CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217150Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 11, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 217150
Product Name, Dosage Form, and Strength:	Cyclophosphamide Injection, 500 mg/5 mL (100 mg/mL), 1,000 mg/10 mL (100 mg/mL), 2,000 mg/20 mL (100 mg/mL)
Applicant/Sponsor Name:	Sandoz Inc
TTT ID #:	2022-1126-3
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on September 7, 2023 for Cyclophosphamide . We reviewed the revised container labels and carton labeling for Cyclophosphamide (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to a recommendation that we made during a previous label and labeling review.[a] Additionally, we sent additional recommendations to the Applicant regarding revising the route of administration and including the diluents required for dilution on the carton labeling.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Iverson, N. Label and Labeling Review for Cyclophosphamide (NDA 217150). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 SEP 05. TTT ID No.: 2022-1126-2.

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NICOLE F IVERSON
09/11/2023 03:49:45 PM

HINA S MEHTA
09/11/2023 03:53:31 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 09/05/2023

To: David Bak, PharmD, BCNSP, Regulatory Project Manager
Division of Hematological Malignancies II (DHM2)

From: Louiza Bako, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for CYCLOPHOSPHAMIDE injection, for intravenous use

NDA: 217150

Background:
In response to DHM2's consult request dated September 9, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for CYCLOPHOSPHAMIDE injection, for intravenous use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 23, 2023, and we do not have any comments at this time.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on August 30, 2023, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Louiza Bako at (301) 796-3970 or Louiza.Bako@fda.hhs.gov.

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/s/

LOUIZA N BAKO
09/05/2023 02:04:23 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 5, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 217150
Product Name, Dosage Form, and Strength:	Cyclophosphamide Injection, 500 mg/5 mL (100 mg/mL), 1,000 mg/10 mL (100 mg/mL), 2,000 mg/20 mL (100 mg/mL)
Applicant/Sponsor Name:	Sandoz Inc
TTT ID #:	2022-1126-2
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on August 30, 2023 for Cyclophosphamide Injection. We reviewed the revised carton labeling for Cyclophosphamide Injection (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to a request from the Office of Pharmaceutical Quality (OPQ) to revise the container labels and carton labeling to include the inactive ingredients and their quantities as applicable. We note the Applicant was unable to include the inactive ingredients on the container labels due to space limitation, which would cause legibility concerns. However, the Applicant has added the inactive ingredients to the carton labeling as requested. OPQ confirmed that inclusion of the inactive ingredients on the container labels is not necessary if there are space constraints.

2 CONCLUSION

The revised carton labeling is unacceptable from a medication error perspective. We note the strength of the inactive ingredients are presented with a trailing zero (e.g. 1,069.0 mg and 2,138.0 mg).

Reference ID: 5237743

3 RECOMMENDATIONS FOR SANDOZ INC

We recommend the following be implemented prior to approval of this NDA:

A. Carton labeling

1. The strength of the inactive ingredients on the 1,000 mg/10 mL and 2,000 mg/20 mL carton labeling are presented with a trailing zero (e.g., 1,069.0 mg and 2,138.0 mg, respectively). Trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed (e.g., 1,069.0 mg is seen as 10,690 mg and 2,138.0, is seen as 21,380 respectively). We recommend revising the strength statement on the 1,000 mg/10 mL and 2,000 mg/20 mL carton labeling to remove the trailing zero.

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 5237743

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/s/

NICOLE F IVERSON
09/05/2023 09:51:40 AM

HINA S MEHTA
09/05/2023 10:32:47 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs, ORDPURM
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
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MEMORANDUM TO FILE

From:	Dina J. Zand, MD, Medical Officer Division of Pediatrics and Maternal Health (DPMH)
Through:	Mona Khurana, MD, Clinical Team Leader, DPMH John J. Alexander, MD, MPH, Deputy Director, DPMH
To:	Division of Hematologic Malignancies 2
Subject:	505(b)(2) application
Applicant:	Sandoz, Inc
Application:	NDA 217150 – 505(b)(2)
Drug:	cyclophosphamide
Drug Class:	alkylating agent
Indication:	Malignant lymphomas: Hodgkin's lymphoma, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma, (b) (4).
Route of Administration:	Intravenous (IV)
Dosage Form:	Liquid solution for injection: 500 mg/5 mL, 1,000 mg/10 mL 2,000 mg/20 mL in multiple-dose vial
Proposed Dosage:	Intravenous: Initial course for patients with no hematologic deficiency: 40 mg/kg to 50 mg/kg in divided doses over 2 to 5 days. Other regimens include 10 mg/kg to 15 mg/kg given every 7 to 10 days or 3 mg/kg to 5 mg/kg twice weekly.
Proposed Frequency:	25 mg/kg IV, Daily

Materials Reviewed:

DARRTS documents submitted to NDA 217150:

- 03/14/2023 DPMH Consultation Request
- 04/12/2023 Response to Information Request

DARRTS documents submitted to PIND (b) (4)

- 12/11/2019 DPMH Memo

DARRTS documents submitted to NDA 19839/S104 and NDA 020990/S060

- 02/22/2023 DPMH Memo

DARRTS documents submitted to NDA (b) (4)

- 02/15/2019 Joint Memo (DMPH and DCaRP)

Consult Request:

The Division of Hematologic Malignancies 2 (DHM2) requests that DPMH opine upon the levels of ethanol and propylene glycol in the proposed 505(b)(2) product cyclophosphamide as it relates to pediatric patients and safe administration. The Applicant submitted NDA 217150 on August 12, 2022, and the PDUFA goal date for this application is June 12, 2023. The Applicant is relying on Cytoxan (NDA 012142) as the listed drug (LD), which is now discontinued but not for reasons pertaining to safety or effectiveness.

This particular cyclophosphamide product contains both ethanol and propylene glycol as excipients. Two cyclophosphamide products are currently FDA approved that either contain neither of these excipients or contain them in much lower amounts. Cyclophosphamide Injection is approved under NDA 212501 (Ingenus) contains a 2-fold higher concentration of cyclophosphamide (i.e., 200 mg/mL) but with lower concentrations of ethanol and propylene glycol (1.55 grams ethanol and 0.085 grams propylene glycol per 500 mg vial) as excipients relative to the proposed Sandoz product. A cyclophosphamide daily dose of 25 mg/kg IV of the Sandoz product would expose patients to 146 mg/kg/dose of ethanol and 48 mg/kg/day of propylene glycol The reference listed drug (RLD) under NDA 012142 does not contain either ethanol or propylene glycol as excipients. This cyclophosphamide injection product, by comparison, contains two-fold levels of ethanol and eleven-fold levels of propylene glycol compared to the product approved under NDA 212501. (Refer to Table 1)

The Division seeks input from DPMH regarding the following:

1. the risks of use of this cyclophosphamide product in pediatric patients given the increased levels of ethanol and propylene glycol compared to the LD
2. suggested edits to Section 5 (Warnings and Precautions) and sub-section 8.4 (Pediatric Use) of labeling

Reference ID: 5236826

Background

Cyclophosphamide

Cyclophosphamide is an alkylating agent commonly used in combination with other chemotherapies to treat multiple types of pediatric cancers, including acute lymphoblastic leukemia (ALL), medulloblastoma, Ewing's sarcoma, rhabdomyosarcoma, Hodgkin lymphoma (cHL), neuroblastoma, mature B-cell non-Hodgkin lymphoma (NHL), and Wilms' tumor. The main safety concerns include cytopenia and infections, hemorrhagic cystitis, and secondary malignancies. The drug was initially FDA approved in 1959.

Excipients (*Ethanol and Propylene Glycol)*

Ethanol and propylene glycol are (b) (4) used in drug manufacturing. As excipients, both can be identified in multiple dosage forms, including those intended for oral, topical, and injectable solutions. Both compounds are used in processed foods and low exposures in medicinal and food products. Ethanol is also produced endogenously by intestinal gut flora.

The enzyme, alcohol dehydrogenase (ADH), and the mitochondrial enzyme, aldehyde dehydrogenase (ALDH2), are responsible for the metabolism of endogenous and exogenous alcohol while ADH is primarily responsible for the metabolism of propylene glycol. ADH enzymatic activity is not fully attained until 5 years of age. Some data suggest that the rate of ethanol clearance in acutely intoxicated children may be similar to adults,[1,2] although adverse effects have been reported in pediatric patients with lower BAC.[3]

- Ethanol

Acute ethanol toxicity in children can present as hypoglycemia, metabolic acidosis, tachycardia, and hypothermia and can also impact the central nervous system (CNS) via psychomotor impairment and behavior changes.[4] Previous DPMH consults contain well written summaries of ethanol metabolism and discussions of potential ethanol toxicity based on the ethanol excipient content of two other FDA approved products, amlodipine[1] and Zoloft[5]. Refer to these documents for more detailed information.

The FDA final rule, passed in 1995, established standards for the maximum concentration of ethanol as an inactive ingredient in over the counter (OTC) drug products (§21 CFR 328.10).[6] By comparison, the FDA does not have regulation or Guidance for Industry on

[1] see Zuccotti GV, Fabiano V. Safety issues with ethanol as an excipient in drugs intended for pediatric use, Expert Opinion on Drug Safety.2011;10(4):499-502.
[2] European Medicine Agency. Committee on Herbal Medicinal Products (HMPC): Reflection paper on ethanol content in herbal medicinal products and traditional herbal medicinal products used in children. 2010, EMEA/HMPC/85114/2008.
[3] Christiansen N. Ethanol exposure through medicines commonly used in paediatrics. Arch Dis Child Educ Pract Ed. 2015;100:101–104.
[4] (b) (4)
[5] NDA 19839/S104, NDA 20990/S060; Reference ID 5129975
[6] Adults and children 12 years of age and older: max 10% ethanol; children ages 6 to 12 years: max 5%

Reference ID: 5236826

acceptable levels of ethanol in prescription drug products. Professional organizations and other regulatory agencies have issued position statements on the pediatric safety of products containing alcohol as an excipient.[7]

- Propylene glycol

Multiple published reports describe adverse effects in pediatric patients after topical,[8] oral,[9,10,11] and intravenous[12] administration of drugs containing propylene glycol as an excipient and in adults with intravenous administration.[13] The reported adverse effects include central nervous system toxicity, hyperosmolality, hemolysis, cardiac arrhythmia, lactic acidosis, seizures, and respiratory depression.

The World Health Organization (WHO) has set a recommendation for a maximum permissible daily intake of propylene glycol as a food additive at 25 mg/kg.[14] However, this recommendation does not include exposure from pharmaceutical products. Based upon reports by Yaucher et al.[15] and Yahwick et al.[16] the European Medicine Agency (EMA) has recommended propylene glycol dose limits to up to 500 mg/kg/day in adult and pediatric patients ≥ 5 years of age and up to 50 mg/kg/day in children ≥ 1 month to < 5 years. These safety limits were considered for both the intravenous (IV), oral and topical limits (including inhalation) as the oral bioavailability is reportedly near 100%.

The European Union's Guideline on Excipients in the Label and Package leaflet of Medicinal Products for Human Use recommends including the statement, "May cause alcohol-like symptoms", on the package leaflet of parental and oral drugs containing propylene glycol at doses more than 400 mg/kg in adults and 200 mg/kg in children.

In the absence of a public FDA guidance identifying safe or acceptable levels of ethanol and propylene glycol as excipients in investigational products intended for pediatric use, DPMH has considered multiple factors to help inform the safety of proceeding with pediatric development.[17] These factors include, but are not limited to, the treatment

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ethanol; children less than 6 years: max 0.5% ethanol

[7] American Academy of Pediatrics Committee on Drugs. Ethanol in Liquid Preparations Intended for Children" Pediatrics. 1984;73:405-407.

[8] Lim TY, Poole RL, Pageler NM. Propylene Glycol Toxicity in Children. Journal of Pediatric Pharmacology and Therapeutics 19 (4): 277-282, 2014.

[9] Martin G and Finberg L. Propylene Glycol: A Potentially Toxic Vehicle in Liquid Dosage Form. The Journal of Pediatrics 77 (5): 877-878, 1970.

[10] Arulanantham K and Genel M. Brief Clinical and Laboratory Observations Central Nervous System Toxicity Associated with Ingestion of Propylene Glycol. The Journal of Pediatrics 93 (3): 515-516, 1978.

[11] Glover ML and Reed MD. Propylene Glycol: The Safe Diluent that Continues to Cause Harm. Pharmacotherapy 16 (4): 690-693, 1996.

[12] Huggon I, James I, Macrae D. Hyperosmolality Related to Propylene Glycol in an Infant Treated with Enoximone Infusion. British Medical Journal 301: 19-20, 1990.

[13] Wilson KC, Reardon C, Theodore AC, et al. Propylene Glycol Toxicity: A Severe Iatrogenic Illness in ICU Patients Receiving IV Benzodiazepines. A Case Series and Prospective, Observational Pilot Study. Chest 128: 1674-1681, 2005.

[14] Joint FAO/WHO expert Committee on Food Additives, Technical Report Series. 539, 1974.

[15] Yaucher N and Fish J. Propylene Glcycol-Associated Renal Toxicity from Lorazepam Infusion. Pharmacotherapy. 2003: 1094-1099.

[16] Yahwak et al. Determination of a lorazepam dose threshold for using the osmol gap to monitor for propylene glycol toxicity. Pharmacotherapy. 2008;28:984-991.

(b) (4)

Reference ID: 5236826

indication (available treatment options, potential co-morbidities), patient age (maturity of enzymes needed for ethanol metabolism), anticipated level of exposure (dose and dose frequency), and concern for saturation of key enzymes in the metabolic pathway (exposure to other drugs or metabolites that may use the same enzyme).[18] In this formulation of cyclophosphamide, the presence of both ethanol and propylene glycol as excipients may saturate alcohol dehydrogenase (ADH), the rate-limiting enzyme for the metabolic pathway shared by both compounds, and potentially increase systemic levels of both, particularly in pediatric patients less than 5 years of age in whom with hepatic function is likely to still be immature.

Cyclophosphamide Dosing in Pediatric Patients

In the absence of specific FDA guidelines for safe levels of ethanol and propylene glycol to include as excipients in investigational products intended for pediatric use, DPMH recommends assessing the benefit risk on a case-by-case basis based on the individual ethanol and/or propylene glycol content, seriousness of the proposed indication, and availability of alternative treatment.

Two NDAs and multiple ANDAs for cyclophosphamide injection are currently approved for a variety of serious and life-threatening indications in the pediatric population.

The Division provided a comparison of the proposed drug product under NDA 217150, to the following two LDs: Cytoxan approved under NDA 012142 and Cyclophosphamide Injection approved under NDA (b) (4).

[18] DARRTS NDA 206814, DPMH memo dated February 16, 2023 (Reference ID 4391842)

Reference ID: 5236826

Table 1: Comparison of the Proposed Drug Product, Relied Upon Listed Drug Product, and Another Approved Product

	Proposed Drug Product Cyclophosphamide Injection, (NDA 217150) Sandoz	**Listed Drug Product Being Relied Upon** Cytoxan® (cyclophosphamide for injection); NDA 012142 currently held by Baxter Healthcare Corporation	**Listed Drug Product** Cyclophosphamide Injection (NDA 212501) Ingenus
Dosage Form; Strength(s)/Presentation	Ready-To-Dilute (RTD) Solution; 100 mg cyclophosphamide per mL (multiple dose vial containing 500 mg/5 mL, 1000 mg/10 mL, and 2000 mg/20 mL RTD solution)	Lyophilized Powder for Reconstitution with or without Further Dilution (single dose 500 mg, 1000 mg, and 2000 mg per vial)	Ready-To-Dilute (RTD) Solution; 200 mg cyclophosphamide per mL (multiple dose vial containing 500 mg/2.5 mL, 1000 mg/5 mL RTD solution)
Formulation Composition	A 1000 mg/10 mL vial of the RTD solution contains (in addition to 1069 mg cyclophosphamide monohydrate equivalent to 1000 mg cyclophosphamide) Absolute Ethanol (5846.7 mg) Propylene Glycol (1917.3 mg)	A 1000 mg/vial contains (in addition to 1069 mg cyclophosphamide monohydrate equivalent to 1000 mg cyclophosphamide) Mannitol (750 mg)	A 1000 mg/5 mL vial of the RTD solution contains (in addition to 1069 mg cyclophosphamide monohydrate equivalent to 1000 mg cyclophosphamide) Absolute Ethanol (3100 mg) Propylene glycol (170 mg) Polyethylene glycol 400 (170 mg) Monothioglycerol (0.69 mg)
Final Drug Concentration at the point of patient administration	For Direct IV Injection, dilute the required volume of the 100 mg/mL RTD solution to a minimum concentration of 20 mg/mL using 0.9% Sodium Chloride Injection, 5% Dextrose Injection, (b) (4) (b) (4) or 0.45% Sodium Chloride Injection For Intravenous Infusion, dilute the required volume of the 100 mg/mL RTD solution to a minimum concentration of 2 mg/mL using 0.9% Sodium Chloride Injection, 5% Dextrose Injection, (b) (4) (b) (4) (b) (4) or 0.45% Sodium Chloride Injection	For Direct IV Injection, reconstitute powder to 20 mg/mL (with 0.9% Sodium Chloride Injection For IV infusion: Reconstitute powder with 0.9% Sodium Chloride Injection or Sterile Water for Injection to 20 mg/mL, and further dilute to a minimum concentration of 2 mg/mL with 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium chloride Injection or 0.45% Sodium Chloride)	For Direct IV Injection, dilute the required volume of the 200 mg/mL RTD solution to a minimum concentration of 20 mg/mL using 0.9% Sodium Chloride Injection, 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium chloride Injection or 0.45% Sodium Chloride Injection For Intravenous Infusion, dilute the required volume of the 200 mg/mL RTD solution to a minimum concentration of 2 mg/mL using 0.9% Sodium Chloride Injection, 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium chloride Injection or 0.45% Sodium Chloride Injection

Source (b) (4)

An example of ethanol level calculations for this product follow:

With a cyclophosphamide dose of 50 mg/kg over 2 days for the first 2 days of administration in a 60 kg adult: 50 mg/kg = 3000 mg/60 kg = 1500 mg/60 kg/day.

At a drug product concentration of 100 mg/mL, the daily total volume is 15 mL. The excipient levels are listed in Table 2 and compared to the range of excipient levels reported in the FDA inactive ingredient database (IID).

Table 2: Drug Product Formulation and Daily Dose in 60 kg Patient

Component	**Amount/mL**	**mg/day**	**Range of Excipient levels reported in the IID/dose***
Cyclophosphamide	100 mg	1500 mg	N/A
Ethanol	584.67 mg	8770 mg	(alcohol) 400-4650 mg
Propylene glycol	191.73 mg	2876 mg	4000-16624 mg

*IID = FDA inactive ingredient database.[19].

[19] https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-approved-drug-products-search-frequently-asked-questions#what%20is%20inactive%20ing

Reference ID: 5236826

In a response to an FDA information request (IR), the Applicant offered that the maximum dose of cyclophosphamide to be given per day in (b) (4) patients would be 25 mg/kg. In this formulation, 100 mg cyclophosphamide contains 584.67 mg ethanol and 191.73 mg propylene glycol. For each dose of 25 mg/kg cyclophosphamide, the Applicant proposes that patients would receive an estimated 146 mg/kg ethanol and (b) (4) mg/kg propylene glycol.

DHM2 reviewed current pediatric protocols from the Children's Oncology Group (COG) detailing cyclophosphamide use in induction and continuation therapy for pediatric patients who might range from approximately 7 days of age to at least 5 years of age. Doses for these protocols ranged from 250 mg/m^2/dose given every 12 hours (500 mg/m^2/daily for at least two days) to 1.8 gm/m^2/day for at least two days.

Comparison of the Applicant's proposed maximum daily doses (MDD) to ethanol and propylene glycol from use of this cyclophosphamide product at the proposed (b) (4) dosing differs with the maximum daily doses calculated based on pediatric dosing identified in COG protocols. The range of MDD for both ethanol and propylene glycol is broad with the highest MDD (mg/kg/day) calculated in the youngest patients (birth to 1 year) in whom the ability to metabolize these excipients may be the most compromised due to hepatic immaturity.

In a response to IR received on July 14, 2023, the Applicant calculated the MDD of ethanol and propylene glycol with dosing of the proposed product at 500 mg/m^2/day and 1800 mg/m^2/day. See Tables 3 and 4.

Table 3: Cyclophosphamide Dosing of 500 mg/m^2/day

BSA	kg	Estimated Age	Cyclophosphamide (mg/kg/day)	Volume per Dose (ml) [1]	Ethanol MDD (mg) [2]	Ethanol MDD (mg/kg/day)[3]	BAC (mg/100 ml) [4]	Propylene glycol MDD (mg) [5]	Propylene glycol MDD (mg/kg/day)[6]
0.23	4.21	Birth	27.9	1.15	672	163	27.15	220	53.42
0.48	11.54	1 year	21.3	2.40	1403	125	20.76	460	40.85
0.59	14.67	2 years	20.5	2.95	1725	120	19.94	566	39.24
0.69	17.51	3 years	19.8	3.45	2017	116	19.28	661	37.94
0.78	20.28	4 years	19.2	3.90	2280	112	18.69	748	36.76
0.87	23.51	5 years	18.4	4.35	2543	108	17.94	834	35.30

Source: DARRTS, NDA 217150, Response to IR received July 14, 2023, page 2 of 10 (Table 1)

Table 4: Cyclophosphamide Dosing of 1800 mg/m^2/day

BSA	kg	Estimated Age	Cyclophosphamide (mg/kg/day)	Volume per Dose (ml) [1]	Ethanol MDD (mg) [2]	Ethanol MDD (mg/kg/day)[3]	BAC (mg/100 ml)[4]	Propylene glycol MDD (mg) [5]	Propylene glycol MDD (mg/kg/day)[6]
0.23	4.21	Birth	100.3	4.14	2421	586	97.73	794	192.30
0.48	11.54	1 year	76.7	8.64	5052	448	74.74	1657	147.05
0.59	14.67	2 years	73.7	10.62	6209	431	71.79	2036	141.26
0.69	17.51	3 years	71.4	12.42	7262	416	69.41	2381	136.57
0.78	20.28	4 years	69.0	14.04	8209	404	67.27	2692	132.35
0.87	23.51	5 years	66.3	15.66	9156	387	64.58	3002	35.30

Source: DARRTS, NDA 217150, Response to IR received July 14, 2023, page 3 of 10 (Table 2)

Reference ID: 5236826

[1] Taking into account Sandoz's Cyclophosphamide product concentration of 100 mg/ml, volume per dose (ml) is calculated as Cyclophosphamide Max Dose (mg/kg/day) x body weight (kg) / 100 mg/ml. Body weights were calculated based on the average body weight of 95th percentile of boys and girls from WHO standards (0-2 years) or CDC (3-5 years). BSA was calculated based on the Dubois-Dubois formula.
[2] Ethanol MDD (mg) is calculated as concentration of ethanol in Sandoz's Cyclophosphamide product (584.67 mg/ml) x volume per dose (ml)
[3] Ethanol MDD (mg/kg) is calculated as Ethanol MDD (mg) / body weight (kg)
[4] BAC = blood ethanol level, BAC was calculated based on the formula from EMA, 2018.

$$BAC\left(\frac{g}{l}\right) = \frac{\text{Ethanol (g)}}{Vd\left(\frac{l}{kg}\right) * \text{body weight (kg)}}, \qquad Vd = 0.6\ l/kg$$

[5] Propylene glycol MDD (mg) is calculated as concentration of propylene glycol in Sandoz's Cyclophosphamide product (191.73 mg/ml) x volume per dose (ml)
[6] Propylene glycol MDD (mg/kg) is calculated as Propylene glycol MDD (mg) / body weight (kg)

The EMA's suggested limit of exposure to propylene glycol (50 mg/kg) is easily surpassed with use of this cyclophosphamide product at the pediatric dosing specified in the COG protocols.

If this cyclophosphamide product is administered to pediatric patients at dosing specified in the COG protocols, patients are likely to receive MDD of ethanol that would result in detectable blood alcohol levels (BAC) associated with known CNS depressant effects.[20] Administration of this cyclophosphamide product to adults at some doses also has the potential to result in BAC levels close to the federal limit (0.08% or 80 mg/100 mL) for legal driving.

The Division asked the Applicant to provide evidence justifying the pediatric safety of the ethanol and propylene glycol levels as excipients in the proposed product. After calculating the anticipated maximum daily dose of ethanol and propylene glycol in pediatric patients with hepatic immaturity as requested by the Division as part of the second IR, the Applicant proposed to add the following to product labeling:

(b) (4)

[redacted]

[20] Blood Alcohol Content (BAC): What It Is & Levels (clevelandclinic.org); accessed August 29, 2023.

Reference ID: 5236826

The Applicant also proposed wording in Section 5 (Warning and Precautions) to address risks of alcohol exposure in adult patients (subsection 5.7 titled "Alcohol Content").

(b) (4)

(b) (4) In the context of the current range of cyclophosphamide dosing for the pediatric population, DPMH determined that labeling for a limitation of use (LOU) statement across the full pediatric population would be more consistent with guidance, as the benefit of provision of the drug outweigh the risk for non-treatment in the case of a patient with an aggressive pediatric cancer.

So that the LOU is not generalized to all products containing cyclophosphamide, DPMH recommended that the language "this Cyclophosphamide Injection product" be used in labeling to distinguish the product from other cyclophosphamide injection products which may contain different amounts of ethanol and/or propylene glycol or not contain either excipient at all.

Recommendations

DPMH concurred specifying that the product is only indicated for adult patients. In addition, the following wording is recommended in the labeling for NDA 217150:

- **Section 1 Indications and Usage**

  Limitations of Use

  This cyclophosphamide product is not indicated for use in pediatric patients due to the to the alcohol and propylene glycol content in this product. If treatment with cyclophosphamide is indicated in a pediatric patient, use a different formulation *[see Warnings and Precautions (5.7), Use in Specific Populations (8.4), and Description (11)]*.

- **Section 5.7 Alcohol Content**

  Due to the alcohol and propylene glycol content of this product, this cyclophosphamide product is not indicated for use in pediatric patients [see Indications and Usage (1) and Use in Specific Populations (8.4)]. If treatment with cyclophosphamide is indicated for a pediatric patient, use a different cyclophosphamide product.

  The alcohol content in a dose of Cyclophosphamide Injection may affect the central nervous system and should be taken into account for patients in whom

[21] Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format (2011)
[22] Guidance for Industry: Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (2018)

Reference ID: 5236826

alcohol intake should be avoided or minimized. Consideration should be given to the alcohol content in Cyclophosphamide Injection on the ability to drive or use machines immediately after the infusion. Each administration of this cyclophosphamide product at 25 mg/kg/day delivers 146.2 mg/kg of ethanol. For a patient with a BSA of 70 kg, this would deliver 10.23 grams of ethanol. Other cyclophosphamide products may have a different amount of alcohol or no alcohol.

Monitor patients for signs of alcohol intoxication during and after treatment. Counsel patients about the possible effects of the alcohol content in this cyclophosphamide product, including possible effects on the central nervous system.

- **Section 8.4 Pediatric Use**

  This cyclophosphamide product is not indicated for use in pediatric patients due to the alcohol and propylene glycol content of this Cyclophosphamide Injection product. (b) (4) If treatment with cyclophosphamide is indicated in a pediatric patient, use a different formulation. Since propylene glycol and alcohol are both metabolized by the same enzymes, co-administration of these excipients may raise systemic exposure to alcohol, particularly in pediatric patients. *[see Indications and Usage (1), Warnings and Precautions (5.7), and Description (11)]*. Other cyclophosphamide products may have a different amount of alcohol or no alcohol.

  Pre-pubescent girls treated with cyclophosphamide generally develop secondary sexual characteristics normally and have regular menses. Ovarian fibrosis with apparently complete loss of germ cells after prolonged cyclophosphamide treatment in late pre-pubescence has been reported. Girls treated with cyclophosphamide who have retained ovarian function after completing treatment are at increased risk of developing premature menopause.

  Pre-pubescent boys treated with cyclophosphamide develop secondary sexual characteristics normally but may have oligospermia or azoospermia and increased gonadotropin secretion. Some degree of testicular atrophy may occur. Cyclophosphamide-induced azoospermia is reversible in some patients, though the reversibility may not occur for several years after cessation of therapy.

- Labeling should clearly reflect levels of ethanol and propylene glycol in mg/ml for appropriate assessment of exposure with drugs containing the same or similar excipients and cumulative exposure.

Reference ID: 5236826

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/s/

DINA J ZAND
09/01/2023 10:02:10 AM

MONA K KHURANA
09/01/2023 11:45:00 AM

JOHN J ALEXANDER
09/01/2023 03:05:42 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 17, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 217150
Product Name, Dosage Form, and Strength:	Cyclophosphamide Injection, 500 mg/5 mL (100 mg/mL), 1,000 mg/10 mL (100 mg/mL), 2,000 mg/20 mL (100 mg/mL)
Applicant/Sponsor Name:	Sandoz Inc.
TTT ID #:	2022-1126-1
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on June 29, 2023 for Cyclophosphamide Injection. We reviewed the revised container labels and carton labeling for Cyclophosphamide Injection (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] We note the Applicant has identified the format of the expiration date as "MMM YYYY" and the area where the machine-readable 2D data matrix barcode will be printed at product commercialization.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Iverson, N. Label and Labeling Review for Cyclophosphamide Injection (NDA 217150). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAR 21. TTT ID No.: 2022-1126.

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NICOLE F IVERSON
07/17/2023 02:29:40 PM

HINA S MEHTA
07/18/2023 04:53:00 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 21, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 217150
Product Name, Dosage Form, and Strength:	Cyclophosphamide Injection, 500 mg/5 mL (100 mg/mL), 1,000 mg/10 mL (100 mg/mL), 2,000 mg/20 mL (100 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sandoz Inc.
FDA Received Date:	August 12, 2022 and November 8, 2022
TTT ID #:	2022-1126
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

Reference ID: 5145349

1 REASON FOR REVIEW

As part of the approval process of the 505(b)(2) NDA for Cyclophosphamide Injection, we review the proposed Cyclophosphamide Prescribing Information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Sandoz Inc., submitted Cyclophosphamide (NDA 217150) Injection on August 12, 2022, a 505(b)(2) application which relies upon the listed drug (LD), Cytoxan (cyclophosphamide) For Injection under NDA 012142. The LD Cytoxan (Cyclophosphamide) by Baxter Healthcare Corp. (NDA 012142) has been discontinued. However, according to Federal Register Cytoxan was not discontinued or withdrawn for safety or efficacy reasons. Multiple Cyclophosphamide ANDAs are marketed as 500 mg/vial, 1 g/vial, and 2 g/vial. We note Cytoxan is also available as tablets under NDA 012141. Baxter Healthcare Corp. acquired NDA 012141 from Bristol Myers Squibb on February 2, 2009 and started marketing Cytoxan tablets under the established name cyclophosphamide in 2022. Baxter Healthcare Corp. also markets Cyclophosphamide for injection under ANDA 040745 approved on May 21, 2008.

The proposed product is being developed as a ready to use liquid formulation to the reference standard (RS) Cyclophosphamide for Injection (ANDA 040745) by Baxter Healthcare Corp. We note the proposed product will be available as 500 mg/5 mL (100 mg/mL), 1,000 mg/10 mL (100 mg/mL), 2,000 mg/20 mL (100 mg/mL).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

Reference ID: 5145349

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Sandoz Inc. submitted a 505(b)(2) NDA to obtain marketing approval for Cyclophosphamide Injection. As noted above the Listed Drug (LD) for this product, Cytoxan (Cyclophosphamide) Injection NDA 012142 is discontinued. For the purposes of this review, we compared the proposed product to only the injectable form of the listed drug. We note that the proposed Cyclophosphamide Injection has the same route of administration (intravenous use) and the same final concentration after reconstitution for direct intravenous injection (20 mg/mL) and further dilution (2 mg/mL) for intravenous infusion, as the LD Cytoxan. However, there are differences in the proposed presentation as Cyclophosphamide Injection will be available in different strengths (500 mg/5 mL, 1,000 mg/10 mL, 2,000 mg/20 mL vs. 500 mg/vial, 1 g/vial, 2 g/vial) and dosage form (injection vs. For injection). Additionally, both products will be indicated for treatment of malignant diseases; however the LD Cytoxan is also indicated for the treatment of minimal change nephrotic syndrome in pediatric patients. See Appendix A for product characteristics comparison of the LD Cytoxan (NDA 012142) and the proposed Cyclophosphamide Injection product (NDA 217150).

We performed a risk assessment of the proposed container labels, carton labeling, and PI to determine whether there are significant concerns in terms of safety related to preventable medication errors. We note areas of the proposed labels and labeling, that could be revised to improve clarity and readability of important information. For the Division, we note the PI lacks clarity in the recommended dosage and storage information after preparation. We also note lack of readability of the strength statement, the use of negative statements, and terminology inconsistent with current labeling practices. For the Applicant, we note terminology inconsistent with the PI, the format of the expiration date is not defined, lack of readability of the strength statement, and a missing product identifier. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed container labels, carton labeling, and PI that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Sandoz Inc. to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Highlights of Prescribing Information and Prescribing Information

1. Dosage and Administration Section

a. We recommend revising the statements, "Intravenous: Initial course for patients with no hematologic deficiency: 40 mg per kg to 50 mg per kg in divided doses over 2 to 5 days. Other regimens include 10 mg per kg to 15 mg per kg given every 7 to 10 days or 3 mg per kg to 5 mg per kg twice weekly." to "Initial course for patients with no hematologic deficiency: 40 mg/kg to 50 mg/kg intravenously in divided doses over 2 to 5 days. Other regimens include 10 mg/kg to 15 mg/kg intravenously given every 7 to 10 days or 3 mg/kg to 5 mg/kg intravenously twice weekly." for enhanced readability.

2. Dosage Forms and Strengths

a. The strengths (1000 mg/10 mL and 2000 mg/20 mL) are presented as large numbers and appear without comma(s). Numbers greater than or equal to 1,000 should contain a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000". We recommend revising the strength statements to include a comma, for example, to read as [1,000 mg/10 mL instead of 1000 mg/10 mL and 2,000 mg/20 mL instead of 2000 mg/20 mL].

B. Full Prescribing Information

1. Dosage and Administration

a. We recommend revising all instances of the term, "cytotoxic" to "hazardous" to be consistent with current labeling terminology.

b. Section (b) (4)

i. We recommend revising the sub heading title, "(b) (4) " to " (b) (4) Recommended Dosage for Malignant Diseases" to consistent with current labeling practices.

ii. We recommend revising the statements, “When used as the only oncolytic drug therapy, the initial course of cyclophosphamide for patients with no hematologic deficiency usually consists of 40 mg per kg to 50 mg per kg given intravenously in divided doses over a period of 2 to 5 days. Other intravenous regimens include 10 mg per kg to 15 mg per kg given every 7 to 10 days or 3 mg per kg to 5 mg per kg twice weekly.” to “When used as the only oncolytic drug therapy, the initial course of cyclophosphamide for patients with no hematologic deficiency usually consists of 40 mg/kg to 50 mg/kg given intravenously in divided doses over a period of 2 to 5 days. Other intravenous regimens include 10 mg/kg to 15 mg/kg given every 7 to 10 days or 3 mg/kg to 5 mg/kg twice weekly.” for enhanced readability.

c. Section (b) (4) Preparation, Handling and Administration

i. (b) (4)

ii. We recommend revising the statement, “(b) (4) :” to “Aseptically withdraw the prescribed dose from the vial and dilute to a minimum concentration of 2 mg/mL by using any of the following diluents:” for added clarity.

iii. We recommend removing the text from Table 1: Storage of Cyclophosphamide and place in paragraph form as follows, “If the diluted solution is not used immediately, store room temperature at xx°F to xx°F (xx°C to xx°C) for up to 24 hours or refrigerated at xx to xx (x°C to x°C) for up to 6 days. We provide this recommendation as both concentrations of diluted solutions are

stored at the same room temperature and refrigerated temperatures regardless of the diluent solution.

2. Dosage Forms and Strengths

    a. The strengths (1000 mg/10 mL and 2000 mg/20 mL) are presented as a large numbers and appears without comma(s) to improve readability. Numbers greater than or equal to 1,000 should contain a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000". We recommend revising the strength statements to include a comma, for example, to read as (1,000 mg/10 mL instead of 1000 mg/10 mL and 2,000 mg/20 mL instead of 2000 mg/20 mL).

3. How Supplied/Storage and Handling

    a. We recommend revising the statement, "(b) (4) (b) (4)." to "Cyclophosphamide is a hazardous drug."

4.2 RECOMMENDATIONS FOR SANDOZ INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. The strengths (1000 mg/10 mL and 2000 mg/20 mL) are presented as a large numbers and appears without comma(s) to improve readability. Numbers greater than or equal to 1,000 should contain a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000". We recommend revising the strength statements to include a comma, for example, to read as (1,000 mg/10 mL instead of 1000 mg/10 mL and 2,000 mg/20 mL instead of 2000 mg/20 mL).
2. (b) (4)
3. We recommend revising the warning, "(b) (4)" to "Hazardous Drug" to be consistent with current labeling terminology.
4. To ensure consistency with the terminology in the Prescribing Information. We recommend revising the recommended dosage statement from, "(b) (4) (b) (4) (b) (4)." to read, "Dosage: See Prescribing Information."

5. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date.
6. (b) (4)

B. Carton Labeling

1. The machine-readable 2D data matrix barcode is missing. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling.
2. Add the net quantity statement "One 5 mL Multiple-Dose Vial", "One 10 mL Multiple-Dose Vial", and "One 20 mL Multiple-Dose Vial" on the principal display panel of the carton labeling in accordance with 21 CFR 201.51(a).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Cyclophosphamide received on November 8, 2022 from Sandoz Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Cyclophosphamide and the Listed Drug		
Product Name	Cyclophosphamide	Cyclophosphamide[a] NDA 012142
Initial Approval Date	N/A	November 16, 1959
Active Ingredient	Cyclophosphamide	Cyclophosphamide
Indication	• Malignant lymphomas (Stages III and IV of the Ann Arbor staging system), Hodgkin's lymphoma, lymphocytic lymphoma (nodular or diffuse), mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma • Multiple myeloma • Leukemias: Chronic lymphocytic leukemia, chronic granulocytic leukemia (it is usually ineffective in acute blastic crisis), acute myelogenous and monocytic leukemia, acute lymphoblastic (stem-cell) leukemia	• Malignant lymphomas (Stages III and IV of the Ann Arbor staging system), Hodgkin's lymphoma, lymphocytic lymphoma (nodular or diffuse), mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma • Multiple myeloma • Leukemias: Chronic lymphocytic leukemia, chronic granulocytic leukemia (it is usually ineffective in acute blastic crisis), acute

[a] Cyclophoshamide [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2013 MAY 7. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/012141s090,012142s112lbl.pdf

	(cyclophosphamide given during remission is effective in prolonging its duration) • Mycosis fungoides (advanced disease) • Neuroblastoma (disseminated disease) • Adenocarcinoma of the ovary • Retinoblastoma • Carcinoma of the breast	myelogenous and monocytic leukemia, acute lymphoblastic (stem-cell) leukemia (cyclophosphamide given during remission is effective in prolonging its duration) • Mycosis fungoides (advanced disease) • Neuroblastoma (disseminated disease) • Adenocarcinoma of the ovary • Retinoblastoma • Carcinoma of the breast • Minimal Change Nephrotic Syndrome in Pediatric Patients: biopsy proven minimal change nephrotic syndrome patients who failed to adequately respond to or are unable to tolerate adrenocorticosteroid therapy
Route of Administration	Intravenous	Oral and Intravenous
Dosage Form	Injection	
Strength	• 500 mg/5 mL (100 mg/mL) • 1,000 mg/10 mL (100 mg/mL) • 2,000 mg/20 mL (100 mg/mL)	Injection • 500 mg/vial • 1 g/vial • 2 g/vial Tablet • 25 mg

<table>
<tr><td></td><td></td><td>• 50 mg</td></tr>
<tr><td>Dose and Frequency</td><td>• Initial course for patients with no hematologic deficiency: 40 mg per kg to 50 mg per kg in divided doses over 2 to 5 days. Other regimens include 10 mg per kg to 15 mg per kg given every 7 to 10 days or 3 mg per kg to 5 mg per kg twice weekly.</td><td>Intravenous
• Initial course for patients with no hematologic deficiency: 40 mg per kg to 50 mg per kg in divided doses over 2 to 5 days. Other regimens include 10 mg per kg to 15 mg per kg given every 7 to 10 days or 3 mg per kg to 5 mg per kg twice weekly.
Oral
• 1 mg per kg per day to 5 mg per kg per day for both initial and maintenance dosing.

Minimal Change Nephrotic Syndrome in Pediatric Patients
Recommended oral dose: 2 mg per kg daily for 8 to 12 weeks (maximum cumulative dose 168 mg per kg). Treatment beyond 90 days increases the probability of sterility in males.</td></tr>
<tr><td>How Supplied</td><td>Cyclophosphamide Injection, 100 mg/mL is a sterile ready-to-dilute, clear, colorless to pale-yellow solution in a multiple-dose vial available in the following strengths:
<table><tr><th>Strength</th><th>NDC Number</th><th>Volume</th></tr></table></td><td>Cyclophosphamide for Injection, USP (lyophilized powder) is a sterile white cake containing cyclophosphamide and mannitol and is supplied in vials for single dose use.

• NDC 10019-988-01 500 mg vial, carton of 1</td></tr>
</table>

<table>
<tr>
<td></td>
<td>
<table>
<tr><td>500 mg/5 mL</td><td>0781-3528-10</td><td>Carton of one 5 mL Multiple-Dose Vial</td></tr>
<tr><td>1,000 mg/10 mL</td><td>0781-3529-10</td><td>Carton of one 10 mL Multiple-Dose Vial</td></tr>
<tr><td>2,000 mg/20 mL</td><td>0781-3530-10</td><td>Carton of one 20 mL Multiple-Dose Vial</td></tr>
</table>
</td>
<td>

NDC 10019-989-01 1 g vial, carton of 1
NDC 10019-990-01 2 g vial, carton of 1

</td>
</tr>
<tr>
<td>Storage</td>
<td>Store vials refrigerated at 2°C to 8°C (36°F to 46°F).</td>
<td>Store vials at or below 25°C (77°F).</td>
</tr>
</table>

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Cyclophosphamide labels and labeling submitted by Sandoz Inc..

- Container labels received on August 12, 2022
- Carton labeling received on August 12, 2022
- Prescribing Information (Image not shown) received on November 8, 2022, available from \\CDSESUB1\EVSPROD\nda217150\0006\m1\us\114-labeling\draft\labeling\draft-labeling-text-pdf.pdf

F.2 Label and Labeling Images

Container labels

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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