CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217110Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA	NDA 217110 SND 3
Link to EDR	\\CDSESUB1\EVSPROD\nda217110\0003
Submission Date	10/20/2022
Submission Type	505(b)2
Brand Name	Melphalan Injection
Generic Name	NA
Dosage Form and Strength	Sterile Solution, 90 mg/mL
Route of Administration	iv injection
Proposed Indication	Melphalan injection is indicated for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate
Applicant	Apotex
Associated IND	IND (b) (4)
OCP Review Team	**Primary Reviewer**: Banu S. Zolnik, Ph.D. **Team Leader**: Ruby Leong, Pharm.D.
OCP Final Signatory	**Deputy Division Director:** Olanrewaju Okusanya, Pharm.D.

1. EXECUTIVE SUMMARY

Apotex Inc. submitted an NDA under section 505(b)(2) pathway for approval of Melphalan Hydrochloride Injection, 90 mg/mL (1 mL). The product is proposed to be packaged in a multidose vial.

The Applicant is relying on FDA's finding of safety and efficacy for Alkeran (melphalan injection) which was approved under NDA 020207. The listed drug (LD) for injection is available in 50 mg/Vial, single-dose vials. The proposed product contains the same active ingredient, in the same concentration after dilution as the LD. It also has the same route of administration and dosing regimen as the LD. The only difference between the proposed product and the LD is the dosage form; it is offered as a ready to dilute solution packaged in a multiple dosage vial versus a powder for reconstitution in single-use vials for Alkeran.

The Applicant requested a biowaiver and the review of the biowaiver request is deferred to Biopharmaceutics. The focus of the clinical pharmacology review will be on the labeling.

1.1 Recommendations

The Office of Clinical Pharmacology recommends **approval** for NDA 217110.

Review Issue	Recommendations and Comments

Pivotal or supportive evidence of effectiveness	NA
General dosing instructions	NA
Dosing in patient subgroups (intrinsic and extrinsic factors)	NA
Labeling	The labeling was updated to be consistent with regulations, current guidances and best practices. The following key modifications were made to the approved labeling documents: **Section 7 Drug Interactions:** • Added a statement regarding consideration of dose reduction in patients with renal insufficiency following concomitant use with cisplatin or cyclosporine. Referred to Dosage and Administration Section 2.2. • FDA recommended adding a specific practical instruction for managing increased lung toxicity due to use with BCNU. The Applicant provided a reference (*Ryu 2010*) which is reviewed below, to support monitoring for increased lung toxicity or considering therapy modification. • Concomitant use with (b) (4) is removed as it is confirmed by the Applicant that (b) (4) . **Subsection 12.2 Pharmacodynamics** • FDA recommended adding this subsection as required by 21 CFR 201.57(c)(13)(i)(B) which states that "Exposure-response relationships (e.g., concentration-response, dose-response) and time course of pharmacodynamic response (including short-term clinical response) must be included if known." If the information is unknown, this subsection must contain a statement about the lack of information **Subsection 12.3 Pharmacokinetics** • FDA recommended removing detailed highly technical PK information as it may not be informative to the health care providers. • FDA requested a literature reference cited under the Elimination subheading regarding a study that showed (b) (4) The Applicant could not locate the reference, therefore deleted the

	following text from the labeling: (b) (4) (b) (4) [redacted] • FDA requested data or literature reference on activity of the metabolites. The Applicant added a statement regarding both monohydroxymelphalan and dihydroxymelphalan are inactive metabolites and (b) (4) The Sponsor provided references (*Brett 2012 and Liia 2008)* which are reviewed below. • FDA requested data or literature to support the statement regarding low melphalan clearance. The Applicant added the following statement (b) (4) [redacted] *13.0 % ± 5.4 %*" and provided references (*Marion; 2006 and Alberts, 1979*) which is reviewed below.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1.1. Addition of specific instruction for managing increased lung toxicity due to concomitant use with BCNU.

The Applicant added the following statement "**Monitor for increased lung toxicity** (b) (4) [redacted] in Section 7.2 Effect of Melphalan on Other Drugs under BCNU subheading. The Applicant cited an editorial to support this statement, Ryu JH. Chemotherapy-induced pulmonary toxicity in lung cancer patients. J Thorac. Oncol. 2010 Sep;5(9):1313-4.

The editorial stated "The mode of onset (acute or insidious) and timing of clinical manifestations associated with chemotherapy-induced pulmonary toxicity is variable and may present during the initial cycle of treatment, after subsequent cycles, or even years later as is the case with carmustine-associated pulmonary fibrosis. The editorial stated the management of chemotherapy induced pulmonary toxicity usually consists of discontinuing the offending drug and administering corticosteroid therapy. The Applicant's added statement appears acceptable with the following modification: "Monitor for increased lung toxicity (b) (4) [redacted]".

2.1.2. Addition of a statement regarding melphalan metabolites are inactive metabolites and (b) (4).

The Applicant added the following statemen (b) (4) [redacted] in the Section 12.3

Pharmacokinetics under the Metabolism subheading. The Applicant cited the following papers to support this statement:

- Glotzbecker B, Duncan C, Alyea E, Campbell B, Soiffer R. Important drug interactions in hematopoietic stem cell transplantation: what every physician should know. Biol Blood Marrow Transplant. 2012 Jul;18(7):989-1006.
- Vainchtein LD, Rosing H, Schellens JHM, Beijnen JH. Ultrasensitive Bioanalytical Assays for Cytotoxic Drugs: Focus on Locally Administered Anti-Cancer Agents. Open Anal Chem J. 2008; 2:10-39.

Although the Glotzbecker et.al. paper states that melphalan undergoes rapid hydrolysis in the plasma to the inactive metabolites monohydroxymelphalan and dihydroxy melphalan, this is a review paper and does not include data. Similarly, although the Vainchtein et.al. paper states that the above-mentioned metabolites are inactive and not cytotoxic, this is also a review paper. However, an original research paper with data and an acceptable bioanalytical methodology confirmed the above mentioned are the metabolites of melphalan (Sweeney DJ, Greig NH, Rapoport SI. High-performance liquid chromatographic analysis of melphalan in plasma, brain and peripheral tissue by o-phthalaldehyde derivatization and fluorescence detection. J Chromatogr. 1985 May 3;339(2):434-9). Another original research paper with data and an acceptable assay methodology showed that monohydroxymelphalan had little had little tumoricidal activity in vitro at concentrations higher than those commonly achieved and dihydroxymelphalan had no potentiating effect on melphalan toxicity (Bosanquet AG, Bird MC. Degradation of melphalan in vitro: rationale for the use of continuous exposure in chemosensitivity assays. Cancer Chemother Pharmacol. 1988;21(3):211-5). With this information, statement about inactive melphalan metabolites can be included in the labeling.

2.1.3. Addition of a statement regarding low melphalan clearance. The Applicant cited the following papers by Marion 2006 and Alberts 1979.

The Applicant added the following statement "(b) (4) **13.0 % ± 5.4 %**" in Section 12.3 Pharmacokinetics under the Excretion subheading. The Applicant cited the following papers:

- Alberts DS, Chang SY, Chen HS, Moon TE, Evans TL, Furner RL, Himmelstein K, Gross JF. Kinetics of intravenous melphalan. Clin Pharmacol Ther. 1979 Jul;26(1):73-80.
- Haubitz M, Peest D. Myeloma--new approaches to combined nephrological-haematological management. Nephrol Dial Transplant. 2006 Mar;21(3):582-90.

The Alberts et. al paper included data with acceptable bioanalytical methodology and appear to support the Applicant's statement with the following modifications: Following radiolabeled doses of intravenous melphalan in 9 patients with cancer, the mean (± SD) excretion of melphalan over 24 hours was 13.0 % ± 5.4 % of the total dose. The Haubitz et al. paper stated

that although the contribution of renal clearance to the overall melphalan elimination appears to be low, dose reduction should be considered in patients with renal insufficiency, since increased bone marrow suppression was observed, which are consistent with the recommendation in Section 2.2 Dosage Modifications for Renal Impairment.

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/s/

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