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APPLICATION NUMBER:

217150Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 217150
Supporting document/s:	1 (sequence number 0001)
Applicant's letter date:	August 12, 2022
CDER stamp date:	August 12, 2022
Product:	Cyclophosphamide Injection
Indication:	Adults with Hodgkin's lymphoma, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma, multiple myeloma, mycosis fungoides, neuroblastoma, adenocarcinoma of the ovary, retinoblastoma, breast carcinoma, (b) (4) (b) (4)
Applicant:	Sandoz, Inc.
Review Division:	DHMII/DHOT
Reviewer:	Simon Williams, PhD
Supervisor:	Brenda Gehrke, PhD
Division Director:	Nicole Gormley, MD (DHMII)
Project Manager:	Dave Bak, PharmD, BCNSP

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1 Executive Summary

1.1 Introduction

The Applicant, Sandoz, Inc., submitted NDA 217150 in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, and is seeking marketing approval for Cyclophosphamide Injection (100 mg/mL; supplied at 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, and (b) (4) sought for the proposed cyclophosphamide formulation, the listed drug (LD), Cytoxan (NDA 012142), and the reference standard (RS), Cyclophosphamide for Injection (ANDA 040745), are the same. The excipient profile of the proposed cyclophosphamide formulation differs from the LD and the RS.

1.2 Brief Discussion of Nonclinical Findings

For the current NDA, the Applicant submitted toxicology studies and assessments to support the proposed formulation and impurity profiles. The data included a non-GLP dose range finding (DRF) study in rats (submitted upon request) where the animals were dosed for 5 consecutive days, a plasma protein binding study, a hemolysis and plasma compatibility study, an excipients assessment, an impurities assessment, and a series of extractables and leachables reports.

Extractables reports were submitted for contact materials in the drug product manufacturing process, including (b) (4) and the container-closure system. The compounds extracted in the various “worst-case” conditions were not at levels determined to be unsafe from a toxicological perspective. The proposed specifications for impurities ImpB, (b) (4) were adequately qualified by the assessments. The high protein binding was comparable between the proposed drug product, the API, and the reference product, and the proposed drug was not hemolytic under the conditions tested. The rat DRF study, while not designed to support safety at the injection site and conducted at sub-therapeutic levels, did not produce any toxicological signals on the skin.

1.3 Recommendations

1.3.1 Approvability

Recommended for approval. There are no Pharmacology/Toxicology concerns with the proposed Cyclophosphamide Injection drug product.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

The high levels of ethanol in the drug product were addressed by a Warning and Precaution and additional language in the label.

2 Drug Information

2.3 Drug Formulation

The proposed formulation for Cyclophosphamide for Injection is presented in the table below:

Formulations for Cyclophosphamide for Injection drug product (excerpted from the Applicant's submission)

Component	Function	Quality Standard	Cyclophosphamide injection, 100 mg/mL				Concentration (% w/w)	Maximum Daily Intake (MDI)	IID[1] Limit for intravenous Route of Administration
			Amount per mL (mg/mL)	Amount per Unit (500 mg/5 mL)	Amount per Unit (1000 mg/10 mL)	Amount per Unit (2000 mg/20 mL)			
Cyclophosphamide (Cyclophosphamide monohydrate)	Drug substance	USP and in-house	100.00 mg (106.9 mg)	500.0 mg (534.5 mg)	1000.0 mg (1069.0 mg)	2000.0 mg (2138.0 mg)	11.32 % (12.11)	1750 mg	N/A
Ethanol absolute[2]	(b) (4)	USP	584.67 mg	2.923 g	5.847 g	11.693 g	66.22 %	10.232g[2]	92 % w/v
Propylene glycol[2]		USP	191.73 mg	958.7 mg	1.917 g	3.835 g	21.71 %	3.355g[2]	63.4 % w/v
Total weight			883.3 mg	4.42 g	8.83 g	17.67 g	/	/	/

[1] IID refers to the Inactive Ingredient Database posted at the FDA website, http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. Last updated 18/01/2022

[2] Please refer to the Excipients safety report (2022_009_VP) included in *Module 4* for more information.

The levels of the excipients are summarized in the table below. The highest dose values are based on the proposed 50 mg/kg over 2 days dosing schedule (25 mg/kg/day).

Excipient levels

Excipient	Quantity (mg)	
	Per mL	Per dose (15 mL/60 kg patient/day)
Ethanol	584.67	8770.05
Propylene glycol	191.73	2875.95

The proposed excipient levels were considered reasonable from a Pharmacology/Toxicology perspective. The inactive ingredient database (IID) contains several intravenously (IV) delivered products with propylene glycol levels greater than the proposed 2.8 grams. The highest ethanol excipient level in IV administered drugs in the IID was 4.65 grams per dose, which is notably lower that the 8.77 grams in the proposed formulation. A Warning and Precaution in the label (Section 5.7) that describes the ethanol content and the potential toxicities in adults was included by the Applicant and has been modified by the labeling team. (b) (4) See the clinical review for additional details regarding this decision.

Comments on Novel Excipients

There are no novel excipients used in the proposed formulation.

2.5 Comments on Impurities/Degradants of Concern

Qualification of impurity specifications

Three identified impurities, ImpB, (b) (4), are proposed to be controlled with specifications that are higher than the qualification threshold of a total daily intake of

0.2% or 3 mg for a drug with a maximum daily dose of 101-2000 mg (ICH Q3B; the maximum daily dose of cyclophosphamide is 1500 mg for a 60 kg patient) and therefore, require qualification. The proposed limits of the 3 impurities are summarized in the table below.

Proposed impurity limits

Impurity	Proposed limit	Cyclophosphamide/dose/day/60kg	Impurity limit at proposed dose	Proposed limit acceptable?
(b) (4)	(b) (4)%	1500 mg	(b) (4) mg	Yes
(b) (4)	(b) (4)%		(b) (4) mg	Yes
ImpB	(b) (4)%		(b) (4) mg	Yes

(b) (4) may have a risk of mutagenicity, (b) (4) (b) (4) This qualifies the proposed specification for (b) (4) (b) (4) Published animal studies support a maximum daily dose of (b) (4) mg/day, which qualifies the proposed specification.

ImpB is a metabolite and degradation product of cyclophosphamide and found in patient urine up to (b) (4) mg. This qualifies the proposed limit.

Extractables/leachables assessments

The Applicant submitted a series of extractables/leachables assessments related to the processing of the Cyclophosphamide for Injection drug product and its high ethanol levels.

(b) (4)

(b) (4)

Based on the acceptable levels of the extracted compounds compared to the worst-case levels that would be in the cyclophosphamide drug product, there are no safety concerns from a Pharmacology/Toxicology perspective.

(b) (4)

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Based on the acceptable levels of the extracted compounds compared to the worst-case levels that would be in the cyclophosphamide drug product, there are no safety concerns from a Pharmacology/Toxicology perspective.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: Cyclophosphamide 200 mg/20 mL 5-day preliminary intravenous toxicity study in rats followed by 3-week recovery period

Study no.:	E0634
Study report location:	4.2.3.7.7
Date of study initiation:	August 2, 2021
GLP compliance:	No
QA statement:	Yes
Drug, lot #, and % purity:	Cyclophosphamide Injection (2000 mg/20 mL), KY1203, 98.9

Key Study Findings

Methods

Doses:	0, 20, 30, or 45 mg/kg
Frequency of dosing:	Daily for 5 days
Route of administration:	Tail vein
Dose volume:	5 mL/kg
Formulation/Vehicle:	Cyclophosphamide Injection drug product dissolved in saline/ Saline
Species/Strain:	Rat/ Sprague Dawley (SD)
Number/Sex/Group:	3
Age:	6-7 weeks
Weight:	150-174 grams
Satellite groups:	None
Unique study design:	No
Deviation from study protocol:	None

This dose range finding study was submitted upon Agency request when it was referred to in an in vitro hemolysis assay. The study was designed to select dose levels for subsequent studies for qualification of cyclophosphamide impurities. All rats were dosed once a day for 5 consecutive days with the Cyclophosphamide drug product at 20, 30, or 45 mg/kg (HEDs = 3.2, 4.9, and 7.5 mg/kg; clinical dose is 25 mg/kg/day). Hunched posture and piloerection were noted in the high dose group and there was dose-dependent weight loss. Dose-dependent decreases in reticulocytes, leucocytes and platelets were noted in all treated animals. No histopathological analysis was conducted. Macroscopic observations included reduced thymus size. The skin was one of the tissues observed but there was no indication of a drug induced effect on the injection site.

Observations and Results

Mortality

One middle dose male, a high dose male and a high dose female were found moribund and euthanized on days 9, 7, and 8, respectively. Common findings included piloerection and hunched posture and post-mortem findings of lymph node and gland discoloration. The findings were determined to be test article related.

Clinical Signs

A hunched posture and piloerection were noted in the high dose animals by the end of the dosing period.

Body Weights/Feed Consumption

Body weight and food consumption were decreased relative to control animals for all treated groups.

Hematology

Dose-dependent decreases in reticulocytes, leukocytes, and platelets were noted.

Clinical Chemistry

An increase in urea was noted in all treatment groups.

Urinalysis

Unremarkable.

Gross Pathology

A reduced thymus size was noted in the treatment groups.

Organ Weights

Decreases in thymus and spleen weight (absolute and relative to body weight) were noted.

Histopathology

Not evaluated.

10 Special Toxicology Studies

Hemolytic Potential and Plasma Compatibility Study of Cyclophosphamide in Human/ 2022_0073_GLP

Key findings

- While the proposed Cyclophosphamide Injection drug product formulation has elevated hemolysis levels compared to the API alone and the reference product, the levels were much lower than the positive control, suggesting relatively low hemolytic potential.

Method

Cyclophosphamide Injection, the API, and the reference product cyclophosphamide were incubated with whole blood from a healthy donor at 0.2, 0.7, 2.8, and 20 mg/mL for

up to 45 minutes prior to absorbance readings at 570 and 600 nm and 660 and 700 nm wavelength pairings of the supernatant to determine the hemoglobin concentrations in mg/dL. A 1% saponin solution was the positive control. Hemolysis was present (recorded as a positive test result) if the hemoglobin index was greater than 500 mg/dL.

Results

Hemolysis test results (excerpted from the Applicant's submission)

Mixture	Hemoglobin[a] (mg/dL)	Test Result	Tube No.
Human blood plus:			
Test article 1			
0.2 mg/mL	9	N	1
0.7 mg/mL	10	N	2
2.8 mg/mL	6	N	3
20 mg/mL	300	N	4
Reference article			
0.2 mg/mL	13	N	5
0.7 mg/mL	13	N	6
2.8 mg/mL	5	N	7
20 mg/mL	6	N	8
Test Article 2			
0.2 mg/mL	10	N	9
0.7 mg/mL	6	N	10
2.8 mg/mL	6	N	11
20 mg/mL	8	N	12
Vehicle	8	N	13
Placebo (5x diluted)	16	N	14
Animal plasma	9	N	15
1% Saponin	>1200	P	16

N = Negative, no hemolysis; P = Positive, hemolysis.

a Hemoglobin index of the mixture supernatants.

Cyclophosphamide: In vitro binding to human plasma proteins/ 2022_0074_non-GLP

Key findings

- The proposed Cyclophosphamide Injection drug product formulation bound to human plasma blood proteins at high levels that were comparable to the API alone and the reference product.

Method

Cyclophosphamide Injection, the API, and the cyclophosphamide reference product were incubated in human plasma from a healthy donor at 350 μg/mL for up to 16 hours prior to the determination of plasma protein binding of cyclophosphamide by equilibrium dialysis.

Results

Plasma protein binding results (excerpted from the Applicant's submission)

Test substance	Nominal conc. range (µg/mL)	Actual conc. range (µg/mL)	Fraction unbound (%)	Fraction bound (%)
Cyclophosphamide monohydrate (API)	50-850	42.3-752	9.52 ± 3.34	90.5 ± 3.34
Cyclophosphamide LIVI formulation	200	192	5.90 ± 2.03	94.1 ± 2.03
Cyclophosphamide reference formulation (RLD)	200	229	7.02 ± 2.23	93.0 ± 2.23

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/s/

SIMON WILLIAMS
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BRENDA J GEHRKE
08/13/2023 02:11:57 PM