CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217110Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	August 18, 2023
From	Shalini Anand, Ph.D. through Sherita McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	217110
Type of Application	505(b)(2)
Applicant	Apotex Inc.
Date of Receipt	20-October-2022
PDUFA Goal Date	20-Aug-2023
Proposed Proprietary/Established Names	Melphalan Injection
Dosage forms / Strength	Injection/ 90 mg/mL
Route of Administration	Intravenous
Proposed Indication(s)	•Indicated for palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.
Recommended:	**Approval**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Clinical (Alexandria Schwarsin, M.D)
- Clinical Pharmacology (Banu Zolnik, Ph.D.)
- ADL (Elizabeth Everhart, MSN, ACNP)
- Pharmacology/Toxicology (Simon Williams, Ph.D.)
- DEMPA (Nicole Iverson, Pharm. D.)
- Drug Product (William Adams, Ph.D.)
- Drug Substance (Raymond Frankewich, Ph.D.)
- Microbiology (Jason God, Ph.D.)
- Manufacturing Process and Facilities (Ephrem Hunde, Ph.D.)
- Biopharmaceutics (Kevin Wei, Ph.D.)

1. Introduction

NDA 217110 was submitted by Apotex Inc. for Melphalan Injection, 90 mg/mL in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. Melphalan is a nitrogen mustard alkylating agent that was originally approved as ALKERAN (Melphalan Hydrochloride) for injection under NDA 020207 in 1992 (discontinued in 2021). Melphalan is an antineoplastic agent that is indicated for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate. The listed drug (LD), ALKERAN is presented as a sterile, lyophilized powder for injection and is packaged in a single-dose vial containing melphalan hydrochloride equivalent to 50 mg of melphalan.

The proposed drug product is supplied as a sterile, clear colorless to yellow colored, ready-to-dilute solution in an amber colored multiple-dose vial. The proposed product has the same active ingredient, route of administration, dosing regimen and concentration after dilution as the listed

drug (LD). The proposed product differs from the LD in terms of dosage form (lyophilized powder vs. concentrate, ready to dilute solution) and contains different inactive ingredients. ALKERAN single-use vial contains melphalan hydrochloride equivalent to 50 mg melphalan and 20 mg povidone. ALKERAN for Injection is reconstituted with a sterile diluent (containing sodium citrate 0.2 g, propylene glycol 6.0 mL, ethanol (96%) 0.52 mL, and water for injection to a total volume of 10 mL). The proposed drug product contains 100.75 mg melphalan hydrochloride (equivalent to 90 mg of melphalan), propylene glycol, monothioglycerol, DOTA (1, 4,7,10 tetraacetic acid, 1, 4,7,10 tetraazacyclododecane), water for injection and polyethylene glycol 400. The proposed drug product is diluted with 0.9% sodium chloride injection, USP to a final concentration of 0.45 mg/mL.

The recommended dosage of melphalan injection is 16 mg/m^2 intravenously over 15 to 20 minutes at 2-week intervals for 4 doses. then at 4-week intervals until unacceptable toxicity.

2. Background

This application presents a new ready-to-dilute formulation of Melphalan Hydrochloride. Melphalan is an alkylating antitumor agent, and it is currently approved for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

The current application contains no clinical data but instead relies on the Agency's determination of safety and efficacy for the listed drug, ALKERN which was previously approved for marketing under NDA 020207 in 1992. ALKERN was discontinued in 2021, hence the Applicant selected Mylan's product approved under ANDA 090270 as a Reference standard (RS) for comparative studies. Both LD and RS drug products contain same active and inactive ingredients.

The proposed drug product is a ready to dilute injection containing 90 mg/mL of Melphalan (1 mL vial fill) and is diluted with 0.9% sodium chloride injection, USP. The Applicant claims that this ready to dilute formulation improves practitioners' convenience by reducing the number of reconstitutions steps.

3. Product Quality

Melphalan Hydrochloride is a small chiral molecule that is produced as a white to off-white powder. The anhydrous form of drug substance was used for the manufacturing of proposed drug product. The drug substance is practically insoluble in water and chloroform, but freely soluble in methanol. The drug substance exhibits isomerism and melphalan is an active L-isomer. Melphalan Hydrochloride drug substance is manufactured, and release tested by (b) (4) (b) (4) The applicant referenced DMF (b) (4) for chemistry, manufacture, and control (CMC) of the drug substance. DMF (b) (4) was reviewed in conjunction with this NDA and deemed adequate to support the approval of NDA 217110. Based on the information provided in the referenced DMF, a shelf life of (b) (4) is established for drug substance (b) (4)

The drug product, Melphalan Injection is supplied as a sterile, clear colorless to yellow colored, ready-to-dilute solution in 3 mL amber multiple-dose vial. Each vial contains 90 mg Melphalan free base (90 mg/mL, 1 mL fill volume) equivalent to 100.755 mg of Melphalan Hydrochloride along with polyethylene glycol 400, propylene glycol, Monothioglycerol, WFI and DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid dihydrate). Sodium hydroxide and hydrochloric acid are used as pH adjuster and (b) (4). DOTA

is a new excipient and is not listed in the IID database. As per the feedback from pharm-tox review team, the proposed level of DOTA in melphalan injection do not pose any safety concerns. All other excipients are of compendial grades. Based on the real time stability data for drug product, the Agency grants a 18 month shelf-life for the drug product when stored under refrigerated conditions (i.e., 2°C and 8°C) and protected from light.

The drug product manufacturing process involves (b) (4) (b) (4) (b) (4) The drug product is manufactured, (b) (4) at AqVida GmbH, Germany site. The finished product sterility testing is performed (b) (4) stability testing is performed at (b) (4). NDA 217110 included total of 6 manufacturing, testing, and packaging facilities. At the time of review, all facilities associated with this application were considered adequate to perform the responsibilities listed in the NDA and are acceptable to support approval of this NDA.

The Applicant submitted comparative physicochemical properties, in vitro protein binding and hemolysis data and literature information to establish a scientific bridge between the proposed product and the relied upon LD product. The submitted data/information indicate that the differences in formulation and dosage form of LD and proposed product are unlikely to impact the disposition and pharmacokinetics of melphalan when administered intravenously. The scientific bridge is deemed adequate as per 21 CFR 320.24(b)(6), and therefore an in vivo pharmacokinetic study was not required.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality recommends APPROVAL of NDA 217110. Based on the available real time stability data, OPQ grants an expiration dating period of **18-months** for the drug product when stored under refrigerated conditions (2°C and 8°C or 36ºF to 46ºF) and protected from light. The proposed product is diluted with 0.9% Sodium Chloride Injection to a final concentration of 0.45 mg/mL. The final admixture is stable for 1 hour when stored at room temperature (15°C -30°C or 59°F -86°F). The partially used vials are stable when stored under refrigerated conditions (2°C to 8°C) in the original carton for 28 days. (See USPI Section 2: DOSAGE AND ADMINISTRATION for in-use period and storage of partially used vials).

6. Clinical Pharmacology

The proposed product contains the same active ingredient as the LD. It also has the same route of administration and dosing regimen as the LD. The proposed product differs from the LD in terms of qualitative and quantitative composition and also is a different dosage form
The Applicant requested a biowaiver and the review of the biowaiver request was deferred to Biopharmaceutics. The Office of Clinical Pharmacology recommends approval for NDA 217110.

7. Non-Clinical Pharmacology/Toxicology

The Applicant submitted toxicology studies to support the proposed formulation and impurity specifications in NDA 217110. Toxicology assessments included a 4-week GLP repeat-dose toxicology study in rats with or without impurities, a blood protein binding assay, and a hemolysis

assay. The high protein binding was comparable between the proposed drug and the reference product, and the proposed drug was not hemolytic.
In the 4-week repeat-dose toxicology study, Sprague Dawley rats (5/sex) were administered 2.25 mg/kg of Melphalan Hydrochloride Injection intravenously weekly for 4 weeks with impurities at concentrations ranging from (b)(4)% to (b)(4)%. The study groups included 4 with 2.25 mg/kg of Melphalan Hydrochloride Injection, of which 3 were also spiked with low, middle, and high concentrations of the impurities of concern. The observed toxicities were comparable between the Melphalan Hydrochloride Injection groups. Based on the levels of the impurities in the animal study, the proposed specification limits are justified from a Pharmacology/Toxicology perspective.

8. Clinical/Statistical-Efficacy
Apotex did not conduct any human clinical studies and therefore efficacy was based on the Prescribing Information for the Listed Drug, ALKERN. The clinical team confirmed that no new clinical data was included in this submission and recommends approval of NDA 217110.

9. Safety
Safety was based on the Prescribing Information for the Listed Drug, ALKERN (melphalan hydrochloride) for injection (NDA 020207).

10. Advisory Committee Meeting N/A

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling
At the completion of labeling negotiations, the USPI was acceptable from the ADL and all review disciplines. The label was deemed to be compliant with Physician Labeling Rule (PLR) [including the Pregnancy and Lactation Labeling Rule (PLLR)] requirements; is consistent with labeling guidance recommendations and with CDER labeling policies; 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.

See the USPI attached to the approval letter for final recommended labeling.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**
  This product relies on the safety and efficacy of the Listed Drug, ALKERN. The Apotex product has the same active ingredient, route of administration, dosing regimen and concentration after dilution as the listed drug (LD). There were no new clinical studies conducted for this 505(b)(2) application.
  The CDTL recommends APPROVAL of NDA 217110 for Melphalan Injection.

- **Risk Benefit Assessment**

Please refer to NDA 020207.

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/s/

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