Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date: June 10, 2024

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Product Name	**Pediatric Labeling Approval Date**	**Application Type/Number**	**Applicant**
Selenious acid injection (selenious acid) intravenous solution	April 30, 2019 August 30, 2021	NDA 209379	American Regent Inc.
Zinc sulfate injection (zinc sulfate) intravenous solution	July 18, 2019 October 28, 2020	NDA 209377	
Tralement (trace elements injection 4) intravenous solution	July 2, 2020	NDA 209376	
Multrys (trace elements injection 4) intravenous solution	June 30, 2021		

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for selenious acid injection, zinc sulfate injection, and Tralement/Multrys (trace elements injection 4) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with selenious acid injection, zinc sulfate injection, and trace elements injection 4 in pediatric patients.

Selenious acid injection is a trace element and was initially approved in the U.S. on April 30, 2019. Selenious acid injection is currently indicated in adult and pediatric patients as a source of selenium for parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Zinc sulfate injection is a trace element and was initially approved in the U.S. on May 5, 1987. Zinc sulfate injection is currently indicated in adult and pediatric patients as a source of zinc for PN when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Tralement/Multrys (trace elements injection 4) is a combination of trace elements (zinc sulfate, cupric sulfate, manganese sulfate, and selenious acid). Trace elements inject 4 is indicated as a source of zinc, copper, manganese, and selenium for PN when oral or enteral nutrition is not possible, insufficient, or contraindicated. Tralement was initially approved in the U.S. on July 2, 2020. Tralement is currently indicated in adult and pediatric patients weighing at least 10 kg. Multrys was approved in the U.S. on June 30, 2021. Multrys is currently indicated in neonatal and pediatric patients weighing less than 10 kg.

This pediatric postmarketing pharmacovigilance review was prompted by six pediatric labeling changes:

- Selenious acid injection
  - April 30, 2019: initial drug approval as a source of selenium in PN in pediatric patients
  - August 30, 2021: new age-appropriate formulation to ensure accurate dosing by volume for pediatric patients weighing less than 7 kg
- Zinc sulfate injection
  - July 18, 2019: initial drug approval as a source of zinc in PN in pediatric patients
  - October 28, 2020: new age-appropriate formulation to ensure accurate dosing by volume for pediatric patients weighing less than 12 kg
- Trace elements injection 4
  - July 2, 2020: initial drug approval (Tralement) as a source of zinc, copper, manganese, and selenium in PN for pediatric patients weight at least 10 kg
  - June 30, 2021: new weight-appropriate formulation (Multrys) for pediatric patients weighing less than 10 kg

DPV reviewed all U.S. serious FAERS reports with trace elements in pediatric patients less than 18 years of age from May 5, 1987, through May 14, 2024, and three reports were identified; however, all reports were excluded from further discussion. There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with trace elements in pediatric patients less than 18 years of age.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for selenious acid injection, zinc sulfate injection, and Tralement/Multrys (trace elements injection 4) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with selenious acid injection, zinc sulfate injection, and trace elements injection 4 in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Selenious acid injection is a trace element and was initially approved in the U.S. on April 30, 2019. Selenious acid injection is currently indicated in adult and pediatric patients as a source of selenium for parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated.[1]

Zinc sulfate injection is a trace element and was initially approved in the U.S. on May 5, 1987. Zinc sulfate injection is currently indicated in adult and pediatric patients as a source of zinc for PN when oral or enteral nutrition is not possible, insufficient, or contraindicated.[2]

Tralement/Multrys (trace elements injection 4) is a combination of trace elements (zinc sulfate, cupric sulfate, manganese sulfate, and selenious acid). Trace elements inject 4 is indicated as a source of zinc, copper, manganese, and selenium for PN when oral or enteral nutrition is not possible, insufficient, or contraindicated. Tralement was initially approved in the U.S. on July 2, 2020. Each mL of Tralement contains zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg. Tralement is currently indicated in adult and pediatric patients weighing at least 10 kg.[3] Multrys was approved in the U.S. on June 30, 2021. Each mL of Multrys contains zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg. Multrys is currently indicated in neonatal and pediatric patients weighing less than 10 kg.[4]

Table 1 shows the pediatric labeling changes for selenious acid injection, zinc sulfate injection, and trace elements injection 4.

Table 1. Timeline of Pertinent Selenious Acid Injection, Zinc Sulfate Injection, and Trace Elements Injection 4 Pediatric Labeling Changes

Date	Labeling Change
Selenious acid injection	
April 30, 2019	• Initial drug approval and new chemical entity • New indication: Source of selenium in parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated in adult and pediatric patients[5]
August 30, 2021	• New strength to develop an age-appropriate formulation to ensure accurate dosing by volume for pediatric patients weighing less than 7 kg[6]
Zinc sulfate injection	

Table 1. Timeline of Pertinent Selenious Acid Injection, Zinc Sulfate Injection, and Trace Elements Injection 4 Pediatric Labeling Changes	
Date	Labeling Change
July 18, 2019	• Initial drug approval (for NDA 209377) • New indication: Source of zinc in PN when oral or enteral nutrition is not possible, insufficient, or contraindicated in adult and pediatric[7]
October 28, 2020	• New strength to develop an age-appropriate formulation to ensure accurate dosing by volume for pediatric patients weighing less than 12 kg[8]
Trace elements injection 4	
July 2, 2020	• Initial drug approval • New indication: Indicated for adult and pediatric patients weighing at least 10 kg as a source of zinc, copper, manganese, and selenium for PN when oral or enteral nutrition is not possible, insufficient, or contraindicated.[9]
June 30, 2021	• New strength to develop a weight-appropriate formulation for pediatric patients weighing less than 10 kg[10]
Abbreviations: kg= kilogram; NDA= new drug application; PN=parenteral nutrition	

For the remainder of this review, unless specified, selenious acid injection, zinc sulfate injection, and trace elements injection 4 will be referred to as trace elements.

A pediatric safety review for trace elements have not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The selenious acid, zinc sulfate, and trace elements injection 4 labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional zinc sulfate, selenious acid, and trace elements injection 4 labeling information, please refer to the full prescribing information.

1.2.1 Selenious Acid Intravenous Injection[1]

----------**CONTRAINDICATIONS**----------
None. (4)

----------**WARNINGS AND PRECAUTIONS**----------
•Pulmonary Embolism due to Pulmonary Vascular Precipitates: If signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation. (5.1)
•Vein Damage and Thrombosis: Solutions with osmolarity of 900 mOsmol/L or more must be infused through a central venous catheter. (2.1, 5.2)
•Aluminum Toxicity: Increased risk in patients with renal impairment, including preterm infants. (5.3, 5.4)
•Monitoring and Laboratory Tests: Monitor selenium concentrations, fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, blood count and coagulation parameters throughout treatment. (5.4, 2.5)

----------**ADVERSE REACTIONS**----------
No selenium-related adverse reactions in patients receiving intravenously administered parenteral nutrition solutions containing selenious acid within the recommended dosage range. (6)

8.4 Pediatric Use
Selenious Acid Injection is approved for use in the pediatric population, including neonates, as a source of selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. Safety and dosing recommendations in pediatric patients are based on clinical experience [see Dosage and Administration (2.6)].

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

1.2.2 Zinc Sulfate Intravenous Injection[2]

----------**CONTRAINDICATIONS**----------
Known hypersensitivity to zinc. (4, 5.6)

----------**WARNINGS AND PRECAUTIONS**----------
• Pulmonary Embolism due to Pulmonary Vascular Precipitates: If signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation. (5.1)
• Vein Damage and Thrombosis: Solutions with osmolarity of 900 mOsmol/L or more must be infused through a central catheter. (2.1, 5.2)
• Aluminum Toxicity: Increase risk in patients with renal impairment, including preterm infants (5.3, 8.4)
• Monitoring and Laboratory Tests: Monitor fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, blood count and coagulation parameters throughout treatment. (5.4, 2.4)
• Copper Deficiency: If signs and symptoms develop, interrupt treatment with Zinc Sulfate Injection and check zinc, copper, and ceruloplasmin levels. (5.5)
• Hypersensitivity Reactions: If reactions occur, discontinue Zinc Sulfate Injection and initiate appropriate medical treatment. (5.6)

----------**ADVERSE REACTIONS**----------
No zinc-related adverse reactions in patients receiving intravenously administered parenteral nutrition solutions

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

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

1.2.3 Trace Elements Injection 4[3, 4]

----------**CONTRAINDICATIONS**----------
Hypersensitivity to zinc or copper (4, 5.7)

----------**WARNINGS AND PRECAUTIONS**----------
• Pulmonary Embolism due to Pulmonary Vascular Precipitates: If signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation. (5.1)

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

Multrys[4]

8.4 Pediatric Use

Multrys is approved for use in neonatal and pediatric patients weighing less than 10 kg as a source of zinc, copper, manganese, and selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. Safety and dosing recommendations in pediatric patients less than 10 kg are based on published literature describing controlled studies of products containing zinc, copper, manganese, and selenium [see Dosage and Administration (2.5)].

Tralement[3]

8.4 Pediatric Use

Tralement is approved for use in pediatric patients weighing at least 10 kg as a source of zinc, copper, manganese, and selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. Safety and dosing recommendations in pediatric patients are based on published literature describing controlled studies of products containing zinc, copper, manganese, and selenium [see Dosage and Administration (2.2)].

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

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 2**.

Table 2. FAERS Search Strategy*	
Date of search	May 15, 2024
Time period of search	May 5, 1987† - May 14, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Cupric Sulfate\Manganese Sulfate\Selenious Acid\Zinc Sulfate‡, Zinc Sulfate, Selenious Acid
MedDRA search terms (Version 27.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † U.S. approval date of zinc sulfate injection ‡ Trace elements injection 4 Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from May 5, 1987, through May 14, 2024, with trace elements.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From May 5, 1987, through May 14, 2024, With Trace Elements

	All Reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	129 (62)	117 (52)	12 (7)
Pediatrics (0 - < 18 years)	12 (3)	11 (3)	2 (1)

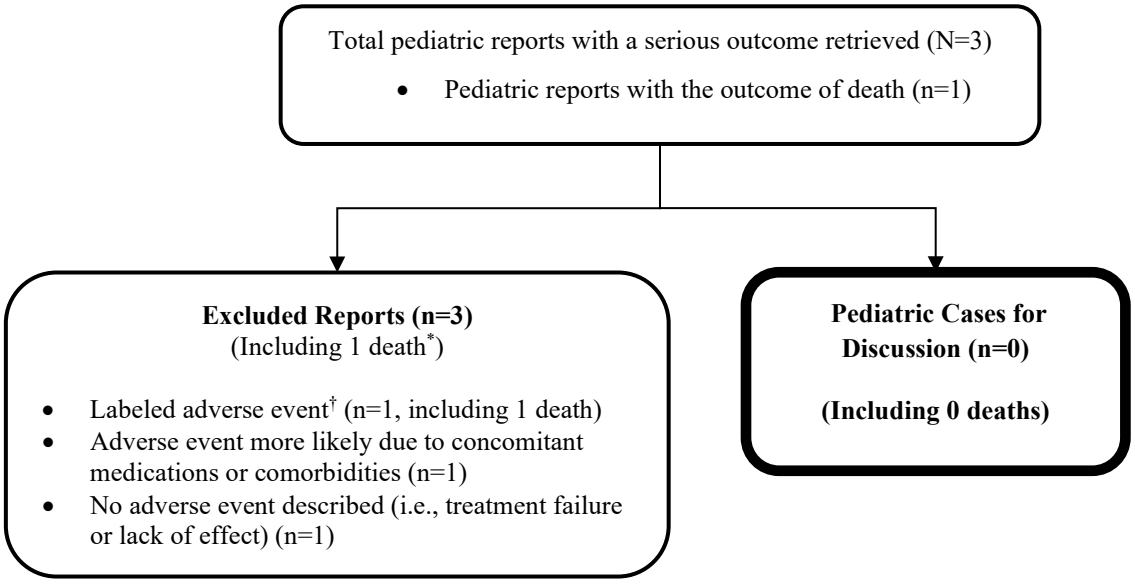
* May include duplicates and transplacental exposures, and have not been assessed for causality

† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved three U.S. serious pediatric reports from May 5, 1987, through May 14, 2024. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all three reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of U.S. Serious Pediatric Cases With Trace Elements



* One excluded U.S. FAERS report described a fatal outcome. The report described an extremely preterm infant born at 26 weeks gestation who died of cardiac failure following a medication error in which the parenteral nutrition solution contained 330 mg/100 mL instead of 330 mcg/100 mL of zinc sulfate (overdosage of 1000-fold). This report is described in the OVERDOSAGE section of the zinc sulfate and trace elements injection 4 labeling.

† Labeled adverse event does not represent increased severity or frequency.

3.1.3 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with trace elements in pediatric patients less than 18 years of age from May 5, 1987, through May 14, 2024, and three reports were identified; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with trace elements in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for trace elements at this time and will continue routine pharmacovigilance monitoring for trace elements.

6 REFERENCES

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10. Dhawan A. Regulatory Project Manager and Clinical Labeling Review for NDA 209376 S-002 Multrys (trace elements injection 4*), injection. June 2021. https://www.fda.gov/media/151047/download?attachment.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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