CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY MEMO

NDA Number	NDA 217150 (SDN 1)
Link to EDR	\\CDSESUB1\evsprod\NDA217150\0001
Submission Date	08-13-22
Submission Type	505(b)(2)
Product Name	Cyclophosphamide injection
Generic Name	Cyclophosphamide
Dosage Form and Strength	Solution; 500 mg/5 mL (100 mg/mL), 1000 mg/10 mL (100 mg/mL), 2000 mg/20 mL (100 mg/mL) in multiple-dose vials
Route of Administration	Intravenous (IV)
Proposed Indication(s)	For treatment of: Malignant Diseases: 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
Proposed dosing regimen	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.
Applicant	Sandoz Inc.
OCP Review Team	Nan Zheng, Ph.D.
OCP Final Signatory	Olanrewaju Okusanya, Pharm.D.

1. Executive summary

Sandoz Inc. (the Applicant) has submitted a New Drug Application for Cyclophosphamide Injection, 100 mg/mL (500 mg/5 mL, 1000 mg/10 mL and 2000 mg/20 mL), under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The Listed Drug (LD) is Cytoxan (Cyclophosphamide for injection) approved under NDA 12142. Cytoxan was discontinued (not for safety/efficacy reasons) and ANDA 40745 is listed as the reference standard (RS) in the Orange Book.

The proposed product is intended for the same indications as the reference standard drug, and it has the same active ingredient and the same proposed dosing regimen as the RS. The Applicant's product is provided as ready-to-dilute liquid while the RS is provided as a powder to be reconstituted. In addition, the Applicant's product contains different excipients from the RS.

There are no clinical pharmacology studies to review for this application. The Applicant submitted a request for Waiver of Clinical Studies, including a summary of literature on the possible excipient-excipient and drug-excipient interaction (link) to support the claim that the

differences in excipients does not contribute to differences in the in vivo performance. The clinical pharmacology review focused on the review of excipient-drug and excipient-excipient interaction potential, specifically related to ethanol and propylene glycol. The clinical pharmacology pertinent sections of the proposed labelling were also reviewed for consistency with current labeling practices.

1.1. Conclusions:

The amount of ethanol and propylene glycol in the formulation is not expected to impact the metabolism of cyclophosphamide by CYP enzymes. However, potential drug-drug interaction between ethanol, propylene glycol, and possibly the metabolite of propylene glycol, due to competition for ADH, cannot be ruled out at the maximum dosing regimen.

2. Clinical pharmacology review

Cyclophosphamide is a prodrug that is activated by hepatic microsomal cytochrome P450s including CYP2A6, 2B6, 3A4, 3A5, 2C9, 2C18 and 2C19, with 2B6 displaying the highest activity. The active metabolite, 4-hydroxycyclophosphamide, and its tautomer aldophosphamide, can undergo further oxidation by aldehyde dehydrogenases (ALDH) to form inactive metabolites. Cyclophosphamide is primarily excreted as metabolites with 10-20% excreted unchanged in urine following IV administration. Cyclophosphamide shows linear PK in the approved dose range but shows nonlinear PK due to saturable metabolism at high doses. Cyclophosphamide appears to induce its own metabolism, resulting in reduced elimination half-life after repeated dosing.

Ethanol is primarily eliminated in the liver by alcohol dehydrogenase (ADH). The pharmacokinetics of ethanol are typically described by a 1-compartment model with concentration-dependent elimination. Holford et al. reported a volume of distribution of 37 L/70 kg using blood concentration, a maximum elimination rate (Vmax) of 8.5 g/h/70 kg or 230 mg/L/h, and a blood concentration at half elimination capacity (Km) of 80 mg/L (or 8 mg/dL)[1]. Similar PK parameters were reported by Gazzaz et al. (Vmax: 6.99 g/h; Km: 82.1 mg/L; V: 31.6 L; mean body weight: 73.4 kg)[2]. In in vitro studies, 1% ethanol inhibited activities of CYP2B6 by 80%, CYP2C19 by 72%, CYP1A1 by 69%, and CYP2D6 by 59% with minor effect on CYP2A6, 2C8, or 2C9, and increased activities of CYP1A2 and CYP3A4[3,4]. In human, Gazzaz et al. reported that repeated dosing with oral ethanol (males: 0.76 g/kg + 0.3 g/kg Q4h x5 doses; females: 0.65 g/kg + 0.26 g/kg Q4h x5 doses) did not show significant effect on the concentration of sensitive CYP substrates including caffeine (CYP1A2), tolbutamide (CYP2C9), omeprazole (CYP2C19), or midazolam (CYP3A), but increased the concertation of dextromethorphan (CYP2D6). A mean concentration of approximately 70 mg/dL blood concentration was maintained for at least 6 hours in the study.

Propylene glycol is primarily eliminated by oxidation through alcohol dehydrogenase. The metabolite, lactaldehyde undergoes further metabolism by ADH and ALDH to form lactic acid.

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[1] Clin Pharmacokinet. 1987 Nov;13(5):273-92.
[2] Clin Pharmacol Ther. 2018 Dec;104(6):1249-1259.
[3] Drug Metab Dispos. 1999 Feb;27(2):246-9.
[4] Toxicol Mech Methods. 2013 Oct;23(8):576-83.

Yu et al. reported apparent volume of distribution of approximately 0.6 L/kg and apparent clearance of approximately 0.1 L/h/kg after repeated oral administration of 20.7 g TID or 41.4 g BID doses[5]. Speth et al. reported nonlinear PK and situatable clearance after 4-hr IV infusion at 3-15 g/m^2 doses (74-370 mg/kg assuming BW = 70 kg / BSA = 1.73 m^2), with a terminal half-life ranging from 1.4 h at the lower doses to 4.4 h at the higher doses[6]. Cross study comparison suggested high oral bioavailability and saturation of metabolism at doses above 0.2 g/kg[7]. Propylene glycol has been reported as an inhibitor of CYP2E1.

The maximum approved dosing regimen for cyclophosphamide injection is 50 mg/kg in divided doses over 2-5 days. In the evaluations below, the maximum dosing regimen is considered as 25 mg/kg QD x2 days administered as an IV injection.

- At this dose level, ethanol exposure is 146 mg/kg per dose. Assuming a short, direct injection, the estimated Cmax of ethanol after a single dose is 24.3 mg/dL assuming a volume of distribution of 0.6 L/kg[8], or as a more conservative estimate, in the range 40-50 mg/dL assuming a 80% absolute oral bioavailability and PK parameters from Gazzaz et al.. The removal of ethanol from human body is expected to be saturated and rapid considering a Vmax of 8 g/h, Km of 8 mg/dL, and total dose of 10.2 g in a 70 kg patient.
- At this dose level, propylene glycol is given at 48 mg/kg per dose and is expected to have a short elimination half-life without saturation of metabolism if administered alone.

Conclusions:

- Given the dose, estimated concentrations, and duration of exposure of ethanol and propylene glycol, as well as available information on the elimination pathways of cyclophosphamide, we do not expect that the amount of ethanol and propylene glycol would impact the metabolism of cyclophosphamide by CYP enzymes.
- Potential drug-drug interaction between ethanol, propylene glycol, and possibly the metabolite of propylene glycol, due to competition for ADH, cannot be ruled out at the maximum dosing regimen. The effect is expected to be higher overall exposure as compared to cases when they are given separately, however, significant accumulation of either ethanol or propylene glycol is not expected based on the estimated elimination half-life in the general population.
- There is insufficient information to comment on potential drug-drug interaction between the metabolites of cyclophosphamide and propylene glycol.

[5] J Pharm Sci. 1985 Aug;74(8):876-9.
[6] Ther Drug Monit. 1987 Sep;9(3):255-8.
[7] EMA: Propylene glycol used as an excipient (link)
[8] EMA: Information for the package leaflet regarding ethanol used as an excipient in medicinal products for human use (link)

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/s/

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