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APPLICATION NUMBER:

217150Orig1s000

CLINICAL REVIEW(S)

NDA 217150 Cyclophosphamide Clinical and Labeling Review

Product	Cyclophosphamide Injection
Applicant	Sandoz, Inc.
Application/Supplement Number	NDA 217150
Type of Application/Submission[1]	505(b)(2) NDA
Is Proposed Labeling in "Old" Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s)	**Treatment of adult** (b) (4) **patients with malignant diseases**: malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
Approved Indication(s)	N/A
Date FDA Received Application	August 12, 2022
Review Classification (Priority/Standard)	Standard
PDUFA Goal Date	September 12, 2023
Review Date	September 12, 2023
Clinical Reviewer	Pamela Seam, MD
Associate Director for Labeling Reviewer	Elizabeth Everhart, MSN, RN, ACNP
Team Leader	Nicholas Richardson, DO, MPH
Signatory	Nicholas Richardson, DO, MPH

This joint Associate Director for Labeling (ADL) and Clinical review provides an evaluation of the relevant information for this application and recommendations on the content and format of the United States Prescribing Information (USPI) to help ensure that the USPI:

- Is compliant with Physician Labeling Rule (PLR) [including the Pregnancy and Lactation Labeling Rule (PLLR)] requirements[2],
- Is consistent with labeling guidance recommendations[3] and with CDER labeling policies, as appropriate,
- Conveys the essential scientific information needed for safe and effective use of the drug,
- Is clinically meaningful and scientifically accurate,
- Is a useful communication tool for health care practitioners, and
- Is consistent with other USPI with the same active moiety, drug class, or similar indication, as appropriate.

Regulatory History

Sandoz, Inc., submitted NDA 217150 in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, and is seeking approval for Cyclophosphamide Injection (100 mg/mL; supplied as 500 mg/5 mL, 1000 mg/10 mL, and 2000 mg/20 mL strengths) for the treatment of patients with malignant lymphomas, multiple myeloma, leukemias, advanced mycosis fungoides, disseminated neuroblastoma, ovarian adenocarcinoma, retinoblastoma, and breast carcinoma. The active pharmaceutical ingredient (API), route of administration, dosing regimen, (b) (4) (b) (4) sought for the proposed cyclophosphamide formulation are the same as the listed drug (LD), Cytoxan (NDA 012142), and the reference standard (RS), Cyclophosphamide for Injection (ANDA 040745). The proposed Sandoz product is a ready to use liquid formulation and the excipient profile of the proposed cyclophosphamide formulation differs from the LD and the RS.

On June 6, 2023, a major amendment to the NDA was issued and the PDUFA date was extended by 3 months to September 12, 2023. Refer to the CMC review for additional information on the data submitted that qualified for a major amendment.

Clinical Review:
Sandoz has developed a ready-to-use (dilute) liquid formulation of the reference product Cyclophosphamide (Baxter), which is a sterile powder. The Sandoz product is available in three presentations, 500 mg/5 ml, 1000 mg/10 ml, and 2000 mg/20 ml. The ready-to-use (dilute) formulation shortens the preparation time in the pharmacy by eliminating the reconstitution step and, per the Applicant, reduces the potential risk of contamination as well as the exposure risk to cytotoxic drug residuals. (b) (4) The Applicant is proposing a 100 mg/ml ready-to-dilute solution formulation in ethanol and propylene glycol.

Maximum Daily Dose:
The recommended dosage is 40 mg/kg to 50 mg/kg in divided doses over 2 to 5 days, which equals 50 mg/kg divided over 2 days (25 mg/kg/day). Based on an average body weight of 70 kg, the maximum daily dose is 25 mg/kg/day x 70 kg = 1750 mg/day.

The maximum daily exposure to the active pharmaceutical ingredient and excipients are summarized in the table below for a 70 kg patient.

Component	**Amount/mL**	**Max Daily Exposure/70 kg**	**Max Levels in IID (IV route)**
Cyclophosphamide	100 mg	1,750 mg	N/A
Ethanol	**584.7 mg**	**10,232 mg**	**4,650 mg**
Propylene glycol	191.7 mg	3,355 mg	16,624 mg

Abbreviations: IID, FDA Inactive Ingredient Database; N/A, not applicable

The maximum daily exposure of ethanol for the proposed drug product exceeds the FDA Inactive Ingredient Database limit and may pose potential safety risks to patients. (b) (4)

To evaluate the risk of ethanol exposure in pediatric patients and any associated pediatric labeling, the Division of Pediatrics and Maternal Health (DPMH) was consulted. See the DPMH consult review for additional information. A summary of the risks and the Division's interpretation and resulting labeling is provided below.

The risk of ethanol exposure was performed by considering the following:

- Assuming a maximum daily cyclophosphamide dose of 25 mg/kg day in patients ≥ 5 years of age, the maximum daily doses of ethanol and propylene glycol that would be delivered are shown below in the following table provided by the Applicant alongside the corresponding blood alcohol content:

Age (years)	Ethanol MDD (mg/kg/day)	Propylene glycol (MDD mg/kg/day)	BAC (mg/100 mL)
5	146.2	47.9	24.4
10	146.2	47.9	24.4
Adult	146.2	47.9	24.4

- Assuming a maximum daily cyclophosphamide dose of 25 mg/kg day in patients < 5 years of age, the maximum daily doses of ethanol and propylene glycol that would be delivered are shown below in the following table also provided by the Applicant alongside the corresponding blood alcohol content:

Age (years)	Ethanol MDD (mg/kg/day)	Propylene glycol (MDD mg/kg/day)	BAC (mg/100 mL)
0	146.3	47.9	24.4
1	146.2	47.9	24.4
2	146.1	47.9	24.4

3	146.1	47.9	24.4
4	146.2	47.9	24.4

- The legal definition of intoxication in the US is a BAC of ≥ 0.08% (≥ 80 mg/dL, [17.4 mmol/L]). The known risks of ethanol exposure in adults based on blood alcohol concentration (BAC) are shown in the following table:

Blood alcohol concentration	Clinical effects
20-50 mg/dL (4.4-11 mmol/L)	Diminished fine motor coordination
50-100 mg/dL (11-22 mmol/L)	Impaired judgment; impaired coordination
100-150 (22-33 mmol/L)	Difficulty with gait and balance
150-250 mg/dL (33-55mmol/L)	Lethargy; difficulty sitting upright without assistance
300 mg/dL (66 mmol/L)	Coma in the non-habituated drinker
400 mg/dL (88 mmol/L)	Respiratory depression

  - The European Guidelines for Excipients in the Label and Package Leaflet of Medicinal Products for Human Use (2003) requires warning statements in the package leaflet for threshold alcohol levels between 15 to less than 75 mg/kg/dose. At these levels, a warning in the package leaflet in respect to effects in young children only is recommended.

    The Applicant noted that the European Guidelines recommend medicinal products with > 3 grams of ethanol per dose include labeling that indicates that the amount of alcohol in the medicinal product may impair the ability to drive or use machines. The Applicant acknowledged the risk of CNS toxicity associated with alcohol use and as a risk mitigation measure, included the following Warning and Precaution in the label:

    > Alcohol content: The alcohol content in a dose of Cyclophosphamide Injection may affect the central nervous system. This may include impairment of a patient's ability to drive or use machines immediately after infusion. (5.7).

- The European Guidelines for Excipients in the Label and Package Leaflet of Medicinal Products for Human Use (2003) provides the following limits on propylene glycol use, expressed in terms of maximum daily dose, that are considered to be safe and with no noticeable effects whatever the duration and the route of administration, with the exception of inhalation. Special attention is required to avoid hyperosmolality, CNS, cardiovascular, and/or respiratory effects during bolus parenteral administration.

Age Group	Neonates up to 28 days or 44 weeks post menstrual age for preterms	1 month (29 days) up to 4 years	5 years up to 17 years and adults
Safety limits	1 mg/kg	50 mg/kg	500 /kg

- The maximum daily exposure to ethanol in pediatric patients at doses used in standard clinical care were requested by FDA and are summarized in tables below provided by the Applicant. The tables shown below demonstrate the calculated Maximum Daily Dose for ethanol and propylene glycol and the BAC for ethanol associated with cyclophosphamide dosing of both 500 mg/m^2/day and 1800 mg/m^2/day. The [redacted] (b) (4)

Table 1: Cyclophosphamide dosing of 500 mg/m²/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

Table 2: Cyclophosphamide dosing of 1800 mg/m²/day

BSA	kg	Estimated Age	Cyclophosphamide (mg/kg/day)	Volume per Dose [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	127.07

- Ethanol and propylene glycol undergo hepatic metabolism. Based on the proposed formulation and a cyclophosphamide maximum daily dose of 25 mg/kg IV, the use of this product has the potential to result in an ethanol exposure of 146 mg/kg/dose and a propylene glycol dose of 48 mg/kg/day. Patients < 5 years with hepatic immaturity could experience a blood alcohol content of 24.4 mg/100 ml and a propylene glycol MDD of 47.9 mg/kg/day. When used at higher doses or in combination with other chemotherapeutic agents that are also metabolized by the liver, the potential for risk for toxicity associated with cyclophosphamide exposure could be increased among patients, particularly pediatric patients.

- Given the risk for toxicity due to ethanol exposure along with concomitant propylene glycol exposure across the various dosages and regimens used, the availability of other cyclophosphamide products, and the limited medical need, the risk outweighs the potential benefit of this cyclophosphamide product in a pediatric population. A Limitation of Use is, therefore, being implemented to ensure safe use. The limitation of use is as follows:
    - This cyclophosphamide product is not recommended to be used in pediatric patients due to the alcohol and propylene glycol content in this product. If treatment with cyclophosphamide is indicated in a pediatric patient, a different formulation is recommended.

Labeling Review:
Throughout the USPI, changes were made by FDA to align with current labeling practice and the labeling of other cyclophosphamide products.

The following substantive labeling changes made by the FDA to the USPI are described below; for final agreed upon labeling, see the approval letter for NDA 217150:

- In the Highlights and throughout the USPI, in places where the TRADENAME should appear, the product was referred to as Cyclophosphamide Injection since it has no proposed tradename. When describing clinical studies or data derived from studies with the LD, the product is referred to as cyclophosphamide.
- In section 1, (b) (4). A Limitations of Use (LOU) was added to note that this cyclophosphamide injection product is not indicated for pediatric patients and that another formulation should be used if cyclophosphamide treatment is indicated for a pediatric patient.
- In subsection 2.1, a new subsection Important Dosing Information added to note that fluid should be given to reduce the risk of urinary tract toxicity and that Cyclophosphamide Injection should be given in the morning.
- Throughout section 2 Dosage and Administration, changes were made to improve readability, align with

current labeling practice, and avoid potentially speculative or promotional claims.

- In section 5 Warnings and Precautions, updates were made to align with current labeling practice throughout.
    - Subsection 5.7 was rewritten to add language denoting the LOU in all pediatric patients due to this cyclophosphamide injection's ethanol and propylene glycol content. Additionally, the ethanol content of this product and the corresponding ethanol (in grams) delivered to a patient per dose were added. Recommendations to monitor patients for signs of alcohol intoxication during and after treatment were added.
- In section 6 Adverse Reactions, revisions were made to include adverse reactions (ARs) in one subsection 6.1 Clinical Trials and Postmarketing Experience to reduce redundancy and better handle clinical trial ARs previously included in subsection 6.2 (Postmarketing Experience).
- Section 7 Drug Interactions was revised to align with current labeling practice and to improve readability and clarity throughout.
- Subsections 8.1-8.3 Pregnancy, Lactation, and Females and Males of Reproductive Potential were revised to align with recommendations in the Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products as well as with current labeling practice.
- Subsection 8.4 Pediatric Use was revised to include the LOU statement and that co-administration of the excipients in this cyclophosphamide product (ethanol and polypropylene) may raise systemic exposure to alcohol, particularly in pediatric patients.
- Section 11 Description was revised to include the name and quantities of all inactive ingredients (dehydrated alcohol and propylene glycol). For the dehydrated alcohol, the amount of alcohol in terms of percent volume was also listed as %v/v (volume per volume).
- Section 12 Clinical Pharmacology was updated throughout to align with current labeling practice and to improve readability and clarity.
    - In subsection 12.2 Pharmacodynamics, a statement that the exposure-response relationship and time course of pharmacodynamic response have not been fully characterized as per 21 CFR 201.57(c)(13)(i)(B).
    - In subsection 12.3 Pharmacokinetics, information about inactive metabolites (those that do not contribute to the overall efficacy or toxicity of the drug) was deleted to align with regulations and recommendations in the Guidance for Industry: Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products – Considerations, Content, and Format.
- Section 17 Patient Counseling was updated to align with changes made in section 5 Warnings and Precautions.

Conclusion(s):

The Applicant is proposing cyclophosphamide 100 mg/ml ready-to-dilute solution formulation in ethanol and propylene glycol. The maximum daily exposure of ethanol for the proposed drug product exceeds the FDA Inactive Ingredient Database limit and may pose potential safety risks to patients. The risk of ethanol exposure was primarily evaluated based on the resulting blood alcohol concentration. The known BAC effects are based on the effect in adults. In adults, the legal definition of intoxication in the US is a BAC of ≥ 0.08% (≥ 80 mg/dL, [17.4 mmol/L]). The effect of BAC in pediatric patients is unknown. At the recommended dose of this cyclophosphamide product at 25 mg/kg/day, a BAC of 24 mg/dL is expected, which correlates with diminished fine motor coordination in adults. Further, at doses used in pediatric protocols to treat pediatric patients with solid tumors at 500 mg/m^2/day and 1800 mg/m^2/day, the potential BAC is 18 to 27 mg/dL and 65 to 98 mg/dL, respectively. Higher doses lead to a BAC over the legal limit in adults. Most notably, the effect of such BAC levels in pediatric patients is unknown and may be increased. Additionally, this cyclophosphamide product also contains propylene glycol, which is hepatically metabolized along with ethanol. The concurrent hepatic metabolism further increases the risk of exposure to ethanol and/or propylene glycol. This is further compounded by the fact that cyclophosphamide is commonly administered in combination with other chemotherapeutic agents and supportive medications that also rely on hepatic metabolism. Based on the totality of information and the assessed risk, this cyclophosphamide product is not safe to be used in pediatric patients under its conditions of use. Therefore, a limitation of use (as described above) will be implemented to ensure safe administration of this cyclophosphamide product.

For adult patients, the risk of ethanol exposure is within accepted limits and consistent with other approved products used to treatment patients with cancer. Thus, the potential benefit in adult patients outweighs the risk. [redacted]$^{(b)(4)}$. However, the level of ethanol exposure is an important identified risk for adults and is included as a Warning & Precaution and included in the

Patient Information section of the label.

Final agreed upon labeling that included (b) (4) (b) (4) (b) (4) the limitation of use for pediatric patients was submitted by the Applicant on September 8, 2023.

References:

[1] Examples include: Original Biologics License Application (BLA), New Molecular Entity (NME) NDA, Original NDA, NDA Efficacy Supplement, 505(b)(2) New Drug Application (NDA), New Chemical Entity (NCE) NDA, NDA Prior Approval Labeling Supplement, NDA CBE-0 Labeling Supplement

[2] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(a) and (e) and 201.80.

[3] See *Prescription Drug Labeling Resources* website for PLR labeling guidances. When final, guidances represent the FDA's current thinking on a topic. Applicants can use an alternative approach if it satisfies statutory and regulatory requirements.

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