion-weighted imaging; EDTA, ethylenediaminetetraacetic acid; EEG, electroencephalogram; FLAIR, fluid attenuation inversion recovery; GI, gastrointestinal; GVHD, graft versus host disease; h/o, history of; HD, hemodialysis; HPN, home parenteral nutrition; IBD, inflammatory bowel disease; ICPMS, inductively coupled plasma mass spectrometry; ICU, intensive care unit; IV, intravenous; LE, lower extremity; LFT, liver function test; Mn, manganese; MRI, magnetic resonance imaging; PN, parenteral nutrition; PO, by mouth; SMA, superior mesenteric artery occlusion; TPN, total parenteral nutrition; tx, treatment; UE, upper extremity; UGI, upper gastrointestinal

Table 47. Case Reports of Parenteral Manganese Toxicity in Children

First Author, Year, Location	Patient Characteristics	Trace Element Daily Dose, Duration	Reported Findings
(Reynolds et al. 1994) United Kingdom	5 d/o premature (35 weeks) girl.	Mn dose: ~50 mcg/kg (44–55 mcg /kg) Duration: 7 months	Ventilated for aspiration pneumonia. Hospitalized for laparotomy and resection of "apple-peel" type jejunal atresia and primary anastomosis. Subsequently, near complete small bowel resection 2/2 adhesion obstruction. Start PN. At 3 months of age, cholestatic liver disease. At 7 months of age, concerns of developmental delay, abnormal dystonic movements of both arms, and microcephaly. At 12 months of age, development and head circumference had stopped. Brain MRI c/w deposition of a paramagnetic trace metal in basal ganglia. At 17 months of age, $[Mn]_{WB}$ 95.7 mcg/L. (reference range 4–11.5 mcg/L). At 18 months of age, died. **Comments**: Case report.

First Author, Year, Location	Patient Characteristics	Trace Element Daily Dose, Duration	Reported Findings
(Ono et al. 1995) Japan	5-y/o boy, s/p GI salmonella when 19 m/o requiring TPN for >24 months	Mn dose: 550 mcg Duration: 35 months	At 53 m/o, severe headache and amnesia w/o specific neuro findings, $[Mn]_{WB}$ 135.0 mcg/L (reference range, 14.6±4.7 mcg/L). Recurrent pancreatitis and renal dysfunction. Brain MRI w/bilateral and symmetrical hyperintense lesions in the basal ganglia, especially the globus pallidus, tectum, tegmentum of midbrain and pons, superior cerebellar peduncle, corpus callosum, and the deep white matter. Stop Mn supplement. After 5 months, $[Mn]_{WB}$ 20.0 mcg/L. Repeat MRI w/ marked improvement of high-intensity lesions, and only residual slight high-intensity lesion in the globus pallidus. Comments: Case report.
(Kafritsa et al. 1998) United Kingdom	9 y/o boy, w/ enteropathy of unknown etiology since 4 m/o.	11 mg/kg/d for 63 m then 0.55 mg/kg/d for 36 months	Patient 1: $[Mn]_{WB}$ from 17.8 mcg/L to 12.4 mcg/L (reference range, 4.0–11.5 mcg/L). MRI from (+) HI deposits to (-) HI deposits.
	2 y/o girl (sister), w/ enteropathy of unknown etiology since 1 m/o.	11 mg/kg/d for 23 m then 0.55 mg/kg/d for 36 months	Patient 2: $[Mn]_{WB}$ from 28.4 mcg/L to 11.5 mcg/L MRI from (+) HI deposits to (-) HI deposits. Comments: Case reports. Normal neurological and developmental examinations. Purpose: To describe the natural history of Mn deposition in the basal ganglia by MRI in two children following the reduction of PN Mn
(Masumoto et al. 2001) Japan	17 y/o boy s/p colectomy and distal ileectomy when 3 y/o.	Dose: Mn ~170 mcg/day Duration: 4 years	Progressive headaches, dizziness and weakness. mild hepatic dysfunction. $[Mn]_{WB}$ 42 mcg/L (reference range, 8–25 mcg/L). brain MRI w/ symmetrical, HI signal of basal ganglia and slightly intensity of thalamus on T1 images. Stop Mn and symptoms disappeared. MRI after 10 months was negative for Mn deposit.
	13 y/o boy s/p colectomy and distal ileectomy when 4 m/o.	Dose: Mn ~43 mcg/day Duration: 5 years	Progressive headaches, dizziness and weakness. Normal liver. Normal $[Mn]_{WB}$ 13 mcg/L. Brain MRI w/ symmetrical HI signal in basal ganglia and less HI signal in thalamus on T1- images. Stop Mn and symptoms disappear. at 5, 10, and 15 months, brain MRI negative and $[Mn]_{WB}$ 23, 13, and 14 mcg/ Comments: Case reports

First Author, Year, Location	Patient Characteristics	Trace Element Daily Dose, Duration	Reported Findings
(Hsieh et al. 2007) Taiwan	10-y/o female, s/p endorectal pull-through procedure when 8 m/o for Hirschsprung disease. s/p long segment of ischemic bowel resected 3 months earlier	Mn dose: 8 mcg/kg Duration: 3 months	Admitted due to a generalized tonic-clonic seizure, consciousness disturbance, fever and low BP, central line infection. MRI w/ symmetric HI signal on T1- in basal ganglia bilaterally, especially in the globus pallidum. WB Mn level 37 mcg/L, (reference range 4–14 mcg/L). Stop Mn. No more seizure episodes. Comments: Case report.

Abbreviations: d/o, days old; GI, gastrointestinal; HI, high intensity; m/o, months old; Mn, manganese; $[Mn]_{WB}$, whole-blood manganese concentration; MRI, magnetic resonance imaging; PN, parenteral nutrition; s/p, status post; TPN, total parenteral nutrition; WB, whole blood; y/o, years old

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14.10. Nonclinical Pharmacology/Toxicology

Drug Product Specifications

Since the active ingredients in the drug product are inorganic, the specifications do not contain acceptance criteria for drug-related compounds. Therefore, the nonclinical safety assessment of the drug product specifications is focused on the acceptance criteria for elemental impurities, as shown in the Applicant's table below.

Table 48. Acceptance Criteria for Elemental Impurities in the Drug Product

Critical Quality Attribute (CQA)	Target	Justification
[redacted] (b) (4)		

[redacted] (b) (4) Regardless, the maximum dose volume [redacted] (b) (4) based on the proposed pediatric dosing recommendations will be used for the nonclinical safety assessment of elemental impurities that may be intentionally added in TPN as nutritional supplements [redacted] (b) (4) This approach will provide a highly conservative safety assessment that is appropriate for the Applicant's revised pediatric dosing recommendations, which was submitted in the amendment dated May 15, 2020.

Elemental Impurities

The Code of Federal Regulations provides labeling requirements for aluminum levels in large and small volume parenteral products used in TPN (21 CFR 201.323). The Applicant established the aluminum acceptance criterion at not more than [redacted] (b) (4) mcg/L. Safety assessment of the aluminum acceptance criterion should be based on the proposed dose level for pediatric patients weighing 10 kg (the lowest weight in the proposed patient population), since these patients will receive the highest dose on bodyweight basis ([redacted] (b) (4) mL/kg/ day). Previously, the Agency recommended that the amount of aluminum in this drug product be controlled to a limit [redacted] (b) (4) mcg/kg/day (Written Response for Pre-IND 123432 dated December 13,

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2017). Based on the maximum potential dose of (b) (4) mL/kg/ day in pediatric patients and the proposed aluminum limit (b) (4) mcg/L), the maximum potential aluminum dose will be (b) (4) mcg/kg/day, which complies with the Agency's recommendation (b) (4) Therefore, the proposed aluminum acceptance criterion is acceptable.

Safety assessment of other elemental impurities is divided into two categories: 1) elements not intentionally added in TPN as nutritional supplements; 2) elements that may be intentionally added in TPN as nutritional supplements. For elemental impurities in the first category, safety assessment of each element is based on compliance of the maximum daily dose with the Permitted Daily Exposure (PDE), as provided in International Conference on Harmonisation (ICH) Guidance Q3D(R1). For safety assessment of elemental impurities, the Applicant analyzed four batches of drug product (b) (4) The Applicant also measured the concentration of (b) (4) . The PDE values for all specified elemental impurities in the drug product are shown in the Applicant's table below. The acceptance criteria are listed under *"American Regent Specification"* in the table.

Table 49. Permitted Daily Exposure (PDE) for Specified Elemental Impurities in the Drug Product (b) (4)

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Leachables Assessment

The original new drug application (NDA) submission contained leachables data (i.e. levels of individual organic leachables) from only one lot of drug product. In response to an Information Request, the Applicant submitted additional leachables data (report # RD-PR-10-0010, Revision 1) in the amendment dated January 10, 2020. In the study report, leachables data from the original drug product lot and three additional lots is presented. The four lots were analyzed after storage under various conditions, which included storage of the vials in both upright and inverted positions. Details of the storage conditions are described in the Applicant's table below.

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Table 50. Description of Samples Analyzed for Leachable Studies

Lot No.	Sample Orientation	Storage Condition	Sample Age at Testing (End-of-Shelf Life = 24m)	Study Reference
RD17-085	Upright	20 - 25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F)	19 months	Initial[1]
RD17-085.RI	Inverted	25°C ± 2°C/60% RH ± 5% RH	26 months	Additional[2]
RD18-007.40I	Inverted	40°C ± 2°C/75% RH ± 5% RH	6 months at 40°C ± 2°C and additional 5 months at 25°C ± 2°C	Additional[2]
RD18-007.RI	Inverted	25°C ± 2°C/60% RH ± 5% RH	11 months	Additional[2]

[1] Reference: (b) (4)
[2] Reference:

The container closure system is a glass vial with (b) (4) stopper. Prior to the leachables study, extractables studies were conducted with the (b) (4) Stoppers, which may have direct contact with the drug product. The compounds targeted for analysis in the leachables studies were identified as extractables. The analytical methods used in the extractables and leachables studies included GC-MS (for volatile and semi-volatile compounds), LC-UV-MS (for non-volatile and semi-volatile compounds), and ICP-MS (for elements).

The results of the leachables studies indicated that the maximum level among the detected leachables was (b) (4) mcg/mL, which is much lower than the Safety Concern Threshold (SCT) of (b) (4) mcg/mL. (b) (4) No compounds in the cohort of concern (b) (4) were detected in the extractables or leachables studies. Therefore, there is no safety concern for the organic leachables.

(b) (4)

Summary of Product Quality Safety Issues

In summary, the proposed acceptance criteria for each of the specified elemental impurities in the drug product provides a reasonable assurance of safety for the potential exposure from Tralement. For most of the specified elemental impurities, safety assessment was based on compliance of the worst-case exposures (mcg/day) with the respective PDE values. The specifications included acceptance criteria for (b) (4) The proposed acceptance criteria for (b) (4) are acceptable, since the maximum potential exposure (mcg/kg/day) to these elements in Tralement will only be a small fraction of the dose levels routinely used in TPN for children. The Applicant agreed to the Agency's request to reduce the (b) (4) limit by (b) (4) thereby reducing the risk of toxicity from (b) (4) In addition, the proposed aluminum acceptance criterion is acceptable as explained above. The safety concerns related to

the potential impurities [redacted] (b) (4) will be addressed post-approval, as described above. Finally, there is no safety concern for the potential exposure to organic leachables, since the levels of all analytes in the leachables evaluation were well below the safety concern threshold.

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14.11. References

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Pharmacologist	Ke Zhang	OII/DPT-II (co-located with DHN)	**Sections: 5** **Reviewed/Edited: 5** **Appendices: 13.10**	**Select up to two:** _X_Authored ___Cleared
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Lead Pharmacologist	David Joseph	OII/DPT-II (co-located with DHN)	**Sections: 5** **Reviewed/Edited: 5** **Appendices: 13.10**	**Select up to two:** _X_Authored _X_Cleared
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Clinical Pharmacology Team Leader	Insook Kim	OTS/OCP/DIIP	**Sections: 6** **Reviewed/Edited**	**Select up to two:** ___Authored _X_Cleared
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Clinical Reviewer	Yao-Yao Zhu	OND/OII/DHN	Sections Authored: 1, 2, 3, 7, 8,9, 11 Reviewed/Edited/Cleared: ALL	**Select up to two:** _X_Authored _X_Cleared
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