CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217110Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	217110
Applicant Name	**Apotex Inc.**
Drug Product Name	Melphalan Hydrochloride Injection
Dosage Form.	Injection
Proposed Strength(s)	90 mg/mL (1 mL)
Route of Administration	Intravenous
Maximum Daily Dose	28.8 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Indicated for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.
Drug Product Description	Melphalan is a is a small molecule nitrogen mustard alkylating, antineoplastic agent. It is indicated for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate. The Listed Drug (LD) for this application is ALKERAN (Melphalan Hydrochloride) for injection. ALKERAN is available in 50 mg single dose vials and was approved under NDA 020207 in 1992 (discontinued in 2021). The proposed product has the same active ingredient, route of administration, dosing regimen and concentration after dilution as the LD. The proposed product differs from the LD in terms of qualitative and quantitative composition and in that it is a ready to dilute injectable solution packaged in a multiple dosage vial. The usual IV dose of Melphalan Hydrochloride Injection is 16 mg/m^2 and the MDD is 28.8 mg.

Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	5 ± 3°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Raymond Frankewich	Haripada Sarker
	Drug Product/ Labeling	Mike Adams	Thomas Oliver
	Manufacturing	Ephrem Hunde	Kshitji Patkar
	Biopharmaceutics	Kevin Wei	Kevin Wei
	Microbiology	Jason God	Julie Nemecek
	Other (specify):	N/A	N/A
	RBPM	Dahlia Walters	
	ATL	Sherita McLamore/Shalini Anand	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: An expiration dating period of **18 months** is granted from for the drug product when stored at 5ºC ± 3ºC conditions.

b. Additional Comments for Action: n/a

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends ***APPROVAL*** of NDA 217110 for the commercialization of Melphalan Hydrochloride Injection 90 mg/mL. Based on our evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the drug product quality perspective. The Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No

Comments: N/A

Additional Lifecycle Comments: N/A

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

The assessment of the draft USPI is based on revisions proposed for the documents in Amendment SD-014.

Assessment of Product Quality Related Aspects of the Prescribing Information: The CMC information regarding storage of the unused and used vial is supported by product quality and stability studies.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Inadequate	Melphalan ~~Hydrochloride~~ injection for IV use Recommendation: Per the Agency guidance: Naming of Drug Products Containing Salt Drug Substances and MAPP 5021.1, the non-proprietary name and strength should be based upon active moiety. Therefore, CMC team recommended deleting the 'Hydrochloride' from drug product name throughout the USPI, Container and Carton label.
Route(s) of administration	Adequate	IV infusion
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	90 mg/mL melphalan (freebase) solution ready-to-dilute
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Inadequate	Recommended text: Injection: 90 mg/ml of melphalan in a multiple-dose vial
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Inadequate	Recommendation: The free base information is not included in the Dosage form and strength section. Refer the section above for recommended text for dosage form and strength section.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Inadequate	Sections 2.2 address (b) (4) Section 2.3 addresses (b) (4) After first use, store the partially used vial refrigerated at 2oC to 8oC [36oF to 46oF] in the original carton for use within 28 days. Retain vial in original carton until contents are used. Recommendation- The in-use stability data (chemical stability) provided in the NDA, do not support the (b) (4) . Therefore, the Applicant will be asked to remove this statement from the USPI.

Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	Statement in section 2.3
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	Adequate	Statement in section 16

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Ready-to-dilute solution
Strength(s) in metric system	Adequate	90 mg/mL
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Adequate	90 mg/mL as the freebase. Established name is Melphalan Injection based on salt policy.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	Clear, colorless to yellow solution
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	Multiple dose vial

Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	Established name is Melphalan ~~Hydrochloride~~ Injection No proprietary name has been accepted.
Dosage form(s) and route(s) of administration	Adequate	Ready to dilute (RTD) solution for IV administration
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Adequate	Formulated as the HCl salt. Strength and dose are based on the freebase.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	hydrochloric acid monothioglycerol polyethylene glycol 400 propylene glycol sodium hydroxide (1,4,7,10-tetraazacyclo dodecane-1,4,7,10-tetraacetic acid dihydrate water for injection Recommendation: List the inactive ingredients in the alphabetical order. Also, the trade/abbreviated name for DOTA excipient should not be included in Section 11 of the USPI, Include the chemical name for DOTA in section 11. Refer USP General Chapter <1091> for additional details.

For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Inadequate	Text is to be edited to: Each mL contains 90 mg melphalan free base equivalent to 100.75 mg melphalan hydrochloride, 170 mg propylene glycol, 5 mg monothioglycerol, 0.5 mg DOTA), 0.025 mL water for injection in polyethylene glycol 400. Sodium hydroxide solution added for pH adjustment. Listing excipients by amount in the formulation is accepted. DOTA is an abbreviation. The chemical name should be added to identify the excipient.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	Adequate	Statement in section 11
Pharmacological/Therapeutic class	Adequate	Melphalan hydrochloride is an alkylating drug.
Chemical name, structural formula, molecular weight	Adequate	Chemical name: 4-[bis(2-chloroethyl) amino]-L-phenylalanine hydrochloride molecular formula: $C_{13}H_{18}Cl_2N_2O_2 \cdot HCl$ Molecular Weight: 341.67
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	Adequate	Melphalan (b) (4) a white to off-white powder, ~~with melting range 199-201°C. P~~practically insoluble in water~~, but freely soluble in 1N HCl and MeOH~~. The pH of the drug product solution after dilution with 0.9% Sodium Chloride ranges from 2.4-3.5. Recommendation: (Th (b) (4) is not relevant information from clinical perspective, therefore CMC team suggested removing that statement from USPI). Included drug product pH information in accordance with labelling review tool. [Information to be deleted as it provides no clinical value.]

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	None were observed.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Solution ready for dilution
Strength(s) in metric system	Adequate	90 mg/mL (freebase)
Available units (e.g., bottles of 100 tablets)	Inadequate	Text is to be edited to: How Supplied Melphalan Injection is a clear colorless to yellow solution supplied in a single carton containing one (1) vial. Each vial contains a clear colorless to yellow solution in a multiple-dose vial for intravenous administration. (NDC 60505-6258-1)
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Clear, colorless to yellow solution NDC 60505-6258-1
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	Multiple dose vial

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Inadequate	Text is to be edited to: Storage and Handling Store melphalan hydrochloride injection at 2°C to 8°C (36°F to 46°F). Melphalan hydrochloride injection is light sensitive. Retain in original carton (b) (4) Recommendations: The in-use stability data (chemical stability) provided in the NDA, do not support (b) (4) Therefore, the Applicant will be asked to remove this statement from the USPI. DMEPA team also suggested to retain the in-use storage conditions only in section 2.3 (not in section 16).

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Store Melphalan Hydrochloride Injection at 2°C to 8°C (36°F to 46°F). Statements "Melphalan Hydrochloride Injection is light sensitive. Retain in original carton when not in use." should be retained.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	

Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. – No comments

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Inadequate	Text is to be edited to: Manufactured by: AqVida GmbH (b) (4) (b) (4) Dassow Germany (b) (4) (b) (4) Manufactured for: Apotex Corp. (b) (4) Toronto, Ontario M9L 1T9 Canada (b) (4)

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information): Not submitted

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT: None

3.0 CONTAINER AND CARTON LABELING

Amendment SD-014

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	
Net contents (e.g., tablet count, volume of liquid)	Adequate	Vial fill volume is not specified in the vial label or carton label.
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Inadequate	BUD is present. Vial label includes only long term storage for the unused vial. Carton labels includes long term storage for the unused vial and for storage after the vial after first dose. Comment to the Applicant: The in-use stability data (chemical stability) provided in the NDA, do not support the (b) (4) Therefore, remove this statement from the carton label.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	Adequate	Multiple dose vial

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	Excipients are not listed on the container or carton label for this information. There may be insufficient space for this information. The applicant will be asked to update the carton label with inactive ingredient information in the labeling negotiations. Comment to the Applicant: Update the carton label to list all the inactive ingredients in the alphabetical order.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Inadequate	"Manufactured by" and "Manufactured for" address information is incorrect; see comment for draft USPI.
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *{Not Adequate}*

Recommendations for USPI

1. Per the Agency Guidance: Naming of Drug Products Containing Salt Drug Substances Salt policy guidance and MAPP 5021.1, the non-proprietary name and strength of the drug product should be based upon active moiety (not on the salt). Therefore, we recommend deleting 'Hydrochloride' from drug product name throughout your labeling (e.g., USPI, Container and Carton labels, etc.).

2. The in-use stability data (chemical stability) provided in the NDA, does not support the (b) (4) Remove this statement from USPI (section 2.3).

3. List the inactive ingredients in alphabetical order in Section 11 of the USPI. Also, the trade/abbreviated name for DOTA excipient should not be included in Section 11 of the USPI. Refer USP General Chapter <1091> for additional details.

4. In USPI Section 17, the addresses for "manufactured by" and "manufactured for" need to be updated to reflect the drug product manufacturing site (Dassow,

Germany) and the NDA holder (Toronto, Canada) as specified in section 3.2.P.3.1 of the NDA.

Recommendations for Container and Carton Labels:

1. Include the Net Content on the carton and container label. It is noted that the release specification included criteria for container content (NLT [redacted] (b) (4) mL). For additional information, refer 21 CFR 201.51.
2. Update the carton label to list all of the inactive ingredients in alphabetical order.
3. The in-use stability data (chemical stability) provided in the NDA, does not support the [redacted] (b) (4). Therefore, remove this statement from the carton label.
4. Revise the addresses for "manufactured by" and "manufactured for" on vial label and the carton label to reflect the drug product manufacturing site (Dassow, Germany) and NDA holder (Toronto, Canada) as specified in section 3.2.P.3.1 of the NDA.

ITEMS FOR ADDITIONAL ASSESSMENT

None.

Overall Assessment and Recommendation: {Not Adequate}

See the recommendations capture above.

Primary Labeling Assessor: William Adams, DNDPI, 06/26/23

Secondary Assessor: Thomas Oliver, Director DNDP

Thomas Oliver

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William Adams

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
Application Number	NDA 217110-ORIG-1
Type of Submission	505(b)(2)
Drug Product Name/ Strength	Melphalan Hydrochloride (HCl) Injection, 90 mg/ml
Route of Administration	Injectable solution for Intravenous (IV) infusion
Applicant Name	Apotex, Inc
Therapeutic Classification/ OND Division	Office of Oncologic Diseases/ Divisions of Hematology-Malignancy 2
LD Number	NDA 020207 ALKERAN® (Melphalan HCl) for Injection (Apotex Inc)/RS: A090270, Mylan
Proposed Indication	Palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate
Submission Date	10-20-2022 (0003(3)) (Original Submission)
Assessment Recommendation	Adequate

A. ASSESSMENT SUMMARY:

Apotex Inc., submitted this 505(b)(2) NDA for a ready-to-dilute (RTD) liquid formulation of Melphalan HCl Injection, 90 mg/ml (1 mL), relying upon FDA's previous findings of safety and efficacy data from the labeling of the Listed Drug (LD) product, Alkeran® (melphalan HCl) Injection (NDA 020207). The proposed drug product has the same indication, active ingredient, route of administration and dosing regimen as the LD whereas they are in different dosage forms (lyophilized powder vs. concentrate) and contain different excipients. 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. This Biopharmaceutics Review evaluates the overall data/information supporting the scientific bridge. The submitted data/information indicate that the differences in formulation and dosage form are unlikely to impact the disposition and pharmacokinetics of melphalan when administered intravenously. Therefore, the scientific bridge is deemed adequate as per 21 CFR 320.24(b)(6).

Recommendation: From a Biopharmaceutics perspective, NDA 217110 for Melphalan Hydrochloride Injection, 90 mg/ml (1 mL), is recommended for **APPROVAL**.

B. LIST SUBMISSIONS BEING ASSESSED (Table):

Document(s) Assessed	Date Received
Original submission/Sequence 0003	10-20-2022
Response to Information Request	03-07-2023[1]

[1] \\CDSESUB1\EVSPROD\nda217110\0009\m1\us\12-cover-letters\response-to-information-request-20230307.pdf

C. BRIOPHARMACEUTICS ASSESSMENT

SUBMISSION:

Drug Substance (DS) and Drug Product (DP) Solubility: the Applicant submitted the solubility data of DS at room temperature (RT) (25±2°C).

Table 1: Solubility (RT) of melphalan (M 3.2.P.2 (0003), PDR-022-00, Pg. 59)

S.No	Medium	Solubility (mg/mL)
1	Water	0.002
2	0.1N HCl (pH 1.2)	0.030
3	0.01 N HCl (pH 2.1)	0.030
4	pH 4.5 Acetate Buffer	0.022
5	pH 5.5 Acetate Buffer	0.030
6	pH 6.8 Phosphate Buffer	0.002
7	pH 8.0 Phosphate Buffer	0.020

Note: Reference: pH Dependent Solubility study Report "RPT/MPH003-00

Table 2: Saturation solubility (RT) of melphalan in formulation vehicle (M 1.12.15 (0003), Pg. 25)

S. No	Parameter	Sample Preparation-1	Sample Preparation-2
1	Description	Clear pale yellowish solution	Clear pale yellowish solution
2	Identification by HPLC	Complies^	Complies^
3	Solubility of Melphalan	167.6 mg/mL	164 mg/mL
Average solubility of Melphalan		165.8 mg/mL	
ARR#		LPAR/052/0253/20	LPAR/052/0254/20

Proposed Drug Product: the proposed formulation is a sterile liquid containing melphalan (b) (4) (polyethylene glycol 400 and propylene glycol (b) (4) DOTA as (b) (4) and monothioglycerol as (b) (4)).

Table 3: Composition of the proposed drug product (M 3.2.P.1 (0003), Pg. 2)

Strength (Label Claim):			90 mg/mL	
Component Grade	Quality Standard	Function	Quantity (mg) per mL	% w/v total unit dose
Melphalan free base (Equivalent to Melphalan Hydrochloride)	In-House	Active Pharmaceutical Ingredient	90 mg* (equivalent to 100.755 mg Melphalan Hydrochloride)	9.0% w/v
Monothioglycerol	USP	(b) (4)	5.00 mg	0.5% w/v
DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid dihydrate)	In-House	(b) (4)	0.50 mg	0.05% w/v
Water for Injection	USP, Ph.Eur	(b) (4)	(b) (4) mg	(b) (4) % w/v
Propylene Glycol	USP, Ph.Eur	(b) (4)	170 mg	17% w/v
Sodium Hydroxide (b) (4)	USP, Ph.Eur	pH adjuster	q.s. to adjust pH of PEG 400 between 6.85-7.25	NA
Hydrochloric acid (b) (4)	USP, Ph.Eur	pH adjuster	q.s. to adjust pH of PEG 400 between 6.85-7.25	NA
Polyethylene Glycol 400	USP/NF, Ph.Eur	(b) (4)	(b) (4)	q.s. to 100%
(b) (4)				
TOTAL				100.00%

(b) (4)

(b) (4)

Reference Standard (RS) product: the Orange Book (as of 02/05/23) shows the LD product is "discontinued" in market, and Mylan's product (A090270) is listed as RS product. The applicant submitted the characterizations of RS and LD products.

Table 4: Characterizations of LD and RS products (M 3.2.P.2 (0003), PDR-022-00, Pg. 15)

S.No	Parameter	Listed Drug (Alkeran) (NDA020207)	Reference Standard Drug Product (ANDA#090270)	Reference Standard Drug product (ANDA#090270)	Reference Standard Drug product (ANDA#090270)	Reference Standard Drug product (ANDA#090270)
		50 mg/vial	50 mg/vial	50 mg/vial	50 mg/vial	50 mg/vial
Sample ID No.		0067/14 0189/14	0038/18	NA	NA	NA
1	Mfg. by/For	Glaxosmith Kline	MYLAN INSTITUTIONAL LLC	MYLAN INSTITUTIONAL LLC	MYLAN INSTITUTIONAL LLC	MYLAN INSTITUTIONAL LLC
	Lot. No.	P283	N1600815	N2100348	N2100526	N2101114
	Expiry Date	January 2015	August 2018	Feb 2023	Apr 2023	Sep 2023
	Analysis Date	May 2014	August 2018	August 2022	August 2022	August 2022
2	Description	White Lyophilized cake	White Lyophilized cake	White Lyophilized cake	White Lyophilized cake	White Lyophilized cake
3	Identification	$	$	$	$	$
4	Reconstitution Time	50 seconds	55 seconds	46 seconds	37 seconds	43 seconds
5	Description of Reconstituted solution	Clear colorless solution	Clear colorless solution	Clear colorless solution	Clear colorless solution	Clear colorless solution
6	pH of the solution	6.54	5.77	5.80	5.81	5.78
7	Visual particles in the reconstituted Solution	No visual particles	No visual particles	No visual particles	No visual particles	No visual particles
8	Osmolality(m Osm/Kg)	1197	1287	1278	1216	1236
9	Assay by HPLC (%)	98.0	102.7	103.5	103.8	103.1
		Related substances				

(b) (4)

[redacted]

Reviewer's Assessment:

The submitted data indicate that melphalan is a low solubility drug substance but it is highly soluble (165.8 mg/mL) in the proposed formulation vehicle. The approved formulation for the RS product (A090270) is Q1/Q2 the same to the LD product[2]. Therefore, using the RS product in comparative studies is deemed acceptable.

According to the labeling, the LD product is supplied with two vials one with melphalan HCl (equivalent to 50 mg base) and povidone (20 mg) in lyophilized form and the other as a diluent vial (sodium citrate: 0.2 g, propylene glycol: 6.0 mL, ethanol (96%): 0.52 mL, and water for injection to a total of 10 mL). Before being administered intravenously, the LD product must be reconstituted by rapidly injecting 10 mL of the supplied diluent directly into the vial of lyophilized powder and shaking vigorously until a clear solution is obtained. The resultant 5 mg/mL solution then is diluted in 0.9% NaCl injection (USP) to a concentration ≤ 0.45 mg/mL. Administer the diluted product over a minimum of 15 minutes. Complete administration within 60 minutes of reconstitution.

[2] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8016a141

The proposed drug product is a ready to dilute injection concentrate containing 90 mg/mL of Melphalan in liquid form and can be directly diluted in normal saline without need for making a premix solution. A summary of the differences between the LD/RS and proposed drug products is shown as below:

Table 5: Comparison of LD/RS and proposed products (M 3.2.P.2 (0003), PDR-022-00, Pg. 12)

S. No	Parameter	Reference standard (ANDA # 090270) and Alkeran			Proposed Ready to dilute Melphalan Hydrochloride injection		
1	Product Presentation	Two Vial System Sterile Lyophilized powder Product Vial Diluent Vial			Sterile clear solution filled into vials		
2	Composition	**Strength: 50 mg/Vial**			**Strength: 90 mg/mL**		
		Melphalan Hydrochloride equivalent to 50 mg of Melphalan	Active Pharmaceutical ingredient	50 mg#	Melphalan Hydrochloride equivalent to 90 mg of Melphalan	Active Pharmaceutical ingredient	100.755 mg
		Povidone	(b) (4)	20 mg	Propylene Glycol	(b) (4)	170 mg
		Sodium Citrate		0.2 g	Monothioglycerol		5 mg
		Propylene glycol		6 mL	DOTA (1, 4,7,10 tetraacetic acid, 1, 4,7,10 tetraazacyclododecane)		0.5 mg
		Ethanol (96%)		0.52 mL	Water for injection		0.027 mL
		Water for Injection	Vehicle	Qs to 10 mL	Polyethylene Glycol - 400		Qs to 1 mL
3	Method of usage	Step-1: Add diluent and reconstitute Step-2: Further dilute in Normal saline and use within 1 hour			Only one step Add required dose to the IV bag and use		
4	Premix stability	Premix and final dilution to be used within 1 hour			No premix storage needed since the formulation is ready to dilute. RTD Product can be stored for shelf life at 2-8°C.		
5	Multidose usage	Not feasible			Feasible		
6	Drug wastage	High			Minimal drug wastage: Ready to Dilute Melphalan Hydrochloride Injection is presented as ready to dilute concentrate that could be used as a multi dose product. This offers flexibility in clinical usage and reduce drug wastage		
7	Ease of reconstitution to make Premix	Low (Vigorous shaking required and few instances of poor reconstitution are encountered)			No reconstitution is needed		
8	Medication errors	Two step dilution is needed, hence probability of error is higher when compared to RTD formulation			Probability of error is minimal since there is no premix preparation		
9	Osmolality of IV solutions for administration	Hypertonic			Isotonic		
10	High dose administered with low IV fluid volume as well as low excipient burden	High excipient burden (b) (4) g of excipient per 100 mg/m^2 dose)			Low excipient burden (only (b) (4) g of excipient per 100 mg/m^2 dose)		

Note: #compensate with % assay, water content and HCl content

Reviewer's Assessment:

The composition differences in the IV infusion solution (by the time of administration) between the proposed and LD product are:

1) *Exclusion of excipients from LD: povidone (b) (4) sodium Citrate (b) (4) ethanol, hydrochloric acid.*
2) *Addition of new excipients to the proposed product: monothioglycerol (b) (4) DOTA (b) (4) Polyethylene Glycol 400.*

In addition, the level of propylene glycol ((b) (4)) was significantly reduced from LD to the proposed product.

BRIDGING (21 CFR § 320. 24 (b)(6)):

Assessment: ***Adequate***

The following physicochemical comparison data have been submitted to support the scientific bridging.

1. Comparison of physicochemical properties of IV Infusion

Table 6: Physicochemical comparison of LD and RS after reconstitution and dilution to 0.45 mg/mL (M 3.2.P.2 (0003), PDR-022-00, Pg. 16)

Test Parameters	Alkeran (Listed Drug)		Melphalan HCl for Injection (Reference Standard)		Melphalan HCl for Injection (Reference Standard)	
Batch No	P283 (Expiry: 01/2015)		N1600815 (Expiry: 08/2018)		N1600815 (Expiry: 08/2018)	
Date of Analysis	Jan 2015		Aug 2017		Aug 2018	
Concentration	0.45 mg/mL in Normal saline at 25°C		0.45 mg/mL in Normal Saline at 25°C		0.45 mg/mL in Normal Saline at 25°C	
Time Point	Initial	1 Hour	Initial	1 Hour	Initial	1 Hour
Description	CCS	CCS	CCS	CCS	CCS	CCS
Identification by HPLC	#	#	#	#	#	#
Assay (%)	95.6	88.2	100.6	95.5	98.6	91.9
pH	5.83	6.35	5.63	5.88	5.77	5.76
Osmolality (mOsm/Kg)	1120	1122	1240	1243	1287	1281
Related Substances by HPLC (%w/w)						(b) (4)
Sample ID No.	0003/15	0005/15	TSR-AD-361 (Page: 12)		0038/18	

CCS: Clear colorless solution; ND: Not Detected

#: The retention time of major peak in the sample solution should match with that of the major peak in the chromatogram of standard preparation

Table 7: Physicochemical comparison of RS versus proposed products (stability batches) (M 3.2.P.2 (0003), PDR-022-00, Pg. 56)

S.No	Parameter	Reference Standard Drug Product (ANDA#090270)	Reference Standard Drug product (ANDA#090270)	Reference Standard Drug product (ANDA#090270)	Reference Standard Drug product (ANDA#090270)	Test product (Batch# CV2101)	Test product (Batch# CV2102)	Test product (Batch# CV2103)
		50 mg/vial	50 mg/vial	50 mg/vial	50 mg/vial	90 mg/mL	90 mg/mL	90 mg/mL
	Sample ID No.	0038/18	NA	NA	NA	NA	NA	NA
1	Mfg. by/For	MYLAN INSTITUTIONAL LLC	MYLAN INSTITUTIONAL LLC	MYLAN INSTITUTIONAL LLC	MYLAN INSTITUTIONAL LLC			(b) (4)
	Lot. No.	N1600815	N2100348	N2100526	N2101114	CV2101	CV2102	CV2103
	Expiry Date	August 2018	Feb 2023	Apr 2023	Sep 2023	NA	NA	NA
	Mfg date	NA	NA	NA	NA	June 2021	July 2021	July 2021
	Analysis Date	August 2018	August 2022	August 2022	August 2022	July 2021	July 2021	July 2021
2	Description	White Lyophilized cake	White Lyophilized cake	White Lyophilized cake	White Lyophilized cake	#	#	#
3	Identification	$	$	$	$	Complies	Complies	Complies
4	Reconstitution Time	55 seconds	46 seconds	37 seconds	43 seconds	NA	NA	NA
5	Description of Reconstituted solution	Clear colorless solution	Clear colorless solution	Clear colorless solution	Clear colorless solution	NA	NA	NA
6	pH of the solution (0.45 mg/mL in 0.9% Sodium chloride Injection, USP)	5.77	5.80	5.81	5.78	2.8	2.9	2.9
7	Visual particles in the reconstituted Solution	No visual particles	No visual particles	No visual particles	No visual particles	NA	NA	NA
8	Osmolality (mOsm/Kg) (0.45 mg/mL in 0.9% Sodium chloride Injection, USP)	1287	1278	1236	1236	NA	NA	NA
9	Assay by HPLC (%)	102.7	103.5	103.8	103.1	100.1	99.8	99.8

Table 8: Comparative physicochemical data of RS and proposed products (stored at RT) diluted to 0.45 mg/mL (M 1.12.15 (0003), Pg. 19)

Test parameters		Reference standard** (Melphalan Hydrochloride for Injection, 50 mg/vial)						Proposed Melphalan Hydrochloride Injection, 90 mg/mL**						Proposed Melphalan Hydrochloride Injection, 90 mg/mL**					
Date of analysis		May 2022		May 2022		May 2022		May 2022		May 2022		May 2022		October 2022		October 2022		October 2022	
Lot No.:		N2100348 (Exp.date: 02/2023)		N2100526 (Exp. Date: 04/2023)		N2101114 (Exp. Date: 09/2023)		CV2101		CV2102		CV2103		CV2101		CV2102		CV2103	
S. No	Time Point	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins
1	Description	*		*		*		#		#		#		#		#		#	
2	Reconstitution time	46 seconds		37 seconds		43 seconds		Not applicable						Not applicable					
3	Description of Reconstituted solution (5 mg/mL)	CCS		CCS		CCS													
4	Description of Diluted solution (0.45mg/mL)	$	$	$	$	$	$	$	$	$	$	$	$	$	$	$	$	$	$
5	pH of the Solution	5.80	5.77	5.81	5.82	5.78	5.80	2.83	2.80	2.87	2.83	2.79	2.81	3.03	3.00	3.05	3.04	3.07	3.05
6	Osmolality (mOsm/kg)	1278	1271	1236	1253	1236	1258	297	300	301	299	304	306	288	299	293	302	289	303
7	Viscosity (mPa.s)	1.2242	1.2176	1.1998	1.2311	1.2254	1.2415	1.0217	1.014	1.0214	1.0253	1.021	1.015	1.0220	1.0210	1.0210	1.0200	1.0220	1.0200
8	Specific gravity (g/mL)	1.0103	1.0107	1.0101	1.0104	1.0109	1.0109	1.0073	1.0074	1.0074	1.0075	1.0069	1.0074	1.0073	1.0073	1.0072	1.0075	1.0073	1.0075
9	Refractive index	1.3409	1.3408	1.3408	1.3408	1.3407	1.3407	1.3347	1.3346	1.3346	1.3347	1.3347	1.3347	1.3349	1.3347	1.3348	1.3346	1.3348	1.3347

*: Off white freeze dried powder, #: Pale yellow color viscous solution free from any visible extraneous matter, CCS: Clear, colorless solution, $: Clear colorless solution free from foreign visible particles.**: Diluted in 0.9% Sodium Chloride Injection, USP

Table 9: Comparative physicochemical data of RS and proposed products (stored at RT) diluted to 0.75 mg/mL (M 1.12.15 (0003), Pg. 20)

Test parameters		Reference standard** (Melphalan Hydrochloride for Injection, 50 mg/vial)						Proposed Melphalan Hydrochloride Injection, 90 mg/mL**						Proposed Melphalan Hydrochloride Injection, 90 mg/mL**					
Date of analysis		May 2022		May 2022		May 2022		May 2022		May 2022		May 2022		October 2022		October 2022		October 2022	
Lot No.:		N2100348 (Exp.date: 02/2023)		N2100526 (Exp. Date: 04/2023)		N2101114 (Exp. Date: 09/2023)		CV2101		CV2102		CV2103		CV2101		CV2102		CV2103	
S.No	Time Point	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins
1	Description	*		*		*		#		#		#		#		#		#	
2	Reconstitution time	39 seconds		41 seconds		44 seconds		Not applicable						Not applicable					
3	Description of Reconstituted solution (5 mg/mL)	CCS		CCS		CCS													
4	Description of Diluted solution (0.75mg/mL)	$	$	$	$	$	$	$	$	$	$	$	$	$	$	$	$	$	$
5	pH of the Solution	5.90	5.92	5.89	5.91	5.90	5.91	2.83	2.78	2.80	2.77	2.80	2.76	2.87	2.85	2.84	2.83	2.89	2.86
6	Osmolality (mOsm/kg)	1363	1365	1372	1368	1360	1345	319	319	317	320	318	324	309	325	306	324	304	320
7	Viscosity (mPa.s)	1.597	1.5986	1.5934	1.5974	1.5962	1.5982	1.138	1.1354	1.1379	1.1351	1.1363	1.1352	1.0200	1.0200	1.0210	1.0190	1.0210	1.0190
8	Specific gravity (g/mL)	1.0141	1.0141	1.0139	1.0140	1.0140	1.0140	1.0080	1.0079	1.0079	1.0079	1.0080	1.0081	1.0072	1.0077	1.0074	1.0078	1.0075	1.0081
9	Refractive index	1.3454	1.3454	1.3453	1.3454	1.3453	1.3454	1.3354	1.3354	1.3354	1.3354	1.3354	1.3354	1.3353	1.3352	1.3353	1.3352	1.3353	1.3351

*: Off white freeze dried powder, #: Pale yellow color viscous solution free from any visible extraneous matter, CCS: Clear, colorless solution, $: Clear colorless solution free from foreign visible particles. **: Diluted in 0.9% Sodium Chloride Injection, USP

Table 10: Comparative physicochemical data of RS and proposed products (stored at RT) diluted to 1.0 mg/mL (M 1.12.15 (0003), Pg. 21)

Test parameters		Reference standard** (Melphalan Hydrochloride for Injection, 50 mg/vial)						Proposed Melphalan Hydrochloride Injection, 90 mg/mL**						Proposed Melphalan Hydrochloride Injection, 90 mg/mL**					
Date of analysis		May 2022		May 2022		May 2022		May 2022		May 2022		May 2022		October 2022		October 2022		October 2022	
Lot No.:		N2100348 (Exp.date: 02/2023)		N2100526 (Exp. Date: 04/2023)		N2101114 (Exp. Date: 09/2023)		CV2101		CV2102		CV2103		CV2101		CV2102		CV2103	
S.No	Time Point	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins	T0	At 60 mins
1	Description	*		*		*		#		#		#		#		#		#	
2	Reconstitution time	41 seconds		38 seconds		47 seconds		Not applicable						Not applicable					
3	Description of Reconstituted solution (5 mg/mL)	CCS		CCS		CCS													
4	Description of Diluted solution (1.0 mg/mL)	$	$	$	$	$	$	$	$	$	$	$	$	$	$	$	$	$	$
5	pH of the Solution	6.00	5.98	5.89	5.86	5.95	5.98	2.62	2.61	2.63	2.61	2.60	2.62	2.75	2.74	2.78	2.76	2.81	2.78
6	Osmolality (mOsm/kg)	1722	1711	1732	1729	1720	1734	341	353	335	327	338	333	333	335	339	342	336	342
7	Viscosity (mPa.s)	1.5819	1.5817	1.5721	1.5738	1.6357	1.5899	1.0211	1.0219	1.0164	1.0222	1.0162	1.0351	1.0190	1.0190	1.0200	1.0190	1.0190	1.0200
8	Specific gravity (g/mL)	1.0162	1.0162	1.0162	1.0162	1.0159	1.0165	1.0089	1.0087	1.0085	1.0083	1.0088	1.0088	1.0087	1.0085	1.0088	1.0083	1.0087	1.0085
9	Refractive index	1.3491	1.3489	1.3491	1.3491	1.3492	1.3492	1.3356	1.3356	1.3356	1.3356	1.3356	1.3356	1.3357	1.3357	1.3357	1.3357	1.3355	1.3355

*: Off white freeze dried powder, #: Pale yellow color viscous solution free from any visible extraneous matter, CCS: Clear, colorless solution, $: Clear colorless solution free from foreign visible particles. **: Diluted in 0.9% Sodium Chloride Injection, USP

Table 11: Physicochemical properties of stability batches (T0/initial, stored at RT) diluted to 0.45 mg/mL (M 3.2.P.2 (0003), PDR-022-00, Pg. 143)

Batch No.:		CV2101			CV2102			CV2103		
S.No	Test parameters/ Time Point	T0	30 mins	60 mins	T0	30 mins	60 mins	T0	30 mins	60 mins
1	Description	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
2	Identification by HPLC	$	$	$	$	$	$	$	$	$
3	pH of the Solution	2.75	2.76	2.79	2.75	2.80	2.81	2.83	2.82	2.83
4	Osmolality (mOsm/kg)	309	309	308	308	307	309	306	304	305
5	Assay (% w/w)	103.3	101.6	98.6	104.6	101.9	99.9	102.6	100.2	97.7
6	Related substances	%w/w								
	(b) (4)	(b) (4)								
	Total Impurities									
7	Particulate matter									
7A	Visible particles	#	#	#	#	#	#	#	#	#
7B	Sub visible particles (Light obscuration Particle Count method)									
	≥ 10 microns	NMT (b) (4) Particles per container	(b) (4)							
	≥ 25 microns	NMT (b) (4) Particles per container	(b) (4)							

CCS: Clear, colorless solution, ND: Not detected, #: Clear solution free from visible particles
$: The retention time of the major peak in the chromatogram of the sample preparation should match with that of the major peak in the chromatogram of Standard preparation.

Table 12: Physicochemical properties of stability batches (T12, stored at RT) diluted to 0.45 mg/mL (M 3.2.P.2 (0003), PDR-022-00, Pg. 146)

Batch No.:		CV2101			CV2102			CV2103		
S.No	Test parameters/ Time Point	T0	30 mins	60 mins	T0	30 mins	60 mins	T0	30 mins	60 mins
1	Description	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
2	Identification by HPLC	$	$	$	$	$	$	$	$	$
3	pH of the Solution	2.94	2.98	2.89	2.96	2.93	2.92	2.93	2.93	2.93
4	Osmolality (mOsm/kg)	291	283	285	282	285	308	307	299	293
5	Assay (% w/w)	104.6	100.4	98.3	98.1	92.8	93.6	103.5	99.5	98.5
6	Related substances	%w/w								
	(b) (4)	(b) (4)								
	Total Impurities									
7	Particulate matter									
7A	Visible particles	#	#	#	#	#	#	#	#	#
7B	Sub visible particles (Light obscuration Particle Count method)									
	≥ 10 microns	(b) (4) Particles per container	(b) (4)							
	≥ 25 microns	(b) (4) Particles per container	(b) (4)							

Table 13: Physicochemical properties of RS batches (stored at RT) diluted to 0.45 mg/mL (M 3.2.P.2 (0003), PDR-022-00, Pg. 150)

S.No	Lot No.:	N2100348			N2100526			N2101114		
	Test parameters/Time Point	T0	At 30 mins	At 60 mins	T0	At 30 mins	At 60 mins	T0	At 30 mins	At 60 mins
1	Description	Off white freeze dried powder			Off white freeze dried powder			Off white freeze dried powder		
2	Reconstitution time	46 seconds			38 seconds			52 seconds		
3	Description of reconstitution solution	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
4	Identification by retention time	$	$	$	$	$	$	$	$	$
5	pH of the solution	5.84	5.80	5.79	5.81	5.75	5.67	5.83	5.79	5.80
6	Osmolality (mOsm/kg)	1235	1241	1242	1241	1203	1244	1215	1211	1230
7	Assay (%w/w)	97.3	94.6	91.5	100.1	96.1	91.7	96.2	92.7	88.5
8	Related substances	%w/w								
	(b) (4)	(b) (4)								
	Total Impurities									

Table 14: Physicochemical properties of stability batches (T0/initial, stored at RT) diluted to 0.75 mg/mL (M 3.2.P.2 (0003), PDR-022-00, Pg. 144)

S.No	Batch No.: / Test parameters/ Time Point	CV2101 T0	CV2101 30 mins	CV2101 60 mins	CV2102 T0	CV2102 30 mins	CV2102 60 mins	CV2103 T0	CV2103 30 mins	CV2103 60 mins
1	Description	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
2	Identification by HPLC	$	$	$	$	$	$	$	$	$
3	pH of the Solution	2.64	2.64	2.64	2.64	2.63	2.66	2.67	2.66	2.69
4	Osmolality (mOsm/kg)	322	321	320	325	322	323	327	328	329
5	Assay (% w/w)	103.8	101.2	99.1	102.4	101	99.4	103.6	101.8	98.4
6	Related substances	%w/w								
	(b) (4)	(b) (4)								
	Total Impurities									
7	Particulate matter									
7A	Visible particles	#	#	#	#	#	#	#	#	#
7B	Sub visible particles (Light obscuration Particle Count method)									
	≥ 10 microns (b) (4) Particles per container	1								
	≥ 25 microns (b) (4) Particles per container									

Table 15: Physicochemical properties of stability batches (T12, stored at RT) diluted to 0.75 mg/mL (M 3.2.P.2 (0003), PDR-022-00, Pg. 147)

S.No	Batch No.: / Test parameters/ Time Point	CV2101 T0	CV2101 30 mins	CV2101 60 mins	CV2102 T0	CV2102 30 mins	CV2102 60 mins	CV2103 T0	CV2103 30 mins	CV2103 60 mins
1	Description	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
2	Identification by HPLC	$	$	$	$	$	$	$	$	$
3	pH of the Solution	2.79	2.77	2.83	2.75	2.76	2.78	2.77	2.73	2.72
4	Osmolality (mOsm/kg)	311	309	305	313	314	320	293	299	298
5	Assay (% w/w)	99.9	97.8	95.5	100.6	98.7	97.6	98.8	96.2	93.0
6	Related substances	%w/w								
	(b) (4)	(b) (4)								
	Total Impurities									
7	Particulate matter									
7A	Visible particles	#	#	#	#	#	#	#	#	#
7B	Sub visible particles (Light obscuration Particle Count method)									
	≥ 10 microns (b) (4) Particles per container									
	≥ 25 microns (b) (4) Particles per container									

Table 16: Physicochemical properties of stability batches (T0/initial, stored at RT) diluted to 1.0 mg/mL (M 3.2.P.2 (0003), PDR-022-00, Pg. 145)

S.No	Batch No.: / Test parameters/ Time Point	CV2101 T0	CV2101 30 mins	CV2101 60 mins	CV2102 T0	CV2102 30 mins	CV2102 60 mins	CV2103 T0	CV2103 30 mins	CV2103 60 mins
1	Description	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
2	Identification by HPLC	$	$	$	$	$	$	$	$	$
3	pH of the Solution	2.57	2.54	2.50	2.55	2.55	2.55	2.53	2.53	2.52
4	Osmolality (mOsm/kg)	343	346	345	341	341	334	343	343	341
5	Assay (% w/w)	103.3	100.5	100.3	102.5	99.7	97.6	102.8	102.1	99.6
6	Related substances	%w/w								
	(b) (4)	(b) (4)								
	Total Impurities									
7	Particulate matter									
7A	Visible particles	#	#	#	#	#	#	#	#	#
7B	Sub visible particles (Light obscuration Particle Count method)									
	≥ 10 microns (b) (4) Particles per container									
	≥ 25 microns (b) (4) Particles per container									

CCS: Clear, colorless solution, ND: Not detected, #: Clear solution free from visible particles

$: The retention time of the major peak in the chromatogram of the sample preparation should match with that of the major peak in the chromatogram of Standard preparation.

Table 17: Physicochemical properties of stability batches (T12, stored at RT) diluted to 1.0 mg/mL (M 3.2.P.2 (0003), PDR-022-00, Pg. 148)

Batch No.:		CV2101			CV2102			CV2103		
S.No	Test parameters/ Time Point	T0	30 mins	60 mins	T0	30 mins	60 mins	T0	30 mins	60 mins
1	Description	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
2	Identification by HPLC	$	$	$	$	$	$	$	$	$
3	pH of the Solution	2.64	2.60	2.60	2.60	2.68	2.67	2.64	2.62	2.63
4	Osmolality (mOsm/kg)	332	329	335	315	334	313	334	323	327
5	Assay (% w/w)	96.9	94.2	92.9	101.9	99.1	96.1	101.1	99.7	98.3
6	Related substances	%w/w								
	(b) (4)	(b) (4)								
	Total impurities									
7	Particulate matter									
7A	Visible particles	#	#	#	#	#	#	#	#	#
7B	Sub visible particles (Light obscuration Particle Count method)									
	≥ 10 microns (b) (4) Particles per container	387	300	280	500	507	200	207	207	100
	≥ 25 microns (b) (4) Particles per container	7	0	0	0	0	7	0	13	0

Reviewer's Assessment:

The submitted physicochemical property comparison data indicate that the IV infusion dilutions of the proposed drug product (stored at RT at t=0 and 12, diluted to 0.45 mg/mL, 0.75 mg/mL and 1.0 mg/mL) show similar/comparable description, identification, assay, impurity (b) (4), specific gravity and refractive index to the RS product, whereas they are different in osmolality, viscosity and pHs. The proposed drug product diluted to 0.45 mg/mL showed osmolality of around 300 mOsm/kg, viscosity of around 1.0 mPa.s and pHs of 2.8-3, while the RS product diluted to 0.45 mg/mL (as per LD labeling) showed osmolality of around 1200 mOsm/kg, viscosity of around 1.2 mPa.s, and pHs of around 5.8. The osmolality of the infusion dilution of the proposed product is lower than the LD/RS product due to low excipient burden (level of propylene glycol) and meets the general requirements for isotonic solutions (260-340 mOsm/kg), indicating the risks for venous irritation or thrombophlebitis caused by high osmolality is considered low. The lower viscosity may result in less resistance of a fluid to flow but the slight difference in viscosity (1.0 mPa.s vs. 1.2 mPa.s) is unlikely to pose any negative impact on the use of product when administered intravenously. The pH of the proposed drug product differs from the RS/LD product and is lower than the commonly acceptable range of pH (b) (4) The Applicant stated that the proposed drug product is more stable in the acidic solution (e.g., forced degradation data) and the IV infusion (diluted product) up to 1.0 mg/mL is nonhemolytic (Hemolysis report# BIO-INV 049) and have comparable resultant pH compared to the RS product after dilution at clinically relevant concentrations in human whole blood (M 1.12.15 (0003), Table 21, Pg.32). Considering the infusion pH may still cause local effects/discomfort at infusion site (e.g., extravasation, endothelial damage with platelet adherence and vessel occlusion and inflammation) and the submitted non-clinical studies (IV local tolerability of in-use solutions in Rabbit and Rat) are not considered adequate for human, the Applicant was requested to provide additional literature information or data from other approved products that are administered intravenously with low pH to support the proposed low-pH IV infusion. Based on the data and information provided in IR response dated 03/07/2023 (M1.2 (0009)), the pH of the proposed drug product after dilution are considered acceptable.

2. In vitro protein binding study (Study No. BIO-DMP 032)

The Applicant performed the *in vitro* protein binding study to compare the protein binding of human plasma, α-acid glycoprotein (AAG) and serum albumin (HSA) between the standard (melphalan HCl), proposed [redacted] (b) (4)) and RS [redacted] (b) (4)) products at low (2.5 µg/mL) middle, (6 µg/mL) and high (55 µg/mL) concentrations.

Table 18: % Bound of standard, Test product and Reference standard product at 1 mg/mL concentration (M 1.12.15 (0003), Pg. 46)

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

Table 19: % Bound of standard, Test product and Reference standard product at 0.75 mg/mL concentration (M 1.12.15 (0003), Pg. 47)

Name of Product		Standard	Test Item	Reference Item
Melphalan Concentration	Protein Solution	% Bound	% Bound	% Bound
2.7 µg/mL	Plasma	49.462	58.044	50.407
6 µg/mL		55.449	53.401	52.419
55 µg/mL		53.271	49.001	53.773
2.7 µg/mL	AAG	5.696	3.723	7.296
6 µg/mL		3.926	5.451	2.027
55 µg/mL		0.876	4.618	5.504
2.7 µg/mL	HSA	57.988	58.675	58.730
6 µg/mL		56.005	59.915	56.996
55 µg/mL		56.399	56.895	54.397

Table 20: % Bound of standard, Test product and Reference standard product at 0.45 mg/mL concentration (M 1.12.15 (0003), Pg. 48)

Name of Product		Standard	Test Item	Reference Item
Melphalan Concentration	Protein Solution	% Bound	% Bound	% Bound
2.7 µg/mL	Plasma	58.969	60.081	51.607
6 µg/mL		57.928	49.882	58.505
55 µg/mL		57.834	55.874	53.149
2.7 µg/mL	AAG	5.703	0.683	8.989
6 µg/mL		10.954	6.645	8.828
55 µg/mL		6.678	8.220	5.633
2.7 µg/mL	HSA	57.728	58.938	52.521
6 µg/mL		62.493	51.489	54.662
55 µg/mL		54.483	55.801	53.712

Reviewer's Assessment:

According to the LD labeling, the mean (±SD) peak melphalan plasma concentrations in myeloma patients given IV melphalan at doses of 10 or 20 mg/m^2 were 1.2 ± 0.4 and 2.8 ± 1.9 mcg/mL, respectively. The average melphalan binding to plasma proteins is highly variable (53% to 92%). HSA is the major binding protein, accounting for approximately 40% to 60% of the plasma protein binding, while AGG accounts for about 20% of the plasma protein binding. Approximately 30% of melphalan is (covalently) irreversibly bound to plasma proteins. The submitted data indicate that the standard, proposed and RS products at therapeutically relevant concentrations are highly bound to the human plasma and HSA and poorly bound to AAG. No significant difference in the percentage of protein bound (or free) melphalan among the standard, test and RS products was observed, indicating the difference in excipients is unlikely to impact of PK (e.g., volume of distribution, clearance) of melphalan due to protein binding.

3. In vitro Hemolysis study (Study No. BIO-INV-049)

The Applicant performed the in vitro hemolysis assay to compare the haemolytic potential by diluting the solution with human whole blood at 1:5 and 1:10 ratio.

Table 21: Haemolysis study results of Melphalan Hydrochloride Injection diluted with human whole blood at 1:5 ratio (M 1.12.15 (0003), Pg. 49)

Sample details	Replicates #	Absorbance at 540 nm	Haemoglobin concentration (mg/mL)	% Haemolysis
Blank control	1	0.038	0.303	-
	2	0.037	0.295	
	3	0.038	0.303	
Negative control (0.9% Sodium chloride injection)	1	0.039	0.311	0.026
	2	0.037	0.295	
	3	0.038	0.303	
Positive control (2% Sodium lauryl sulfate in water)	1	0.382	3.049	26.404
	2	0.379	3.025	
	3	0.380	3.033	
In-use solution of Proposed Melphalan HCl injection (0.45 mg/mL) in Normal saline	1	0.039	0.311	0.103
	2	0.040	0.319	
	3	0.038	0.303	
In-use solution of Proposed Melphalan HCl injection (0.75 mg/mL) in Normal saline	1	0.038	0.303	0.052
	2	0.039	0.311	
	3	0.038	0.303	
In-use solution of Proposed Melphalan HCl injection (1.0 mg/mL) in Normal saline	1	0.038	0.303	0.309
	2	0.038	0.303	
	3	0.049	0.391	
In-use solution of Reference standard Melphalan HCl for injection (0.45 mg/mL) in Normal saline	1	0.040	0.319	0.077
	2	0.038	0.303	
	3	0.038	0.303	
In-use solution of Reference standard Melphalan HCl for injection (0.75 mg/mL) in Normal saline	1	0.040	0.319	0.103
	2	0.039	0.311	
	3	0.038	0.303	
In-use solution of Reference standard Melphalan HCl for injection (1.0 mg/mL) in Normal saline	1	0.038	0.303	0.051
	2	0.039	0.311	
	3	0.038	0.303	

Table 22: Haemolysis study results of Melphalan Hydrochloride Injection diluted with human whole blood at 1:10 ratio (M 1.12.15 (0003), Pg. 50)

Sample details	Replicates #	Absorbance at 540 nm	Haemoglobin concentration (mg/mL)	% Haemolysis
Blank control	1	0.038	0.303	-
	2	0.037	0.295	
	3	0.038	0.303	
Negative control (0.9% Sodium chloride injection)	1	0.039	0.311	0.026
	2	0.037	0.295	
	3	0.038	0.303	
Positive control (2% Sodium lauryl sulfate in water)	1	0.382	3.049	26.404
	2	0.379	3.025	
	3	0.380	3.033	
In-use solution of Proposed Melphalan HCl injection (0.45 mg/mL) in Normal saline	1	0.039	0.311	0.103
	2	0.039	0.311	
	3	0.039	0.311	
In-use solution of Proposed Melphalan HCl injection (0.75 mg/mL) in Normal saline	1	0.039	0.311	0
	2	0.037	0.295	
	3	0.037	0.295	
In-use solution of Proposed Melphalan HCl injection (1.0 mg/mL) in Normal saline	1	0.037	0.295	-0.051
	2	0.037	0.295	
	3	0.037	0.295	
In-use solution of Reference standard Melphalan HCl for injection (0.45 mg/mL) in Normal saline	1	0.038	0.303	0.051
	2	0.039	0.311	
	3	0.038	0.303	
In-use solution of Reference standard Melphalan HCl for injection (0.75 mg/mL) in Normal saline	1	0.039	0.311	0.103
	2	0.039	0.311	
	3	0.039	0.311	
In-use solution of Reference standard Melphalan HCl for injection (1.0 mg/mL) in Normal saline	1	0.039	0.311	0.077
	2	0.039	0.311	
	3	0.038	0.303	

Reviewer's Assessment:

The submitted data indicate that the proposed drug product diluted to 0.45 mg/mL, 0.75 mg/mL and 1.0 mg/mL are non-hemolytic (% Haemolysis < 10% as per the submitted criteria (Amin & Dannenfelser et al).

4. Justification on changes (level/add/remove) in excipients.

The Applicant stated that all the excipients except DOTA used in the formulation are listed in the IID database for the intended route of administration and quantities are within the IID.

Table 23: List of excipients and their quantity administered in the proposed drug product in comparison with the LD product (M 1.12.15 (0003), Pg. 35)

Excipients used in Proposed Melphalan Hydrochloride injection		Excipients used in Melphalan Hydrochloride for Injection	
Ingredient	Qty. of excipient administered at drug dose of 16 mg/m² i.e., 28.8 mg (0.4 mg/kg))	Ingredient	Qty. of excipient administered at drug dose of 16 mg/m² (i.e., 28.8 mg (0.4 mg/kg))
Polyethylene glycol 400	(b) (4)	Povidone**	11.52 mg (0.16 mg/kg)
Monothioglycerol	1.6 mg (0.02 mg/kg)	Sodium citrate #	115 mg (1.64 mg/kg)
Propylene glycol	54.4 mg (0.77 mg/kg)	Propylene glycol#	3580 mg (51 mg/kg)
DOTA	0.16 mg (0.002 mg/kg)	Ethanol (96%)#	230 mg (3.28 mg/kg)
Sodium hydroxide	q.s to adjust pH		
Hydrochloric acid	q.s to adjust pH		
Water for Injection	8.64 mg (0.123 mg/kg)	Water for Injection#	1890 mg (27 mg/kg)
Total qty. of excipients for each dose	(b) (4)	Total qty. of excipients for each dose	5826.52 mg (83 mg/kg)

*Indication not on FDA label. The data is used for calculation purposes only.
** Excipient of lyophilized drug product
# Excipients of sterile diluent for Alkeran

Table 24: Quantity of excipients administered for proposed drug product at highest approved dose (M 3.2.P.2 (0003), PDR-022-00, Pg. 38)

Excipient	Quantity per mL	Quantity of excipients administered at highest dose of 180 mg*
Propylene glycol	170 mg	340 mg
Monothioglycerol	5 mg	10 mg
Polyethylene glycol 400	(b) (4)	(b) (4)
DOTA (1,4,7,10 tetraacetic acid 1,4,7,10 tetraazacyclododecane)	0.5 mg	1.0 mg
Water for Injection	(b) (4) mg	(b) (4) mg
Sodium hydroxide	q.s. to adjust pH of (b) (4)	q.s. to adjust pH of (b) (4)
Hydrochloric acid	q.s. to adjust pH of	q.s. to adjust pH of

*Maximum daily dose of Melphalan is 100mg/m² (100 mg x 1.8 m² = 180 mg)

Table 25: Evaluation of excipients used in formulation with respect to IID limit (M 3.2.P.2 (0003), PDR-022-00, Pg. 37)

Ingredients	Concentration of inactive ingredients in the proposed Melphalan Hydrochloride RTD injection		Maximum concentration reported in IID
	Qty /mL	% w/v	
Propylene glycol	170 mg	17	16624 mg (Intravenous Injection)
Monothioglycerol	5 mg	0.5	(b) (4) mg (Intravenous injection)
Polyethylene glycol 400	(b) (4)		(b) (4)
DOTA (1,4,7,10 tetraacetic acid 1,4,7,10 tetraazacyclododecane)	0.5 mg	0.05	Not yet listed in IID database, however it is used in prior approved product DOTAREM Injection (NDA: 204781). The levels of DOTA in Ready to Dilute Melphalan Hydrochloride Injection at highest dose is less than the absolute levels of DOTA in DOTAREM at highest dose.
Water for Injection	(b) (4) mg	(b) (4) %	Not applicable
Sodium hydroxide	q.s. to adjust pH (b) (4)	q.s. to adjust pH of (b) (4)	ADJPH
Hydrochloric acid	q.s. to adjust pH (b) (4)	q.s. to adjust pH of (b) (4)	ADJPH

1 IID is FDA inactive ingredient database. Data base last updated July 18, 2022
1 MDE (Maximum Daily Exposure)

Table 26: Excipients used in FDA prior approved products (M 3.2.P.2 (0003), PDR-022-00, Pg. 40)

S.No	Application #	Product Name	Excipient	Excipient concentration per mL	Max. drug dose as per PIL	Qty. of excipient dosed at max. dose
1	N020954	Busulfex for injection	PEG 400	0.67 mL (b) (4)	56 mg	6.25 g
2	N208194	Bendeka Injection	PEG 400	(b) (4) mg	216 mg	~ 8.64 g
3	N020124	Diazepam injection	Propylene glycol	400 mg	30 mg	2400 mg
4	N019922	Corlopam Injection	Propylene glycol	518 mg	40 mg	2100 mg
5	N009330	Lanoxin injection	Propylene glycol	400 mg	0.5 mg	800 mg
6	N010151	Dilantin injection	Propylene glycol	400 mg	50 mg	400 mg
7	N020207	Alkeran for injection	Propylene glycol	0.6 mL	28.8 mg	3500 mg
8	N204781	Dotarem injection	DOTA	(b) (4) mg	5.276 g (14 mL)	2837.9 mg
9	N208194	Bendeka injection	Monothioglycerol	5 mg	216 mg	43.2 mg
10	022046	Bupivacaine HCl with epinephrine injection	Monothioglycerol	0.001 mL	90 mg	0.018 mL (22.5 mg)

Reviewer's Assessment:

Melphalan is eliminated from plasma primarily by chemical hydrolysis to monohydroxy melphalan and hydroxy melphalan. Aside from these hydrolysis products, no other melphalan metabolites have been observed in humans. Melphalan and its metabolites are excreted by the kidneys. The provided literature information (M 2.5. Clinical Overview and M1.12.5 Request for Waiver of In vivo Bioavailability Studies) indicate the changes (addition/removal/level changes) in excipients (e.g., polyethylene glycol, monothioglycerol and DOTA) are unlikely to impact the elimination and disposition of melphalan from systemic circulation. The safety of the excipient changes (levels) is pending upon the Pharm/Tox review.

BIOPHARMACEUTICS INFORMATION REQUEST date: 2-14-2022:

1) The submitted data show that the pHs of proposed drug product after dilution (<3) are lower than the relied upon Listed Drug product. We have concerns regarding the onset reaction at the site of IV infusion. Provide literature information or data from any other approved products that are administered IV with low pH to justify the low infusion pH (<3).

2) Provide literature information or supporting data to demonstrate that the changes in excipients (povidone, sodium citrate, DOTA, polyethylene glycol 400, propylene glycol, monothioglycerol) at the highest proposed dose will not impact the clearance of melphalan from systemic circulation.

BIOPHARMACEUTICS INFORMATION REQUEST RESPONSE RECEIVED ON 03-07-2023 (M.1.2 (0009))

For detailed repose refer to the link below and electron version of the submission is available in EDR as supporting document number 10
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Reviewer Comment:

The Applicant's response was reviewed in relevant sections of the scientific bridging assessment as adequate and supporting data/justification is included throughout this review document.

Kevin Wei

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CHAPTER VII: MICROBIOLOGY

Product Information	(b) (4) solution for injection
NDA Number	217110
Assessment Cycle Number	1
Drug Product Name/ Strength	Melphalan Hydrochloride Injection / 90 mg/mL
Route of Administration	IV
Applicant Name	Apotex, Inc.
Therapeutic Classification/ OND Division	OOD/DHM2
Manufacturing Site	AqVida GmbH Werkstraße 21 Dassow City, Dassow, Germany 23942
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: This review assesses sterility assurance for the (b) (4) manufacturing process. All deficiencies have been adequately addressed.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD 0003	**10/20/2022**
eCTD 0008	**3/6/2023**
eCTD 0010	**3/30/2023**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: Information Requests were issued by the Agency, dated 2/6/2023 and 3/9/2023. The applicant's responses were received on 3/6/2023 and 3/30/2023 and are addressed in the appropriate sections of this review.

Concise Description of Outstanding Issues: None

Supporting Documents:

- A214809MR01.docx, dated 9/3/2021 (Inadequate)
- A214809MR02.docx, dated 7/13/2022 (Adequate)

S DRUG SUBSTANCE

N/A. Drug substance is supplied non-sterile.

Assessment: *Adequate*

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Sterile, clear colorless to yellow solution.

- **Drug product composition –** The drug product formulation is provided in the table below. The proposed batch size is (b) (4)

Strength (Label Claim)				90 mg/mL (1 mL)		
Component Grade	Quality Standard	Function	%w/w	Quantity (mg) per mL	Exhibit batch Quantity per Batch (kg) (b) (4)	Proposed Commercial Batch Quantity per Batch (kg) (b) (4)
Water for Injection	USP, Ph.Eur	(b) (4)	(b) (4) % w/v	(b) (4) mg		
Propylene Glycol	USP, Ph.Eur		17% w/v	170 mg		
Sodium Hydroxide (b) (4)	USP, Ph.Eur	pH adjuster	NA	q.s. to adjust pH (b) (4)		
Hydrochloric acid (b) (4)	USP, Ph.Eur,	pH adjuster	NA	q.s. to adjust pH (b) (4)		
(b) (4)						
Polyethylene Glycol 400	USP/NF, Ph.Eur	(b) (4)	q.s. to 100%	q.s. to 1 mL		

- **Description of container closure system –**

Primary packing material	Item code
3 mL Amber USP (b) (4) glass vials	(b) (4)
(b) (4)	
(b) (4)	

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Jason God

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Julie Nemecek

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