CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214759Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	214759
Applicant Name	Medac Gesellschaft für klinische Spezialpräparate mbH
Drug Product Name	GRAFAPEX (treosulfan) for injection
Dosage Form.	Powder for reconstitution
Proposed Strength(s)	1 g/vial and 5 g/vial
Route of Administration	Intravenous
Maximum Daily Dose	10 g/m2
Rx/OTC Dispensed	Rx
Proposed Indication	GRAFAPEX is an alkylating drug indicated for use in combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult and pediatric patients >1 year old with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).
Drug Product Description	The drug product, (b) (4) (treosulfan) lyophilized powder for injection, is presented as a (b) (4), white, sterile, lyophilized powder for injection in single use glass vials containing 1000 mg or 5000 mg treosulfan. The drug product is intended to be reconstituted prior to administration in 0.45% or 0.9% NaCl, USP, 5% glucose, or sterile water for Injection, USP to a concentration of 50 mg/mL.
Co-packaged product information	N/A
Device information:	N/A

Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F), USP controlled room temprature conditions.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Kabir Shahjahan	Haripada Sarker
	Drug Product/ Labeling	Olen Stephens	Shalini Anand
	Manufacturing	Jin Lee	James Norman
	Biopharmaceutics	N/A	N/A
	Quality Microbiology	Julie Nemecek	Bryan Riley
	RBPM	Dahlia Walters	
	ATL	Shalini Anand	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: An expiration dating period of **24 months** is granted for the drug product when stored at USP controlled room temprature storage conditions i.e., 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F).

b. Additional Comments for Action: n/a

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4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends ***APPROVAL*** of NDA 214759 for the commercialization of GRAFAPEX (treosulfan) for injection. 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	**-**	**N/A**
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

OPQ Memo Regarding Resubmission

NDA 214759 was resubmitted following a complete response letter through SDN 0070 on April 30, 2024. There were no new changes to Module 3 in this resubmission including no changes to the manufacturing, packaging, and testing facilities. The deficiencies in the most recent NDA resubmission were primarily clinical and nonclinical in nature. This resubmission includes revised labeling, which is reviewed herein. Aside from the labeling review, OPQ will confirm with OPMA that the manufacturing, packaging, and labeling sites remain adequate to support approval of the NDA.

Product Information	Treosulfan powder, for solution for injection
NDA Number	214-759
Assessment Cycle Number	3
Drug Product (DP) Name / Strength	1 g and 5 g per vial
Route of Administration	Intravenous infusion after reconstitution
Drug Product Manufacturer	Oncotec Pharma Produktion GmbH Am Pharmapark 06861 Dessau-Roßlau Germany Contact Person: Dr. Stefan Huth Phone +49 34901 885 7000 Fax +49 34901 885 7871 email contact@oncotec.de FEI: 3009238374 DUNS: 366308617
RLD Information (Brand Name of Product, Applicant)	NA
RLD/RS Number	NA
Proposed Indication	Conditioning treatment prior to allogenic hematopoietic stem cell transplantation in adult patients with acute myeloid leukemia and melodysplastic syndromes
Cross Referenced Applications	(b) (4) DMF (b) (4) for Treosulfan drug substance

	IND 54,552

Assessment Recommendation: *Adequate*

Assessment Summary: **The drug product is a (b) (4), lyophilized powder of treosulfan with no excipients available in two presentations of 1 g and 5 g per vial. The drug product is intended to be reconstituted prior to administration in 0.45% or 0.9% NaCl, USP, 5% glucose, or Water for Injection, USP to a concentration of 50 mg/mL. The primary risks for this product are (b) (4). Specified impurities are controlled (b) (4) as per ICH Q3B (R2) (b) (4) and justified by the indication of use for the product. (b) (4). (b) (4) The limits are expanded to no more than (b) (4)% for these two (b) (4). Because of the high dose for this product, there is no recommended permitted daily exposure as per ICH Q3B (R2). The nonclinical and clinical pharmacology reviewers were consulted to confirm that the initial exposure of the two (b) (4)% does not represent a safety risk. Internal communications (email 2/24/2021) confirmed this limit is acceptable. Degradation also results (b) (4). This trend is evident in the in-use stability data, but the applicant notes that there have been no incidence of (b) (4) at the proposed dose and pH range. Through 24-hours of in-use testing, pH remains (b) (4), consistent with the drug product release/stability specifications.**

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #1	Comments
Sterility	High	Refer to microbiology review		

Endotoxin	High	Refer to microbiology review		
Assay	Low	(b) (4) lyophilized cake with high content	Low	
Physical stability	Low	Crystalline; reconstitution time provides adequate control	Low	
Uniformity of Dose	Low	(b) (4) lyophilized cake with high content	Low	
pH	Medium	Change in pH indicates degradation	Medium	Notable pH change is noted during in-use period beyond (b) (4) days, but not within the 24-hour in-use period.
Moisture content	Low	Supported by stability data	Low	
Cake Appearance	Low	Supported by stability data	Low	

List Submissions being assessment (table):

Document(s) Assessed	Date Received
0070	**4/30/2024**

Highlight Key Issues from Last Cycle and Their Resolution: NDA 214759 was recommended for approval from OPQ in the last review cycle and there are no new CMC issues that would prevent approval.

Concise Description of Outstanding Issues (List Bullet Points with Key Information and Update as Needed): None

Primary Drug Product Assessor Name and Date: Olen Stephens 9/5/2024

Secondary Assessor Name and Date: Shalini Anand 9/5/2024

Olen Stephens

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Shalini Anand

Digitally signed by Shalini Anand
Date: 9/05/2024 09:18:34AM
GUID: 52795e43000905f07ea0803d93709d84

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Product label negotiation is on-going at the time of this review. Several edits are being coordinated with DMEPA through the clinical RPM and are highlighted below. During the first review cycle, some edits were sent to the applicant. Those changes as well as some changes initiated by the applicant are captured here.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Grafapex	Adequate
Established name(s)	Treosulfan	Adequate
Route(s) of administration	For injection, for intravenous use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	1 g/vial 5 g/vial	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
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.	Single-dose	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
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)	Treosulfan for injection is dissolved with 0.45% or 0.9% Sodium Chloride or 5% Glucose Injection or Water for Injection, USP with shaking. The solution can be warmed (b) (4) to improve solubility. The reconstituted solution can be administered from glass vials, (b) (4) bags. a 24 h in-use period when stored at 20-25 ºC.	Adequate; minor edits to formatting suggested by DMEPA

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Lyophilized powder for injection	Adequate
Strength(s) in metric system	1 or 5 g	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	NA	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	White, sterile powder	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single dose	Adequate

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Grafapex (treosulfan)	Adequate
Dosage form(s) and route(s) of administration	Powder for injection	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	None	
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.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Statement of being sterile (if applicable)	Present	Adequate
Pharmacological/ therapeutic class	Alkylating agent	Adequate
Chemical name, structural formula, molecular weight	Present; Order of the section was adjusted to first describe the drug substance and then the drug product. Minor editorial changes for clarity.	Adequate
If radioactive, statement of important nuclear characteristics.	NA	

Other important chemical or physical properties (such as pKa or pH)	Solubility and hygroscopicity properties included; statements about [redacted] (b) (4) were removed	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Lyophilized powder for Injection	Adequate
Strength(s) in metric system	1 g and 5 g	Adequate
Available units (e.g., bottles of 100 tablets)	1 vial per carton	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	White powder with space reserved for NDC numbers	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
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.	Single dose	Adequate

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

Item	Information Provided in the NDA	Assessor's Comments
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.)	Grafapex is a cytotoxic drug, which requires a reference to OSHA handling in section 15.	Requires reference in Section 15: "OSHA Hazardous Drugs." *OSHA*. http://www.osha.gov/SLTC/hazardousdrugs/index.html
If the product contains a desiccant, ensure the size	NA	

and shape differ from the dosage form and desiccant has a warning such as "Do not eat."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	The applicant resubmitted this label to state (b) (4) [redacted].	Inadequate; (b) (4) [redacted] They are instructed to add storage conditions such as, "Store at room temperature (25°C/77°F). (Excursions permitted between 15°C and 30°C)."
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."	NA	
Include information about child-resistant packaging	NA	

1.2.5 Other Sections of Labeling: None

1.2.6 Manufacturing Information After Section 17 (for drug products)

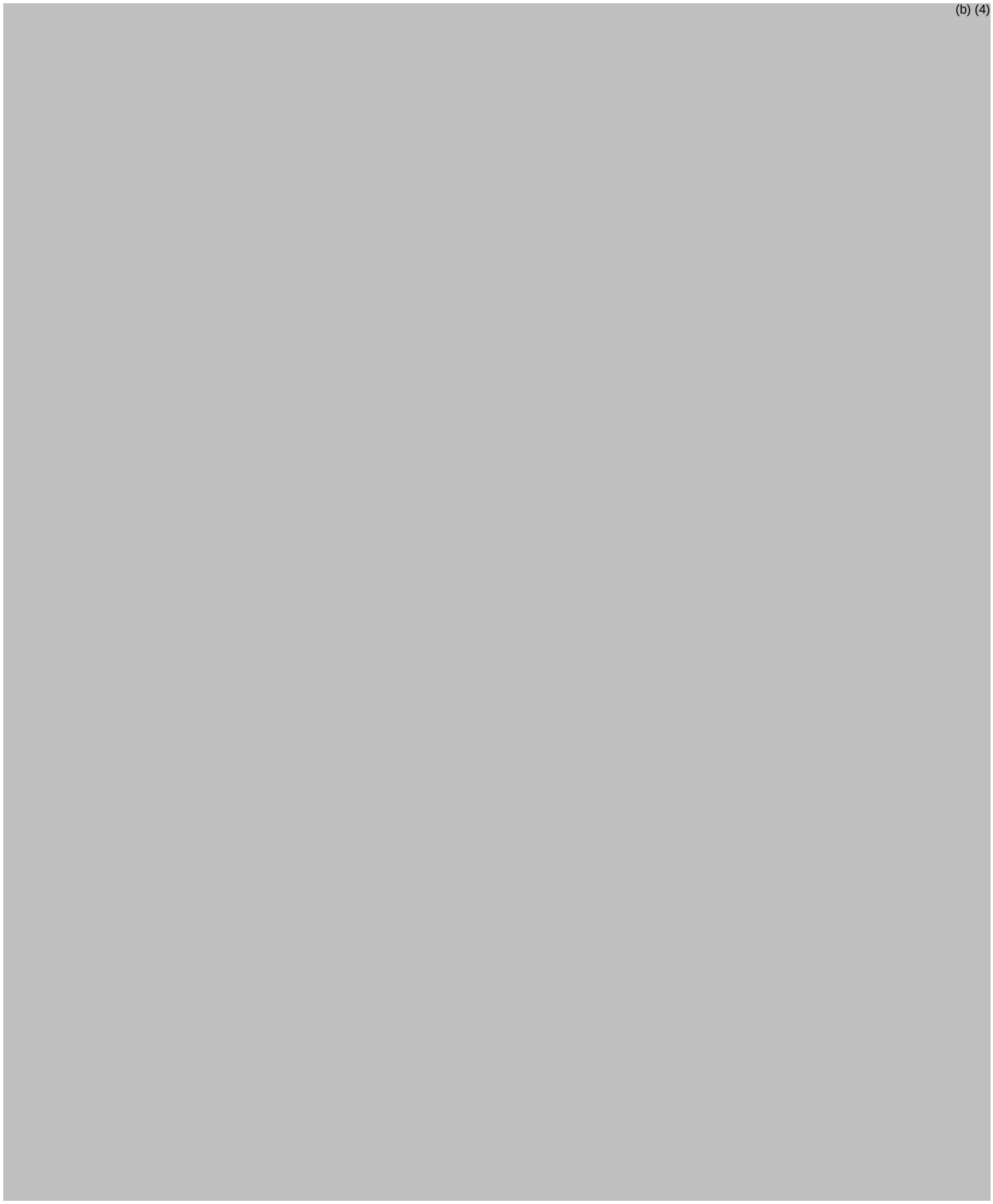
Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Medac GmbH Theaterstr. 6 22880 Wedel Germany	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Several edits were required for the product label. These edits were be coordinated with DMEPA through the clinical RPM during on-going label negotiations.

3.0 CARTON AND CONTAINER LABELING

(b) (4)



Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	GRAFAPEX® (treosulfan) (b) (4) for injection	Appropriate font size and prominence. Dose strength may need to be moved.
Dosage strength	1 g and 5 g per vial	Adequate
Route of administration	Intravenous injection	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	
Net contents	1 g per vial and 5 g per vial	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	Space reserved for NDC	Adequate
Lot number and expiration date	Space designated on labels	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4) . For the carton container, excursion statements need to be added.	Defer to DMEPA regarding space constraints and medication error for information on the product vial.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	'single-dose vial'	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	

Bar code	Present	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Present	Adequate
Medication Guide (if applicable)	NA	
No text on Ferrule and Cap overseal	Complies	Adequate
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.	NA	
And others, if space is available	(b) (4); in-use storage conditions	Adequate

Assessment of Carton and Container Labeling: All comments resolved during labeling negotiations.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Labeling negotiations are being negotiated with the applicant. The edits noted above are currently being discussed with the clinical division and DMEPA. Comments were prepared for the applicant and final label approval will occur after this review is finalized.

Primary Labeling Assessor Name and Date: Olen Stephens 8/9/2024

Secondary Assessor Name and Date: David Claffey, 8/9/2024

Olen Stephens

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David Claffey

Digitally signed by David Claffey
Date: 8/09/2024 01:42:06PM
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/s/

SHALINI ANAND
10/29/2024 06:32:57 PM

Recommendation: APPROVAL

NDA 214759
Review #1

Drug Name/Dosage Form	Treosulfan powder, for solution for injection
Strength	1000 mg/ vial and 5000 mg/vial
Route of Administration	IV
Rx/OTC Dispensed	Rx
Indication	Indicated as conditioning treatment prior to allogenic hematopoietic stem cell transplantation in adult patients with acute myeloid leukemia and myelodysplastic syndromes
Applicant	medac Gesellschaft für klinische Spezialpräparate mbH
US agent, if applicable	Frank Schmidberger

SUBMISSION(S) REVIEWED	*DOCUMENT DATE*	*DISCIPLINE(S) AFFECTED*
Original Submission	*8/11/2020*	*All*
Amendment	*8/18/2020*	*Micro,*
Amendment	*9/16/2020*	*Micro*
Amendment	*10/8/2020*	*DP, micro, process/facilities*
Amendment	*10/13/2020*	*micro*
Amendment	*12/7/2020*	*micro*
Amendment	*1/12/2021*	*micro*
Amendment	*1/21/2021*	*DP, micro, process/facilities*
Amendment	*1/28/2021*	*DP*
Amendment	*2/8/2021*	*micro*
Amendment	*2/12/2021*	*DP*
Amendment	*2/26/2021*	*micro*
Amendment	*3/5/2021*	*process/facilities*
Amendment	*3/17/2021*	*process/facilities*
Amendment	*3/19/2021*	*process/facilities*

Quality Review Team

DISCIPLINE	*PRIMARY REVIEWER*	*SECONDARY REVIEWER*
Drug Substance	*Kabir Shahjahan*	*Paresma Patel*
Drug Product	*Olen Stephens*	*Anamitro Banerjee*
Process and Facility	*Jin Lee*	*Ying Zhang*
Microbiology	*Elizabeth Bearr*	*Gouri Chattopadhyay*
Biopharmaceutics	*n/a*	*n/a*
Regulatory Business Process Manager	*Rabiya Haider*	*n/a*
Application Technical Lead	*Sherita McLamore*	*n/a*
Environmental	*Olen Stephen*	*Anamitro Banerjee*

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type II			N/A	04/05/2021	Reviewed in conjunction with NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	54,552	Drug substance development

2. CONSULTS

N/A

Executive Summary

1. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 214759 for (b) (4)® (treosulfan) powder, for solution for injection, 1 g and 5 g per vial. As part of this action, OPQ recommends 24-month expiration period for the drug product when stored at room temperature (25°C/77°F). There are no outstanding issues and no post-approval product quality agreements to be conveyed to the applicant.

2. Summary of Quality Assessments

1. Product Overview

NDA 214759 was submitted for (b) (4)® 1000 mg and5000 mg powder for solution for infusion in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Treosulfan is a pro-drug of a bifunctional alkylating agent with cytotoxic activity to hematopoietic stem cells. Treosulfan kills cells, especially cells that develop rapidly, such as bone marrow cells, by attaching to their DNA while they are dividing. Treosulfan is currently approved in several European countries. It is a new molecular entity (NME) that was granted Orphan Designation (April 2015) and is indicated as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).

Treosulfan is a small chiral molecule that is produced as a single enantiomer by (b) (4) of Finland. Treosulfan contains two stereogenic centers giving rise to four possible stereoisomers. Treosulfan acts as pro-drug and is converted non-enzymically in a physiological environment to an alkylating monoepoxide and diepoxide upon release of methanesulfonic acid. The drug product, (b) (4) (treosulfan) lyophilized powder for injection, is supplied as a (b) (4), white, sterile, lyophilized powder for injection in single use glass vials containing 1g (1000 mg) or 5g (5000 mg) of the active. Both the 1g and 5g vials are designed to be diluted with sodium chloride (0.45% or 0.9%), 5% glucose injection or water for injection and administered as 2-hour intravenous infusion. The resulting infusate is a clear, colorless, sterile 50 mg/mL solution.

The recommended dosage of treosulfan is 10 g/m² body surface area (BSA) per day as a two-hour intravenous infusion given on 3 consecutive days before hematopoietic stem cell infusion.

Based on the information provided in this application (original submission and amendments in responses to information requests), OPQ considers all review issues to be adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 214759 and a **24**-month expiration period for the drug product may be granted when (b) (4) stored under controlled room temperature.

Proposed Indication(s) including Intended Patient Population	Indicated as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).
Duration of Treatment	Treatment may continue until disease progression or until unacceptable toxicity occurs.
Maximum Daily Dose	10 g/m² body surface area
Alternative Methods of Administration	None

2. Quality Assessment Overview

Drug Substance

The drug substance, Treosulfan, is a small, chiral molecule that is produced as an enantiomerically pure, white, non-hygroscopic, crystalline solid with a melting range of 101.5°C to 105.0°C. Treosulfan contains two stereogenic centers giving rise to four possible stereoisomers. It acts as a pro-drug and is converted non-enzymically in a physiological environment to alkylating monoepoxide and diepoxide upon release of methanesulfonic acid. Treosulfan exhibits polymorphic behavior and two forms ((b) (4) , the OPMA reviewer confirmed that (b) (4) is noted in the executed batch records and process failures were not anticipated due to similarity in solubility of the two forms.

Treosulfan drug substance was originally investigated under IND 54,552 and is manufactured and release tested by (b) (4) of Finland. The applicant references DMF (b) (4) for the manufacture and control of the drug substance; accordingly, limited information was included in the NDA. DMF (b) (4) was reviewed in conjunction with this NDA. Based on the information in the referenced DMF, a (b) (4) month retest period has been established for the drug substance and NDA 214759 is recommended for approval from a drug substance perspective.

Drug Product and Drug Process

The drug product, (b) (4) (treosulfan) lyophilized powder for injection, is presented as a (b) (4), white, sterile, lyophilized powder for injection in single use glass vials containing 1000 mg or 5000 mg treosulfan. The drug product is intended to be reconstituted prior to administration in 0.45% or 0.9% NaCl, USP, 5% glucose, or Water for Injection, USP to a concentration of 50 mg/mL.

The drug product is manufactured by Oncotec Pharama Production GmbH of Germany at a commercial batch size of (b) (4) Kg ((b) (4) vials) for the 1000 mg presentation and (b) (4) Kg ((b) (4) vials) for the 5,000 mg presentation. The drug product manufacturing process includes (b) (4)

(b) (4)

The applicant demonstrated the suitability and robustness of the manufacturing process for the drug product at the proposed commercial scale. The description of the manufacturing process includes appropriate in-process controls and operating parameters and is described in sufficient detail to support the approval of this NDA.

The drug product specification included controls for all critical quality attributes for lyophilized powder for injection and comply with compendial standards: appearance, identification, assay, control of related substances, water content, residual solvent, content uniformity, particulate matter per USP<788> and USP<790>, sterility, bacterial endotoxins USP<85>, crystalline content, container closure integrity test, and test for reconstituted solution. The applicant included a risk assessment consistent with ICH Q3D. Accordingly, elemental impurities were not monitored in the drug product specification. Specified impurities are controlled (b) (4) in accordance with ICH Q3B (R2) (b) (4) and justified by the indication of use for the product.

The drug product specifications are consistent with ICH Q6A recommendations and are based on batch analyses and stability data. The drug product specifications are adequate to establish the drug product identity, potency, and purity, and provide adequate controls to ensure the quality of the drug product throughout the product expiry. The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

The drug product is packaged in a colorless glass vials closed with rubber stoppers and aluminum seals including a flip-off cap which does not contact the drug product.

The applicant proposed a 24-month shelf life and a 24-hour in-use period for the drug product and provided data for both the commercial lyophilized powder and the reconstituted solution of treosulfan (of note, a (b) (4) in-use period was originally proposed, but the applicant was told to (b) (4) the in-use period to 24 hours, consistent with US pharmacy practices). In support of the 24-month expiry, the applicant provided 12-months of long term (25°C/60%RH) and 6 months accelerated (40°C/ 75%RH) packaged in the commercial container closure system and stored in the inverted orientation and (b) (4) of in-use stability data for the drug product reconstituted with WFI and 0.45% NaCl (no data for glucose).

The applicant requested a 24-month expiry for the drug product when stored under controlled room temperature (25°C/60%RH) and a 24 hour in-use period. With the exception of the pH for the reconstituted solution, the stability data showed consistency

over time and supports the proposed expiry. The product reviewer noted (b) (4) . This trend was evident in the in-use stability data, but the Applicant indicates that no evidence of (b) (4) was observed at the proposed dose and pH range. The Applicant proposed that the shelf-life began (b) (4) . This is proposal is acceptable as it is consistent with agency's current practice and expectations. As the proposed in-use period exceeds the agency's current practice and expectations for a reconstituted product (i.e. 24 hours under refrigerated conditions and 4 hours at room temperature), the microbiology team was consulted regarding the proposed in-use period.

Therefore, based on the available stability data provided, the applicant proposed, and the OPQ accepts the expiration dating period of **24-months** for the drug product when stored at stored under controlled room temperature. In addition, the agency accepts the proposed **24 hour in-use period** for the reconstituted drug product when stored room temperature as this proposal was deemed acceptable by the micro team.

NDA 214759 is recommended for approval from a drug product and drug process perspective with an assigned drug product expiry of 24-months.

LIFE-CYCLE CONSIDERATIONS as noted by Product Reviewer:
In-use stability data of the reconstituted drug product to 20 mg/mL is included in this report, but since the product label does not direct dilution to this concentration, the results are of little relevance other than demonstrating container compatibility. The pH of the more dilute solutions are not impacted compared to the 50 mg/mL solutions, as would be expected. At the end of the (b) (4) in-use study, the (b) (4) specification is exceeded (typically (b) (4) %) at this lower concentration. Because the product will not be labeled to be reconstituted to 20 mg/mL or have a (b) (4) in-use period, this out of specification (OOS) result will not be raised as a deficiency, but future labeling review should not allow the lower concentration or longer in-use periods without justification.

Quality Microbiology
The microbiology review focused on the validation studies support the sterilization of (b) (4) . The drug product is a sterile lyophilized powder. Sterilization is achieved via (b) (4) . The final product is tested for sterility and bacterial endotoxins. The Applicant has provided an adequate description of the overall manufacturing process to assure the microbiological quality of the subject drug product.

The validation information supporting the (b) (4) manufacturing demonstrates that the sterilization processes are controlled and are suitable for (b) (4) at the drug

product manufacturing facilities. Accordingly, this application is recommended for approval from a quality microbiology perspective.

Facilities: NDA 214759 included 5 sites:

- (b) (4)
- **Oncotec Pharma Produktion GmbH (FEI 3009238374)**– Drug Product manufacture, (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

All facilities listed in NDA 214759 were deemed acceptable for the responsibilities listed in the application. Accordingly, NDA 214759 is recommended for approval from a compliance perspective.

Environmental Assessment

The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(b). The categorical exclusion cited is appropriate based on the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is therefore acceptable and granted.

3. Special Product Quality Labeling Recommendations (NDA only)

n/a

4. **Final Risk Assessment (see Attachment)**

Included in Drug Product review. Of note, all risks were adequately mitigated with the exception of the control of pH which remains a medium risk.

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Product label negotiation is on-going at the time of this review. Several edits are being coordinated with DMEPA through the clinical RPM and are highlighted below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Grafapex	Adequate
Established name(s)	Treosulfan	Adequate
Route(s) of administration	Intravenous	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	1,000 mg/vial 5,000 mg/vial	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
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.	Single-use	Changed to 'single-dose vial' for clarity and consistency with current labeling practices

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
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)	Treosulfan for injection is dissolved with 0.45% or 0.9% Sodium Chloride, USP or 5% Glucose Injection, USP or Water for Injection, USP with shaking. The solution can be warmed (b) (4) to improve solubility. The reconstituted solution can be administered from glass vials, (b) (4) bags	Adequate; revised to a 24 h in-use period.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Lyophilized powder for injection	Adequate
Strength(s) in metric system	1000 or 5000 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	NA	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	White, sterile powder	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single use	Changed to 'single-dose vial' for clarity and consistency with current labeling practices

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Grafapex (treosulfan)	Adequate; changed after approval from OSE
Dosage form(s) and route(s) of administration	Powder for injection	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	None	
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.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Statement of being sterile (if applicable)	Present	Adequate
Pharmacological/ therapeutic class	Alkylating agent	Adequate
Chemical name, structural formula, molecular weight	Present	Adequate
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa or pH)	No chemical or physical properties discussed	Applicant was be instructed to include "Treosulfan is soluble in water (7% m/v) at 25^{o}C. Treosulfan is not hygroscopic"

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Lyophilized powder for Injection	Adequate
Strength(s) in metric system	1000 mg and 5000 mg	Adequate
Available units (e.g., bottles of 100 tablets)	1 vial per carton	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	White powder with space reserved for NDC numbers	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
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.	Single use	Changed the term 'single-use' to 'single-dose vial'

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

Item	Information Provided in the NDA	Assessor's Comments
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.)	Grafapex is a cytotoxic drug, which requires a reference to OSHA handling in section 15.	Requires reference in Section 15: "OSHA Hazardous Drugs." *OSHA*. http://www.osha.gov/SLTC/hazardousdrugs/index.html
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	NA	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at room temperature (25°C/77°F)	Adequate
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."	NA	
Include information about child-resistant packaging	NA	

1.2.5 Other Sections of Labeling: None

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Medac GmbH Theaterstr. 6 22880 Wedel Germany	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Several edits were required for the product label. These edits were be coordinated with DMEPA through the clinical RPM during on-going label negotiations.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	GRAFAPEX® (treosulfan) (b) (4) for injection	Appropriate font size and prominence. Dose strength may need to be moved.
Dosage strength	1 g and 5 g; 1000 mg per vial and 5000 mg per vial	Difference in units may cause confusion. Defer to DMEPA
Route of administration	Intravenous injection	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	
Net contents (e.g. tablet count)	1000 mg per vial and 5000 mg per vial	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	Space reserved for NDC	Adequate
Lot number and expiration date	Space designated on labels	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4)	Defer to DMEPA regarding space constraints and medication error
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Not present	Applicant revised label to state 'single-dose vial'
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Bar code	Present	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Present	Adequate
Medication Guide (if applicable)	NA	
No text on Ferrule and Cap overseal	Complies	Adequate
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.	NA	
And others, if space is available	None	Applicant instructed to add the descriptor 'sterile' to refer to the drug product on the container and carton label.

Assessment of Carton and Container Labeling: All comments resolved during labeling negotiations.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Labeling negotiations were completed with the applicant. The edits noted above have been discussed with the clinical division and DMEPA. Comments

were prepared for the applicant and final label approval will occur after this review is finalized.

Primary Labeling Assessor Name and Date: Olen Stephens 3/19/2021

Secondary Assessor Name and Date: Anamitro Banerjee, 3/29/2021

Olen Stephens

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Anamitro Banerjee

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	**214759**
Assessment Cycle Number	01
Drug Product Name/ Strength	(b) (4) (Treosulfan), 1000 mg/5000 mg powder for solution for infusion (Orphan Drug)
Route of Administration	Infusion
Applicant Name	medac Gesellschaft für klinische Spezialpräparate mbH
Therapeutic Classification/ OND Division	Type 1-New Molecular Entity/ CDER/OND/OOD/DHM1
Manufacturing Site	Oncotec Pharma Produktion GmbH, Dessau-Roßlau, Germany
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary: The submission is **recommended** for approval based on sterility assurance.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original NDA Submission (SEQ 0001)	08/11/2020
Stability Data (SEQ 0003)	08/18/2020
Quality Information (SEQ 0006)	09/16/2020
Response to an FDA CMC Request for Information (RFI)	10/08/2020
Quality Response to Information Request (Microbiology)	10/13/2020
Quality Response to Information Request (Microbiology)	12/07/2020
Quality Response to Information Request (Microbiology)	01/12/2021
Quality Response to Information request (CMC)	01/21/2021
Quality Response to Information Request (Microbiology)	02/08/2021
Quality Response to Information request (CMC)	02/12/2021
Quality Response to Information Request (Microbiology)	02/26/2021

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

Remarks: The drug product is a single-dose sterile dry powder without preservatives. The drug product is (b) (4) **A microbiology Early IR letter was issued on 09/30/2020 and response received on 10/13/2020. The response to the Microbiology IRs issued 12/21/2020 was received on 01/12/2021. Stability section is updated**

from information provided in the response to the CMC IR dated 1/21/2021. The information provided in the quality amendment dated 2/8/2021 and dated 2/26/2021 have been added to the respective sections below.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

Supporting Documents:

- (b) (4)

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(3.2. P.2.1. Description and Composition of the Drug Product)

- **Description of drug product –** The drug product, (b) (4) or Treosulfan, is a white crystalline powder in a colorless glass single-dose vial with a rubber stopper and aluminum cap; the drug product is manufactured by (b) (4). The bulk solution pH is (b) (4). Treosulfan is administered by intravenous infusion after reconstitution. The reconstituted solution contains 50 mg Treosulfan/1 ml and appears as a clear colorless solution. Treosulfan is an alkylating prodrug indicated as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation in adult patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).
- **Drug product composition** –

Ingredient	Amount per Vial		Function	Reference
	1,000 mg presentation	5,000 mg presentation		
Treosulfan	1000 mg	5000 mg	API	DMF (Current Version)

The solvent water is removed during the manufacturing process and thus not a part of the drug product. (b) (4)

- **Description of container closure system for 1000mg and 5000 mg presentations** (0001 & 0006/ 3.2.P.2.5. Microbiological Attribute/ Qualification of Primary Packaging/*pharmaceutical-development.pdf*, Page: 148/222;

Component		Description
Vial	1000 mg	30 (b) (4) colorless (b) (4) 20 mm clear (b) (4), glass injection vials
	5000 mg	100 colorless (b) (4) 20 mm clear (b) (4), glass injection vials
Stopper		Injection stopper ((b) (4), 20 mm (b) (4) stopper, (b) (4)
Aluminum Seal		Crimp caps, 20 mm, combined, protruding, center tear-off, blue, without flip off print, Aluminum Cap (bottom part)/ Plastic-disc (upper part)

(b) (4)

Reviewer's Assessment: **Adequate**

The applicant provided an adequate description of the drug product composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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MICROBIOLOGY LIST OF DEFICIENCIES – None

The following deficiencies are considered: ☐ Major ☐ Minor

Primary Microbiology Assessor Name and Date: Gouri Chattopadhyay, Ph.D., 02/28/2021
Secondary Assessor Name and Date: Elizabeth Bearr, Ph.D., 02/28/2021

Gouri Chattopadhyay

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Elizabeth Bearr

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/s/

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