Division of Hepatology and Nutrition

REGULATORY PROJECT MANAGER and CLINICAL LABELING REVIEW

Applications:

Application	Supplement	Product Name	Date of Submission	Date of Receipt
NDA 209376	S-002	Tralement (trace elements injection 4*), Injection	12/11/2020	12/11/2020

Applicant: American Regent, Inc.

Labeling Reviewed:

Material	Submit Date	Receipt Date	Compared to
Prescribing Information (PI)	12/11/2020	12/11/2020	12/2020 last approved PI

Background and Summary Description

This Prior Approval supplemental new drug application provides for the addition of a new strength (1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL), and this new strength is to fulfill the following postmarketing requirement (PMR) under the Pediatric Research Equity Act (PREA) for:

PMR 3877-02: To develop a weight-appropriate formulation for pediatric patients weighing less than 10 kilograms.

Final report: 12/2020

Review

Regarding the new strength of 1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL developed under PREA PMR, PeRC concurred with the Division's assessment that the new strength fulfilled the above PREA PMR.

In the January 5, 2021 submission, the Applicant proposed [redacted] (b) (4) as the new proprietary name for this new strength. The Division and DMEPA raised safety concerns relating to the proposed [redacted] (b) (4) as part of the new proprietary name because [redacted] (b) (4)

[redacted]. The Division and DMEPA held a teleconference with the Applicant on Friday, March 12, 2021 to convey these concerns. The Applicant acknowledged the Agency's safety concerns and subsequently withdrew the proposed proprietary name [redacted] on March 16, 2021.On March 17, 2021 the Applicant proposed a new proprietary name "Multrys" for this new strength.

The existing approved strength of Tralement (zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg) is indicated for use in pediatric patients weighing at least 10 kg. The increased accuracy of dosing by volume using this new strength (1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL) in pediatric patients weighing < 10 kg would ultimately enhance the safety by "(1) allowing precise dosing and titration with automated equipment in admixing PN; (2) improving sterility by limiting the need for manual manipulation; and (3) minimizing dosing errors potentially introduced with manual manipulation", three main concerns raised during the review of the original NDA submission (refer to the Unireview of Tralement® dated 7/02/2020 in DARRTS). Thus, instructions regarding this new strength would be appropriate to include in the Dosage and Administration section of the labeling. DHN proposed adding the following language in Section 2.5 (underlined) to the PI, and the Applicant agreed. Please note that the rest of the PI language for this new strength "Multrys" are largely similar to the approved "Tralement" PI.

Rationale for recommended dosage in pediatric patients weighing < 0.59 kg

During the review cycle, the non-clinical, clinical pharmacology, clinical, and pediatrics review teams recognized that for neonates weighing < 0.6 kg, daily administration of the smallest volume of Multrys, 0.2 mL, would lead to excess administration of manganese (Mn). Published literature provides evidence that excess Mn can accumulate in the central nervous system which can lead to brain injury and developmental delay. Therefore, the review teams proposed every other day dosing of Multrys of 0.2 mL (i.e., 200 µL) to be added to PN. This would achieve a safe dose of Mn in a volume that can be accurately added to the PN. However, every other day dosing of Multrys in this age group would result in a deficit of zinc, copper, and selenium that would likely lead to deficiencies of these trace elements Therefore, in the full prescribing information (FPI), the review team included Table 2 as noted below so that healthcare providers would know to supplement these trace elements while a neonate weighing < 0.6 kg is taking Multrys.

2.5 Recommended Dosage in Pediatric Patients and Monitoring Considerations

1 https://www.cdc.gov/growthcharts/clinical_charts.htm

Multrys is a fixed-combination product. Each mL of Multrys provides zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg.

Recommended Dosage for Pediatric Patients Weighing 0.4 kg to 0.59 kg

- The total recommended dosage of Multrys is 0.2 mL **every other day.**

- Daily supplementation of Zinc, Copper, and Selenium will be needed to meet daily requirements (See Table 2 below).

Recommended Dosage for Pediatric Patients Weighing 0.6 kg to less than 10 kg

- The recommended dosage of Multrys is 0.3 mL/kg/day rounded to nearest 0.1 mL for up to a maximum of 1 mL per day.

- The recommended volume of Multrys to be added to parenteral nutrition ranges from 0.2 mL per day to 1 mL per day based on body weight, see Table 1 below.

Table 1. Recommended Daily Volume of Multrys and Corresponding Amount of Each Trace Element (mcg)

Body Weight	Recommended Daily Volume	Amount of Trace Element Provided by the Corresponding Multrys Volume			
		Zinc mcg	Copper mcg	Manganese mcg	Selenium mcg
0.6 kg to 0.8 kg	**0.2 mL**	200	12	0.6	1.2
0.9 kg to 1.1 kg	**0.3 mL**	300	18	0.9	1.8
1.2 kg to 1.4 kg	**0.4 mL**	400	24	1.2	2.4
1.5 kg to 1.7 kg	**0.5 mL**	500	30	1.5	3
1.8 kg to 2 kg	**0.6 mL**	600	36	1.8	3.6
2.1 kg to 2.3 kg	**0.7 mL**	700	42	2.1	4.2
2.4 kg to 2.6 kg	**0.8 mL**	800	48	2.4	4.8
2.7 kg to 2.9 kg	**0.9 mL**	900	54	2.7	5.4
3 kg to 9.9 kg	**1 mL**	1,000	60	3	6

Additional Trace Element Supplementation with Multrys

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

- To determine the additional amount of supplementation that is needed, compare the calculated daily recommended dosage based on the body weight of the patient to the amount of each trace element provided by Multrys and enteral nutrition sources.

Table 2: Daily Requirement for Trace Element Supplementation for Pediatric Patients

Trace Element	Patient Weight (kg)	Daily Requirement*
Zinc	Less than 3 kg	400 mcg/kg/day
	3 kg to 5 kg	250 mcg/kg/day
	5 to 10 kg	100 mcg/kg/day
Copper	-	20 mcg/kg/day
Selenium	-	2 mcg/kg/day
Manganese**	-	1 mcg/kg/day

*Multrys is not recommended for pediatric patients who may require a lower dosage of one or more of these individual trace elements.
**Avoid additional manganese supplementation with Multrys use. Accumulation of manganese in the brain can occur with long-term administration with higher than the recommended dosage of 1 mcg/kg/day *[see Warnings and Precautions (5.3)].*

For pediatric patients weighing less than 3 kg, Multrys does not provide the recommended daily dosage of zinc.

- Zinc: For patients weighing less than 3 kg, add Zinc Sulfate to provide total daily recommended dose of 400 mcg/kg/day using parenteral and/or enteral routes of administration.

For pediatric patients weighing 0.4 kg to 0.59 kg and 4 kg to 9.9 kg, Multrys does not provide the recommended daily dosage of copper or selenium.

- Copper: For patients weighing 0.4 to 0.59 kg or 4 kg to 9.9 kg, add Cupric Chloride to provide total daily recommended dose of 20 mcg/kg/day using parenteral and/or enteral routes of administration.

- Selenium: For patients weighing 0.4 to 0.59 kg or 4 kg to 9.9 kg, add Selenious Acid to provide total daily recommended dose of 2 mcg/kg/day using parenteral and/or enteral routes of administration.

Monitoring

- Monitor zinc, copper, and selenium serum concentrations and manganese whole blood concentrations during long-term administration of parenteral nutrition.

- Trace element concentrations may vary depending on the assay used and the laboratory reference range. The collection, processing, and storage of the blood samples should be performed according to the laboratory's sample requirements for analysis.

Warnings and Precautions section 5.7

One other section of labeling that was substantially revised was Warnings and Precautions section 5.7 "Hypersensitivity Reactions with Zinc and Copper". The text was simplified, and extensive description of the symptoms of hypersensitivity were shortened because this clinical background information is not needed in labeling.

5.7 Hypersensitivity Reactions with Zinc and Copper

Postmarket safety reporting has identified zinc hypersensitivity in patients receiving zinc-containing insulin products and copper hypersensitivity in women receiving copper-containing intrauterine devices, providing evidence that patients may experience hypersensitivity reactions when exposed to these metals. If hypersensitivity reactions (e.g., pruritis, angioedema, dyspnea, rash, urticaria) occur in patients receiving Multrys in parenteral nutrition, discontinue Multrys, and initiate appropriate medical treatment *[see Contraindications (4)]*.

The labeling was sent to the Applicant on May 6, 2021 and May 19, 2021; and we received the agreed upon labeling on May 12, 2021 and May 19, 2021.

The DMEPA team reviewed the PI and Carton & Container Labels and provided recommendations in the labeling sent to the applicant on May 6, 2021 and May 13, 2021. The sponsor agreed with the recommendations and submitted the revised Carton & Container Labels which were reviewed by DMEPA (Dr. Sherly Abraham's review dated June 7, 20221 in DARRTS).

Prescribing Information

The version of the PI submitted on May 19, 2021 is considered to be final.

Recommendation(s)

This supplement is recommended for approval.

Reviewers

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