CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217110Orig1s000

CLINICAL REVIEW(S)

Combined Clinical and Labeling Review of the Prescribing Information

Product Title	Melphalan Injection
Applicant	Apotex Corp.
Application/Supplement Number	NDA 217110
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/A
Is Labeling Being Converted to PLLR? (Y/N)	N/A
Proposed Indication(s)	For the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.
Approved Indication(s)	N/A
Date FDA Received Application	October 20, 2022
Review Classification (Priority/Standard)	Standard
PDUFA Goal Date	August 20, 2023
Review Date	August 18, 2023
Clinical Reviewer	Alexandria Schwarsin, MD
Associate Director for Labeling Reviewer	Elizabeth Everhart, MSN, RN, ACNP
CDTL	Bindu Kanapuru, MD

This joint Associate Director for Labeling (ADL) and Clinical review provides 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

NDA 217110 was submitted as a 505(b)(2) NDA under the Federal Food, Drug, and Cosmetic Act for Melphalan Injection, 90 mg/mL. Melphalan is a small molecule alkylating agent. NDA 217110, Melphalan Injection, is proposed for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

The Applicant stated that the listed drug (LD) for NDA 217110 is Alkeran (melphalan hydrochloride), for injection. Alkeran is available in 50 mg single dose vials and was approved under NDA 020207 in 1992 and discontinued in 2021. The Applicant also noted that the proposed product has the same active ingredient, route of administration, dosing regimen, and concentration after dilution as the LD and it differs from the LD in its qualitative and quantitative composition and is a ready to dilute injectable solution packaged in a multiple dose vial.

The Applicant has stated they are only pursuing for indications and dosing regimen per the listed drug ALKERAN®. The proposed indication is for palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

During review of this application the 505(b)2 committee noted that the FDA's Orange Book: *Approved Drug Products with Therapeutic Equivalence Evaluations*, identified Apotex Inc. as the NDA holder for Alkeran

(melphalan hydrochloride) NDA 020207. The Applicant submitted information from published literature to support the safety and efficacy of melphalan injection and identified that this published literature is required for approval (response dates July 13, 2023 and August 2, 2023).

The Applicant has an Agreed Pediatric Study Plan (Agreed PSP-1) for melphalan hydrochloride for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

Clinical Review:

No clinical data was submitted with this Application. The submission relied on submitted literature to support information included in Sections 6.1 and 14 of the proposed labeling. The clinical studies described in the submitted published literature evaluated drug products containing melphalan, and therefore, the data on adverse events from these studies are scientifically relevant to the proposed product. Further, one clinical study described in the published literature evaluated the safety and effectiveness of oral or intravenous injection melphalan products for the treatment of multiple myeloma, which is scientifically relevant to the proposed melphalan injection product for the treatment of multiple myeloma (language reviewed by 505(b)2 committee)

The Prescribing Information was reviewed, and substantial labeling changes were made and are described below.

Labeling Review:

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 217110:

Highlights:

- The product title was changed to remove the salt (hydrochloride) from the established name to align with the CDER Salt Policy.
- As this product does not have a proposed proprietary name, where a proprietary name is typically used, one letter title case, i.e., Melphalan Injection, will be used throughout, along with directive statements specific to this particular product. In places in the label where data being described are derived from studies for the listed drug or information from literature, “melphalan” will be used.
- Other formatting changes to comply with the SRPI (selected requirements for the prescribing information) and PLR made throughout the Highlights, Table of Contents, and the Full Prescribing Information.

Section 2:

- In section 2.1 Recommended Dosage, any proposed claims of (b) (4) were removed, and the section updated to align with guidance and current labeling practice.
- A new section 2.2 Dosage Modifications for Adverse Reactions was added and a table for recommended dosage modifications for bone marrow suppression moved here from section 6.1 and modified to align with current labeling practice.
- In section 2.3 Dosage Modifications for Renal Impairment, all information pertaining to preparation and administration moved to that subsection.

Section 4:

- The Contraindication statement was revised to change the terminology from (b) (4) to hypersensitivity and to note that reactions have included anaphylaxis.
- A cross reference to section 5.4 was added.

Section 5:

- The language in section 5.1 Bone Marrow Suppression was updated to provide a succinct description of the and directive statements for the monitoring and management of bone marrow suppression.
- A recommendation to provide prophylactic antiemetics was added to section 5.2 Gastrointestinal Toxicity.
- A recommendation to discontinue Melphalan Injection was added to section 5.4 Hypersensitivity.
- In section 5.5 Secondary Malignancies, a sentence about chromatid or chromosome damage in humans was relocated from section 13 Nonclinical Toxicology. Additional edits were made in section 5.5 to shorten the warning to convey the most important information.
- In section 5.6 Embryo-Fetal Toxicity, the warning was updated to align with recommendations in the PLLR

(the pregnancy and lactation labeling rule).

Section 6

- In section 6.1 Adverse Reactions, [redacted] (b) (4) and a dosage adjustment table for bone marrow suppression (WBCs and platelets) from the clinical trial was relocated to section 2.3.

Section 7

- Practical instructions for preventing or managing the clinically significant drug-drug interactions were added.

Section 8

- Changes were made throughout sections 8.1-8.3 to align with PLLR recommendations and current labeling practice.
- In section 8.6 Renal Impairment, detailed information moved to section 12 to align with guidance recommendations.

Section 10

- This section modified to align with regulations and to align with current labeling practices, including qualifying the non-approved dosages mentioned in relation to the recommended dosage.

Section 12

- In section 12, substantial changes were made to align with guidance and regulation, including the addition of a subsection 12.2 Pharmacodynamics to describe that the exposure-response relationship and time course of pharmacodynamic response is unknown.

Section 13

- Relocated any proposed human data to the appropriate subsection (i.e., section 5 and section 8).

Section 14

- Information that is included in the LD label was added to provide more data concerning the clinical trial, including the two study arms and the dosing regimen used in the study.

Section 16

- All vial storage after use information relocated to subsection 2.4 Preparation and Administration.

TL Review: I have reviewed and concur with the recommendations detailed above.

[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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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