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APPLICATION NUMBER:

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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 217110
Supporting document/s:	3 (sequence number 0003)
Applicant's letter date:	October 20, 2022
CDER stamp date:	October 20, 2022
Product:	Melphalan Hydrochloride Injection
Indication:	Multiple myeloma
Applicant:	Apotex, Inc.
Review Division:	DHMII/DHOT
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1 Executive Summary

1.1 Introduction

The Applicant, Apotex, Inc., submitted NDA 217110 in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, and is seeking marketing approval for Melphalan Hydrochloride Injection (90 mg/mL) for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate. The active pharmaceutical ingredient (API), route of administration, dosing regimen, and indications sought for the proposed melphalan formulation and ALKERAN are the same. The excipient profile of the proposed melphalan formulation differs from ALKERAN.

1.2 Brief Discussion of Nonclinical Findings

For the current NDA, the Applicant submitted toxicology studies to support the proposed formulation and impurity specifications. 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.

1.3 Recommendations

1.3.1 Approvability

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

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

The Applicant did not make notable changes relevant to the Pharmacology/Toxicology related sections of the proposed label, but modifications were made by the Agency to be consistent with the Pregnancy and Lactation Labeling Rule (PLLR) format and to align with other melphalan labels.

2.3 Drug Formulation

The proposed formulation is compared with ALKERAN in the table below:

Comparison of formulations between the proposed and ALKERAN drug products (excerpted from the Applicant's submission)

Item	ALKERAN® (Melphalan Hydrochloride) for Injection, 50mg/Vial (Apotex Inc.)	Melphalan Hydrochloride Injection, 90 mg/mL (1 mL) (Apotex Inc.)
Conditions of Use	ALKERAN for Injection is indicated for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.	Melphalan Hydrochloride Injection is indicated for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.
Active Ingredient(s)	Melphalan Hydrochloride	Melphalan Hydrochloride
Inactive Ingredients	Povidone	Polyethylene glycol 400
	Sodium citrate	Monothioglycerol
	Propylene glycol	Propylene glycol
	Ethanol (96%)	DOTA
		Sodium hydroxide
		Hydrochloric acid
Dosage Form	Lyophilized power for injection	Sterile solution
Route of Administration	Intravenous injection	Intravenous injection
Strength(s)	50 mg/Vial	90 mg/mL (1 mL)
Dilution	Dilute to 0.45 mg/mL with 0.9% Sodium Chloride Injection, USP for intravenous infusion	Dilute to 0.45 mg/mL with 0.9% Sodium Chloride Injection, USP for intravenous infusion

The levels of the excipients are summarized in the table below. The dose values are based on the proposed 16 mg/m^2 (0.43 mg/kg) dosing schedule (4 doses every 2 weeks).

Excipient levels

Excipient	Quantity (mg)	
	Per mL	Per dose (0.288 mL/60 kg patient)
Monothioglycerol	5.0	1.44
DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid dihydrate)	0.5	0.144
Propylene Glycol	170	49
Polyethylene Glycol 400	(b) (4)	(b) (4)
Sodium Hydroxide	q.s.	N/A
Hydrochloric acid	q.s.	
(b) (4)		

The proposed excipient levels are reasonable, including DOTA, which is used as a (b) (4) in an imaging agent (DOTAREM; NDA 204781) at levels up to 3 mg/dose.

2.4 Comments on Novel Excipients

There are no novel excipients used in the proposed formulation.

2.5 Comments on Impurities/Degradants of Concern

The proposed levels of impurities were qualified in a GLP repeat-dose toxicology study that is described in a later section. The range of levels over which the impurities were qualified in the toxicology study are summarized in the table below.

Qualification range of impurities (excerpted from the Applicant's submission)

Name of impurity	Qualification %	Shelf life specification
(b) (4)	(b) (4)	(b) (4)

The doses of the impurities used in the rat study were at levels comparable to or higher than those for the proposed specifications. This is summarized in the table below where the rat study impurity doses derived from the melphalan dose of 2.25 mg/kg, or 13.5 mg/m^2, are compared to the impurity doses for the proposed specification at the clinical dose of 16 mg/m^2.

Summary table of qualifying impurity doses from the rat toxicology study compared to the specification doses

Impurity	Qualification study (at highest level)		Proposed specification (NMT)	
	%	Dose (mg/m^2)	%	Dose (mg/m^2)
(b) (4)	(b) (4)		(b) (4)	(b) (4)

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: 28-day repeated toxicity study of melphalan hydrochloride injection (90 mg/mL) enriched with impurities by intravenous (infusion) route

Study no.:	[redacted] 463
Study report location:	4.2.3.7.6
Date of study initiation:	April 29, 2022
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Melphalan Hydrochloride Injection (90 mg/mL), [redacted] (low dose impurity spike: [redacted] mid dose impurity spike: [redacted] high dose impurity spike: [redacted] %

Key Study Findings

- The 2.25 mg/kg dose was selected for this study based on the results of a dose range finding study. The toxicities related to the melphalan drug product with or without impurities administered to Sprague Dawley rats were comparable between the groups.

Methods

Doses: 2.25 mg/kg + low, mid, and high dose impurity spikes

Study design

Group	Description	Dose Volume (mL/kg)	Number of animals (per sex/per group)
G1	Saline	5	5
G2	Vehicle (placebo)		
G3	2.25 mg/kg Melphalan + low dose impurities		
G4	2.25 mg/kg Melphalan + mid dose impurities		
G5	2.25 mg/kg Melphalan + high dose impurities		
G6	2.25 mg/kg Melphalan		

Levels of individual impurities

Name of Impurity	Group impurity levels (%)		
	G3 (low dose)	G4 (mid dose)	G5 (high dose)
(b) (4)	(b) (4)		

Frequency of dosing: Days 1, 7, 14, 21, and 28
Route of administration: Intravenous infusion
Dose volume: 5 mL/kg
Formulation/Vehicle: The Melphalan HCl Injection drug product formulation was used for the placebo and test article conditions
Species/Strain: Rat/Sprague Dawley
Number/Sex/Group: 6
Age: 5-6 weeks
Weight: 133-150 grams
Satellite groups: None
Unique study design: No
Deviation from study protocol: None that impacted the study outcome

Observations and Results

Mortality

Deaths were noted in all melphalan-dosed groups. The death rates were melphalan-related and comparable across the test article groups.

Death rates

Group	Total mortalities (M/F)
G1/G2	0/0
G3	3/1
G4	2/0

Group	Total mortalities (M/F)
G5	3/1
G6	4/1

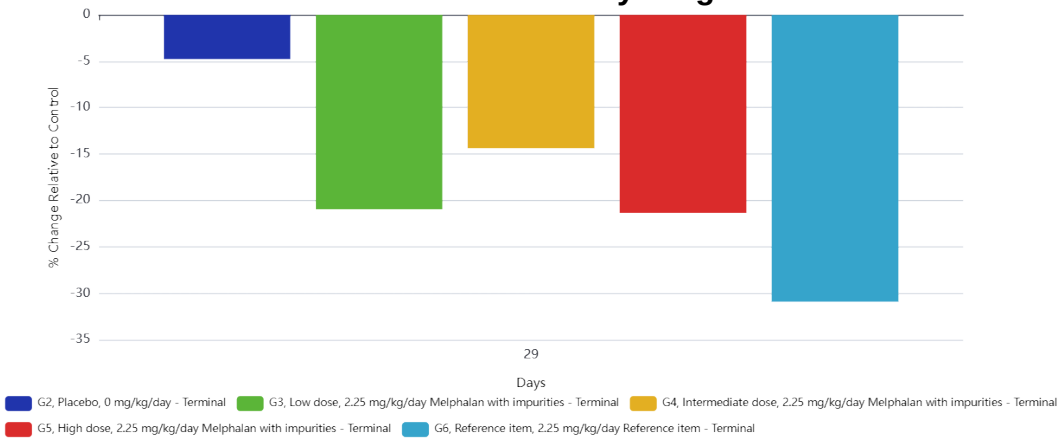
Clinical Signs

Common clinical signs in the test article groups included piloerection, dehydration, and diarrhea. These were comparable across the test article groups and demonstrated reversibility.

Body Weights

Test article groups had notably reduced rates of body weight gain compared to control conditions by the end of the dosing period. The differences showed reversibility by the end of the recovery period.

Combined terminal male and female body weights



Feed Consumption

Sporadic test article-induced reductions in food consumption were noted among group 6 and group 5 animals. This does not suggest an association with impurities.

Ophthalmoscopy

Unremarkable.

Hematology

Notable changes were seen in the white blood cell populations, which were reduced across test article conditions.

Selected hematology findings

Test	Units	Male						Female					
		G1	G2	G3	G4	G5	G6	G1	G2	G3	G4	G5	G6
Basophils	10^9/L	0.1	-6.5%	-75.8%	-54.3%	-59.7%	-67.7%	0.05	-64.0%	-30.0%	-28.0%	-15.0%	-50.0%
Eosinophils		0.1	90.0%	-100.0%	-95.8%	-62.5%	25.0%	0.14	68.1%	-76.5%	-92.8%	-65.6%	-85.5%
Leukocytes		20.6	-8.6%	-83.8%	-66.9%	-55.5%	-78.7%	11.54	-41.7%	-32.5%	-57.1%	-26.0%	-46.3%
Lymphocytes		17.0	-21.5%	-89.3%	-78.8%	-66.1%	-85.8%	7.75	-44.89%	-57.3%	-61.4%	-44.9%	-65.4%
Platelet Volume	fL	7.0	30.3%	22.8%	42.2%	34.6%	39.7%	7.1	3.6%	45.0%	35.6%	39.7%	34.8%

Clinical Chemistry

Unremarkable.

Urinalysis

Unremarkable.

Gross Pathology

Small thymus and spleen sizes in the test article groups were the notable findings.

Organ Weights

Unremarkable.

Histopathology

Adequate Battery: yes.

Peer Review: yes.

Histological Findings
Observations made across the test article groups included cellular loss in the thymus, spleen, and lymph nodes.

Selected microscopic findings

Organ/ Tissue	Finding	Severity*	Male						Female					
			G1	G2	G3	G4	G5	G6	G1	G2	G3	G4	G5	G6
SPLEEN		# Animals Examined	5	5	5	5	5	5	5	5	5	5	5	5
	CELLULARITY; DECREASED	1 OF 5											3	2
		2 OF 5				1	1						2	1
		4 OF 5			2	1	3	3			1			
		Total			2	2	4	3			1		5	3
	CONGESTION	1 OF 5											1	
		2 OF 5					1						1	
		4 OF 5					3							
		Total					4						2	
EPIDIDYMIS		# Animals Examined	5	5	3	2	5	5	0	0	0	0	0	0
	CELL DEBRIS	1 OF 5						1						
		2 OF 5						1						
		Total						2						
LUNG		# Animals Examined	5	5	3	2	5	5	5	5	1	0	5	5
	CONGESTION	1 OF 5												1
		2 OF 5					2							
		3 OF 5						2						
		Total					2	2						1
	INFLAMMATION	4 OF 5						1						
		Total						1						
LYMPH NODE, MANDIBULAR		# Animals Examined	5	5	5	5	5	5	5	5	5	5	5	5
	APOPTOSIS; INCREASED	2 OF 5					1							
		3 OF 5						1						
		Total					1	1						
	CELLULARITY; DECREASED	2 OF 5									1			1
		3 OF 5			1		3	1						
		4 OF 5						1						
		Total			1		3	2			1			1
THYMUS		# Animals Examined	5	5	5	5	5	5	5	5	5	5	5	5
	CELLULARITY; DECREASED	1 OF 5		1	1								2	1

Organ/ Tissue	Finding	Severity*	Male						Female					
			G1	G2	G3	G4	G5	G6	G1	G2	G3	G4	G5	G6
		2 OF 5												1
		4 OF 5			1	2	3	4			1			
		Total		1	2	2	3	4			1		2	2
		Total			1						1			
	CYST					1					1			
		Total				1					1			

* Microscopic findings were graded by a severity scale of grade 1 (minimal), grade 2 (mild), grade 3 (moderate), and grade 4 (marked)

Toxicokinetics

No toxicokinetics studies were conducted.

Dosing Solution Analysis

Dosing samples were analyzed by HPLC. The impurity levels were as indicated.

10 Special Toxicology Studies

Study Title/Number: Evaluation of Human Plasma Protein, Human α-Acid Glycoprotein and Human Serum Albumin Binding of Melphalan Hydrochloride, Monohydroxy Melphalan and Dihydroxy Melphalan by High Throughput Dialysis (HTD) Method/BIO-DMP 032

Key findings

- Melphalan hydrochloride standard, test item, and reference item were highly bound to plasma and human serum albumin.
- Melphalan hydrochloride standard, test item, and reference item were poorly bound to alpha acid glycoprotein.
- The % binding of the melphalan test article was comparable to the standard and reference items.

Methods

Plasma protein binding of melphalan hydrochloride standard, test item and reference item was performed in human plasma, α- acid glycoprotein and human serum albumin in low, middle, and high concentrations. HPLC was used to evaluate binding after a 4-hour incubation period.

Results

Summary table of protein binding at 1 mg/mL protein concentration (excerpted from the Applicant's submission)

Name of Product		Standard	Test Item	Reference Item
Melphalan Concentration	Protein Solution	% Bound	% Bound	% Bound
2.7 µg/mL	Plasma	57.273	56.530	55.309
6 µg/mL		57.409	57.910	57.457
55 µg/mL		53.920	51.783	55.140
2.7 µg/mL	AAG	10.938	9.072	6.260
6 µg/mL		6.679	3.877	11.509
55 µg/mL		10.224	9.022	8.607
2.7 µg/mL	HSA	59.972	62.008	61.592
6 µg/mL		58.410	50.699	62.746
55 µg/mL		55.720	52.831	62.060

Study Title/Number: In Vitro Blood Compatibility (Hemolysis) Study of Melphalan Hydrochloride 90 mg/mL Injection in Human Blood in Human Blood/ BIO-INV 049

Key findings

- Melphalan hydrochloride did not show hemolysis at any of the concentrations tested.

Methods

Melphalan hydrochloride test and reference items were incubated at concentrations of 0.45, 0.75, and 1.0 mg/mL with red blood cells from 3 healthy volunteers for 30 minutes prior to an evaluation of hemoglobin levels compared to a saline negative control and a Triton X-100 detergent positive control.

Results

Summary of hemolysis assay findings (excerpted from the Applicant's submission)

Sample	Replicates	Absorbance at 540 nm	Hemoglobin Concentration (mg/mL)*	% Hemolysis
Blank control	R1	0.038	0.303	-
	R2	0.037	0.295	
	R3	0.038	0.303	
	Mean	**0.038**	**0.300**	
	±SD	**0.001**	**0.005**	
Negative Control	R1	0.039	0.311	**0.026**
	R2	0.037	0.295	
	R3	0.038	0.303	
	Mean	**0.038**	**0.303**	
	±SD	**0.001**	**0.008**	
Positive control	R1	0.382	3.049	**26.404**
	R2	0.379	3.025	
	R3	0.380	3.033	
	Mean	**0.380**	**3.036**	
	±SD	**0.002**	**0.012**	
Test Item (0.45 mg/mL) (1:5)	R1	0.039	0.311	**0.103**
	R2	0.040	0.319	
	R3	0.038	0.303	
	Mean	**0.039**	**0.311**	
	±SD	**0.001**	**0.008**	
Test Item (0.75 mg/mL) (1:5)	R1	0.038	0.303	**0.052**
	R2	0.039	0.311	
	R3	0.038	0.303	
	Mean	**0.038**	**0.306**	
	±SD	**0.001**	**0.005**	
Test Item (1.0 mg/mL) (1:5)	R1	0.038	0.303	**0.309**
	R2	0.038	0.303	
	R3	0.049	0.391	
	Mean	**0.042**	**0.332**	
	±SD	**0.006**	**0.051**	

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/s/

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