CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214759Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	January 14, 2025
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 214759
Product Name, Dosage Form, and Strength:	Grafapex (treosulfan) for Injection, 1 gram/vial and 5 gram/vial
Applicant Name:	Medac Gesellschaft für klinische Spezialpräparate mbH
FDA Received Date:	January 13, 2025
TTT ID #:	2022-814-2
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Medac Gesellschaft für klinische Spezialpräparate mbH submitted revised container labels and carton labeling received on January 13, 2025 for Grafapex. We reviewed the revised container labels and carton labeling for Grafapex (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Medac Gesellschaft für klinische Spezialpräparate mbH implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Kundreskas, J. Review of Revised Label and Labeling for Grafapex (NDA 214759). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 DEC 23. TTT ID: 2022-814-1.

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/s/

JODY K KUNDRESKAS
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NICOLE F IVERSON
01/14/2025 11:18:27 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 23, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 214759
Product Name, Dosage Form, and Strength:	Grafapex (treosulfan) for Injection, 1 gram/vial and 5 gram/vial
Applicant Name:	Medac Gesellschaft für klinische Spezialpräparate mbH
FDA Received Date:	October 1, 2024 and December 6, 2024
TTT ID #:	2022-814-1
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Medac Gesellschaft für klinische Spezialpräparate mbH submitted revised container labels and carton labeling received on October 1, 2024 for Grafapex. We reviewed the revised container labels and carton labeling for Grafapex (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The container labels and carton labeling are unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error, below.

3 RECOMMENDATIONS FOR MEDAC GESELLSCHAFT FÜR KLINISCHE SPEZIALPRÄPARATE MBH

A. General Comments (Container Labels and Carton Labeling)

1. The word (b) (4) is not required on the container labels and carton labeling and its presence clutters the Principal Display Panel (PDP), reducing readability of important information. We recommend removing the word (b) (4) to improve readability of the container labels and carton labeling.

B. Container Labels

1. The route of administration statement lacks prominence. The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP. We recommend ensuring there is adequate white space between the route of administration statement and the statement "WARNING: Hazardous Drug" to improve prominence of the route of administration statement.
2. As currently presented, YYYYMMM, the expiration date format does not follow recently revised USP General Chapter <7> formatting guidelines. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend revising the expiration date format you intend to use. USP <7> requires the year, in YYYY format, to be listed at the beginning of the expiration date. When all-numeric dates are used, they must be formatted using the year, the month, and, if applicable, the day, separated by hyphens or forward slashes in one of the following formats: YYYY-MM-DD or YYYY-MM. When alphanumeric dates are used, months must be displayed using at least three letters in one of the following formats: YYYY-MMM-DD or YYYY-MMM. Revise your expiration

[a] Kundreskas, J. Label and Labeling Review for Grafapex (NDA 214759). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 APR 30. TTT ID: 2022-814.

date to contain hyphens or forward slashes separating the year and month to comply with USP <7> formatting guidelines.

C. Carton Labeling

1. As currently presented in the post-reconstitution stability section, the finished dosage form is listed as “for injection”. Per USP General Chapter <1121> Nomenclature, and to ensure consistency throughout the label, the dosage form should be “for Injection”. Revise the dosage form to “for Injection”.

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JODY K KUNDRESKAS
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NICOLE F IVERSON
12/23/2024 12:56:32 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 23, 2024

To: Bradley McKenzie, Regulatory Project Manager
Division of Hematologic Malignancies I (DHM1)

From: Melissa Khashei, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, Team Leader, OPDP

Samia Alam, Regulatory Review Officer, OPDP

Subject: OPDP Labeling Comments for GRAFAPEX (treosulfan) for injection, for intravenous use

NDA: 214759

Background:

In response to DHM1's consult request dated May 1, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for GRAFAPEX (treosulfan) for injection, for intravenous use.

PI:

OPDP's review of the proposed PI is based on the draft labeling accessed from Sharepoint on December 20, 2024, and our comments are provided below.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on December 11, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Meliss Khashei at (301)796-7818 or Melissa.Khashei@fda.hhs.gov.

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/s/

MELISSA KHASHEI
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	August 14, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 214759
Product Name, Dosage Form, and Strength:	Grafapex (treosulfan) for Injection, 1 gram/vial and 5 gram/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Medac Gesellschaft für klinische Spezialpräparate mbH
FDA Received Date:	April 30, 2024
TTT ID #:	2022-814
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 INTRODUCTION

As part of the approval process for Grafapex (treosulfan) for Injection, we reviewed the proposed Grafapex Prescribing Information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Medac Gesellschaft für klinische Spezialpräparate mbH previously submitted NDA 214759 on August 11, 2020. We completed a label and labeling review at that time.[a] The application received a Complete Response (CR) letter on July 30, 2021 due to issues with the clinical and statistical submissions.[b] Our recommendations were communicated to the Applicant on February 19, 2021. The Applicant provided revised container labels and carton labeling on April 8, 2021 and June 14, 2021 and we completed two label and labeling review memos.[c,d]

Medac Gesellschaft für klinische Spezialpräparate mbH submitted a response to the CR letter on April 21, 2022, which received an Acknowledge Incomplete Response letter on May 16, 2022 due to not providing substantial evidence of effectiveness.[e]

Medac Gesellschaft für klinische Spezialpräparate mbH submitted a response to the CR letter on August 10, 2022, which received an Acknowledge Incomplete Response letter on September 15, 2022 due to not providing substantial evidence of effectiveness.[f]

Thus, Medac Gesellschaft für klinische Spezialpräparate mbH submitted a response to the incomplete CR letter as a Class 2 Resubmission on April 30, 2024.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 214759.

Table 1. Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

[a] Iverson, N. Label and Labeling Review for Grafapex (NDA 214759). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 19. OSE RCM No.: 2020-1687.
[b] Kolibab, K. Complete Response for NDA 214759. Silver Spring (MD): FDA, CDER, OND, Division of Hematologic Malignancies 1 (DHM 1) (US); 2021 JUL 30.
[c] Iverson, N. Review of Revised Label and Labeling Memorandum for Grafapex (NDA 214759). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 20. OSE RCM No.: 2020-1687-1.
[d] Iverson, N. Review of Revised Label and Labeling Memorandum for Grafapex (NDA 214759). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 22. OSE RCM No.: 2020-1687-2.
[e] Baird, A. Acknowledge Incomplete Response for NDA 214759. Silver Spring (MD): FDA, CDER, OND, Division of Hematologic Malignancies 1 (DHM 1) (US); 2022 MAY 16.
[f] McKenzie, B. Acknowledge Incomplete Response for NDA 214759. Silver Spring (MD): FDA, CDER, OND, Division of Hematologic Malignancies 1 (DHM 1) (US); 2022 SEP 15.

3 CONCLUSION

The proposed Grafapex Prescribing Information (PI), container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Hematologic Malignancies 1 (DHM 1) in Section 4 and for Medac Gesellschaft für klinische Spezialpräparate mbH in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Prescribing Information

1. Section 2 Dosage and Administration
    a. Throughout Section 2.1, *Recommended Dosage,* the route of administration is described as "intravenously", which does not specify how to administer the product intravenously (e.g., intravenous infusion or bolus). This lack of information may lead to wrong technique drug administration errors. We recommend revising the route "intravenously" to "intravenous infusion" to minimize the risk of the product being administered as an intravenous bolus.
    b. In Section 2.2, *Preparation and Administration Instructions*, the instruction to prepare the product using aseptic technique is missing. Failure to provide this instruction may result in preparation medication errors. We recommend adding a bullet in the first position that states "Use aseptic technique to prepare GRAFAPEX.".
    c. As currently presented in Section 2.2, *Preparation and Administration Instructions*, the abbreviations "EVA" and "PO" are used, without being defined. Using abbreviations that are not defined may lead to confusion as to their meaning. We recommend defining these abbreviations and providing the abbreviation in parenthesis.
    d. In Section 2.2, *Preparation and Administration Instructions,* the warning about reconstituting with Sterile Water for Injection in children less than or equal to 12 years of age is not located near the reconstitution instructions. Separating these instructions may result in this warning being overlooked. We recommend relocating this warning to be part of the content of the bullet regarding reconstitution instructions.
    e. In Section 2.2, *Preparation and Administration Instructions,* the instructions regarding inspection of the reconstituted solution are not located near the reconstitution instructions. Separating these instructions may result in this instruction being overlooked. We recommend relocating these instructions to be underneath the bullet "Shake the vial(s) to dissolve.". Additionally, the concentration of the reconstitution statement is duplicative, and should be removed. Revise to "Inspect the reconstituted solution for discoloration and particulate matter. The

reconstituted solution appears as a clear colorless solution. Solutions showing any sign of precipitation should not be used.".

f. In Section 2.2, *Preparation and Administration Instructions,* the bullet regarding solubility issues is not located near the reconstitution and inspection instructions. Separating these instructions may result in this instruction being overlooked. We recommend relocating this bullet to underneath the inspection instructions bullet.

g. In Section 2.2, *Preparation and Administration Instructions,* the instruction to discard the unused portion of the single-dose vials is missing. Inclusion of this discard statement helps minimize the risk of the entire contents of the vial being given as a single dose. We recommend adding the statement "Discard any unused portion left in the vial(s)." to the end of the bullet that starts with "Determine the volume of 0.05 g/mL reconstituted solution needed…".

h. In Section 2.2, *Preparation and Administration Instructions,* the unit of measure is missing from some of the temperature references. Unclear storage information may lead to confusion and potential risk of deteriorated drug medication errors. We recommend adding the unit of measure after each numerical degree. Revise "If not used immediately store reconstituted GRAFAPEX solution at room temperature 20° to 25°C (68° to 77°F) for up to 24 hours." to "If not used immediately store reconstituted GRAFAPEX solution at room temperature 20°C to 25°C (68°F to 77°F) for up to 24 hours.".

2. Section 16 How Supplied/Storage and Handling

a. As currently presented, the <u>How Supplied</u> Section lacks clarity. Lack of clarity may contribute to important information being overlooked. We recommend presenting the section as follows:

<u>How Supplied</u>

GRAFAPEX is a white, sterile, lyophilized powder for reconstitution. It is supplied in a carton containing one single-dose vial.

<u>Presentation</u>	<u>NDC</u>
1 g/vial	xxxxx-xxx-xx
5 g/vial	xxxxx-xxx-xx

b. The specific storage conditions are missing from the <u>Storage and Handling</u> Section. The special handling and storage conditions are required 21 CFR 201.57(c)(17). Add the storage conditions to Section 16 in accordance with 21 CFR 201.57(c)(17).

5 RECOMMENDATIONS FOR MEDAC GESELLSCHAFT FÜR KLINISCHE SPEZIALPRÄPARATE MBH

A. General Comments (Container Labels and Carton Labeling)

1. As currently presented, the finished dosage form is listed as “For injection”. Per USP General Chapter <1121> Nomenclature, the dosage form should be “for Injection”. Revise the dosage form to “for Injection” in accordance with USP General Chapter <1121> Nomenclature.
2. As currently presented, the statement (b) (4) (b) (4) does not specify how to administer the product intravenously (e.g., intravenous infusion or bolus). This lack of information may lead to wrong technique drug administration errors. We recommend revising the statement to “For intravenous infusion after reconstitution” to minimize the risk of the product being administered as an intravenous bolus. Additionally, we recommend this statement be displayed in sentence case, rather than all capital letters, as it currently appears more prominent than other important information on the Principal Display Panel (PDP), such as the established name.
3. The warning statement, (b) (4) is not consistent with current labeling terminology. Hazardous products require special handling procedures, and the language should be updated to reflect current terminology. We recommend revising this warning statement to “WARNING: Hazardous Drug” in bold font on the PDP of the container label and carton labeling (space permitting, or on the side panel for space constraints). Note that the word (b) (4) is does not need to be included in the warning statement. Additionally, we recommend (b) (4) the warning, as it currently appears more prominent than other important information on the PDP, such as the established name.
4. As currently presented, MMMYYYY, the expiration date format does not follow recently revised USP General Chapter <7> formatting guidelines. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend revising the expiration date format you intend to use. USP <7> requires the year, in YYYY format, to be listed at the beginning of the expiration date. When all-numeric dates are used, they must be formatted using the year, the month, and, if applicable, the day, separated by hyphens or forward slashes in one of the following formats: YYYY-MM-DD or YYYY-MM. When alphanumeric dates are used, months must be displayed using at least three letters in one of the following formats: YYYY-MMM-DD or YYYY-MMM. Revise your expiration date to comply with USP <7> formatting guidelines.

B. Container Labels

1. As currently presented, the package type term, single-dose vial, and discard statement are not located on the PDP of the container label. Visibility of the correct package type term and discard statement will promote proper use of the drug product. The lack of this information may lead to wrong technique medication errors during preparation of the product. We recommend relocating the statements “Single-dose Vial. Discard Unused Portion.” to the PDP (b) (4) (b) (4), if space allows. Note that on small labels, the “Rx only” statement can be removed or relocated to the side panel, if space is needed.

2. As currently presented, the "LOT" and "EXP" statement locations are not next to the placeholder locations for the lot number and expiration date on the container labels. Ensure the lot number and expiration date on the container labels align with the lot number and expiration date abbreviations (i.e., LOT and EXP) to minimize the risk of misinterpretation.
3. The unit of measure is missing from some of the temperature references. Unclear storage information may lead to confusion and potential risk of deteriorated drug medication errors. We recommend adding the unit of measure after each numerical degree. Revise "Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]." to "Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].".

C. Carton Labeling

1. As currently presented, the net quantity statement "One Single-dose Vial" on the PDP does not have the discard statement "Discard unused portion." located next to it. (b) (4) (b) (4). Inclusion of the discard statement next to the package type term helps minimize the risk of the entire contents of the vial being given as a single dose and duplicative information leads to clutter on the labeling. We recommend revising the statement "One Single-dose Vial" on the PDP to read as "One Single-Dose Vial. Discard Unused Portion." and removing the duplicative statement (b) (4) (b) (4). See Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018).
2. The storage conditions of the lyophilized powder are missing from the labeling. Not including the storage conditions may result in the risk of product being stored incorrectly and lead to deteriorated drug medication errors. Add the storage information for the lyophilized powder, ensuring that it aligns with the storage conditions listed in Section 16 of the Prescribing Information.
3. The route of administration statement lacks prominence. The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP. We recommend increasing the prominence of the route of administration by ensuring there is adequate white space underneath this statement by relocating the hazardous warning statement, "Rx only", and the net quantity and discard statement further down the PDP. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
4. The statement (b) (4) is inconsistent with the terminology in the Prescribing Information (b) (4) and contains duplicative information that is contained within the route of administration statement. To reduce clutter on the labeling, we recommend removing this

statement. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Grafapex received on April 30, 2024 from Medac Gesellschaft für klinische Spezialpräparate mbH.

Table 2. Relevant Product Information for Grafapex	
Initial Approval Date	N/A
Active Ingredient	treosulfan
Indication	• Acute Myeloid Leukemia GRAFAPEX is indicated in combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation in adult and pediatric patients > 1 year old with acute myeloid leukemia. • Myelodysplastic Syndrome GRAFAPEX is indicated in combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation in adult and pediatric patients > 1 year old with myelodysplastic syndrome.
Dosage Form	for Injection
Strength	1 gram/vial and 5 gram/vial
Route of Administration	Intravenous infusion
Dose and Frequency	The recommended dose of GRAFAPEX is 10 g/m^2 intravenously given daily for three days, beginning on Day -4 prior to transplantation in combination with fludarabine as outlined in Table 1. (b) (4)
How Supplied	GRAFAPEX is a white, sterile, lyophilized powder for reconstitution supplied as 1 g or 5 g single-dose vials. GRAFAPEX is distributed as unit cartons of one vial treosulfan 1 g NDC xxxxx-xxx-xx and one vial treosulfan 5 g NDC xxxxx-xxx-xx.
Storage	(b) (4) GRAFAPEX is a hazardous drug. Follow applicable special handling and disposal procedures
Container Closure	Colorless glass vials closed with rubber stoppers and aluminum seals including a flip off cap.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Grafapex labels and labeling submitted by Medac Gesellschaft für klinische Spezialpräparate mbH.

- Prescribing Information received on April 30, 2024, available from \\CDSESUB1\EVSPROD\nda214759\0070\m1\us\114-labeling\114a-draft-label\draft-label-text-redline.pdf
- Container labels received on April 30, 2024
- Carton labeling received on April 30, 2024

B.2 Container Labels and Carton Labeling Images

Container labels:

(b) (4)

[redacted]

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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APPENDIX C. PREVIOUS DMEPA REVIEWS

On July 23, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, 'treosulfan' and '214759'. Our search identified three previous reviews[h,i,j], and we considered our previous recommendations to see if they are applicable for this current review.

[h] Iverson, N. Label and Labeling Review for Grafapex (NDA 214759). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 19. OSE RCM No.: 2020-1687.

[i] Iverson, N. Review of Revised Label and Labeling Memorandum for Grafapex (NDA 214759). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 20. OSE RCM No.: 2020-1687-1.

[j] Iverson, N. Review of Revised Label and Labeling Memorandum for Grafapex (NDA 214759). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 22. OSE RCM No.: 2020-1687-2.

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JODY K KUNDRESKAS
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NICOLE F IVERSON
08/15/2024 03:19:53 PM

CLINICAL INSPECTION SUMMARY

Date	January 30, 2023
From	Anthony Orencia, M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., F.A.A.P., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Chatchada Karanes, M.D., Medical Officer Donna Przepiorka, M.D., Ph.D., Medical Team Leader R. Angelo de Claro, M.D., Division Director Amy Baird, Chief Regulatory Project Manager Bradley J. McKenzie, PharmD, Regulatory Project Manager Division of Hematology Malignancies 1 (DHM1) Office of Oncology Drugs
NDA	NDA 214759
Applicant	medac Gesellschaft für klinische Spezialpräparate m.b.H.
Drug	GRAFAPEX™ (treosulfan)
NME	Yes
Division Classification	Conditioning agent/preparative regimen
Proposed Indication	Preparative regimen for allogeneic hematopoietic stem cell transplantation in adult and pediatric patients
Review Type	Priority Review
Consultation Request Date	August 12, 2022
Summary Goal Date	February 5, 2023
Action Goal Date	February 10, 2023
PDUFA Date	February 28, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This New Drug Application (NDA 214759) was resubmitted in response to the Complete Response Letter (CRL) received by the sponsor on July 30, 2021. Additional clinical data from Study C-FludT.14/L were submitted to the Agency in support of this NDA for the drug treosulfan, proposed (a) in combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation in adult and pediatric patients age over one year, with acute myeloid leukemia, and (b) in combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation in adult and pediatric patients age over one year, with myelodysplastic syndrome.

Two foreign clinical investigators (Prof. Drs. Dietrich Beelen and Matthias Stelljes in Germany) were inspected with specific directive from DHM1 to verify the provided laboratory data collected by these sites in the resubmission.

Based on the inspections, the selected laboratory study data audit on differential blood count components, derived from the two clinical investigator sites in Germany are considered reliable. The study data submitted to the Agency for assessment appear acceptable in support of the proposed indication for this application, in response to FDA's Complete Response Letter.

II. BACKGROUND

This NDA resubmission is in response to the Complete Response Letter (CRL) received by the sponsor on July 30, 2021. This resubmission is within one year after the date of the CRL, provided in accordance with all requirements described under 21 CFR 314.110.

The resubmission provided additional blood count parameters and bone marrow blasts data for Study MC-FludT.14/L. DHM1 requests field inspection to focus on the review of those specific laboratory data for enrolled patients at two clinical study sites involved in Study MC-FludT.14/L for this resubmission.

In the resubmission, Study MC-FludT.14/L remains the sole study in support of the applicant's NDA, proposed for treosulfan as a conditioning therapy prior to allogeneic hematopoietic stem cell transplantation in patients considered ineligible to standard conditioning regimens. Specifically, the resubmitted application is for two following indications: (1) In combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult and pediatric patients over 1 year old with acute myeloid leukemia (AML), and (2) In combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation in adult and pediatric patients over 1 year old with myelodysplastic syndrome (MDS).

In the original submission, clinical data from Study Mc-FludT.14/L was submitted to the Agency in support of NDA 214759 for treosulfan. Two clinical investigators (Dietrich Beelen, M.D. with 113 enrolled subjects as described below, and Eva Wagner-Drouet, M.D. with 30 enrolled study subjects) were inspected for Study Mc-FludT.14/L. Based on the inspections, the conduct at the study sites was adequate and study data derived from Dr. Beelen's and Dr. Wagner's clinical investigator sites appeared reliable.

For this resubmission, DHM1 requested FDA inspection to focus on source data for submitted available laboratory results during scheduled patient visits in subjects who enrolled in the study, not for subject disposition, inclusion/exclusion criteria adverse event/serious adverse event, concomitant (non-study) medications or study endpoints, which have been inspected for the original NDA submission.

Study MC-FludT.14/L

Study MC-FludT.14/L Trial II (also known as MC-FludT.14/L_A) was a randomized, parallel-group, open label, multicenter, international, group-sequential phase III non-inferiority trial to evaluate efficacy and safety of treosulfan-based conditioning versus (vs.) a busulfan-based reduced intensity conditioning (RIC) treatment prior to allogeneic hematopoietic stem cell transplantation.

The sponsor was blinded with respect to aggregated analyses until data extraction for the interim analysis reported in CTR version 1.0 dated September 15, 2017. For the analysis described in this CTR dated March 5, 2020, the sponsor was unblinded.

The primary objective for this study was to compare event-free survival (EFS) within two years after transplantation between treosulfan-based conditioning and busulfan-based conditioning. Events were defined as relapse of disease, graft failure or death (whatever occurred first).

The primary efficacy endpoint was event-free survival. Event-free survival within two years after transplantation was defined as the primary endpoint of the trial. EFS was measured from time of end of HSCT (= Day 0) to time of event. Events were defined as relapse of disease, graft failure or death (whatever occurred first). Relapse/progression incidence: Relapse/progression incidence was defined as the probability of having a relapse/progression within two years of allogeneic hematopoietic stem cell transplantation. Graft failure: The incidence of graft failure was defined as the probability of having a graft failure (primary or secondary) within two years after allogeneic hematopoietic stem cell transplantation.

This study was multicenter with, 31 sites in total. 20 sites in Germany, six sites in Italy, two sites in France, two sites in Poland, and a single site in Hungary. A total of 570 patients enrolled in the Phase 3 study: 280 subjects received treosulfan and 290 patients received busulfan. Date first patient enrolled in Trial II was on January 13, 2013. The date last patient completed Trial II, including post-surveillance was on January 25, 2018.

III. RESULTS

1. **Prof. Dr. Dietrich Beelen (previously Dr. Rudolf Trenschel)/Site 01**
   Universitätsklinikum Essen
   Klinik für Knochenmarktransplantation
   Hufelandstr. 55
   45122 Essen
   Germany

   Inspection dates: October 24 to 28, 2022

   A previous FDA inspection was conducted from October 26 to 30, 2020 at this site for the original NDA submission. A total of 113 subjects were screened, and 113 study patients were enrolled at the site. Sixty-five study subjects received study treatment and remained in Study Mc-FludT.14/L. There were 45 subjects who died, two patients were lost to follow-up, and one patient was withdrawn due to adverse event prior to receiving treatment. The inspection was classified No Action Indicated (NAI), with no FDA 483, Inspectional Observations, issued.

   Dr. Dietrich Beelen was the re-inspected party instead of Dr. Rudolf Trenschel at Site 01, Essen, Germany. The study was closed with 114 subjects enrolled (Note: an additional site participant was added to the previous inspection of total enrolled subjects).

The current inspection focused on a highly targeted review of selected source data to verify resubmitted clinical data and a limited portion of Compliance Program 7348.811, "Clinical Investigators and Sponsor-Investigators" as requested by the review division. A limited scope of this inspection concentrated on study MC-FludT.14/L- Trial II, "Clinical phase III trial to compare treosulfan-based conditioning therapy with busulfan-based reduced-intensity conditioning (RIC) prior to allogeneic hematopoietic stem cell transplantation in patients with AML or MDS considered ineligible to standard conditioning regimens." Items covered during the last inspection for the same protocol were not reviewed again during this inspection unless specifically requested in the FDA CDER assignment memorandum to ORA.

The sponsor of this study is medac Gesellschaft für klinische Spezialpräparate mbH.

The US contact is located at Clinipace Inc., 3800 Paramount Parkway, Suite 100, Morrisville, NC 27560.

For human subject records, the ad-hoc data submission was approved by the Ethics Committee. Previously, in the initial submission of data to FDA, the follow-up (visit) case report forms had a simple 'yes/no' indicator field to identify subject relapse. The resubmission required a new case report template for the follow-up visits where the following information was newly transcribed from original source records into new CRFs such as (1) assessment date of relapse status (2) blood count or differential blood count sample date and values (3) bone marrow assessment (if done), (4) chimerism assessment (if done), or (5) confirmation from clinical site representative and calendar date. All transcription of recorded data was confirmed as performed by Dr. Beelen or Andrea Weggen (clinical site study coordinator).

Two experienced senior ORA field representatives from FDA reviewed and confirmed existence of laboratory records for all 114 subjects. All subject source documentation at the site was confirmed to be paper-based, and no electronic source data was captured during the study.

The current inspection focused on the following laboratory values at all study visits for all subjects, such as hemoglobin, platelets, leukocytes. A spot check of the differential blood count components, including neutrophilic granulocytes, eosinophilic granulocytes, basophilic granulocytes, lymphocytes, monocytes, and leukemic blasts.

In addition to these laboratory values at the study site, FDA examined and collected selected documentation of other precursor cell components that were identified in the manual differential blood counts in the laboratory documentation. Some of the differential blood counts were obtained from manual or automated processes.

At the close out site inspection, FDA inspectors discussed the need to ensure all records are appropriately archived so they can be reviewed if needed. The following transcription errors were noted during the inspection.

Abridged examples:

Subject	Visit	Visit Date	Discrepancy
(b) (6)	Screening Visit	(b) (6)	CBC differential values were reported from a mix of automated and manual differential measurements. • Reported neutrophil (71.2%), eosinophil (1.6%), and basophil (0.3%) values were taken from the automated differential • Reported lymphocyte (18%) and monocyte (10%) values were taken from the manual differential.
			Both automated and manual CBC differentials were performed, but automated values were reported in the CRF.
			Both automated and manual CBC differentials were performed, but automated values were reported in the CRF.
	Day 20		Both automated and manual CBC differentials were performed, but automated values were reported in the CRF.
	Day -3		Both automated and manual CBC differentials were performed, but automated values were reported in the CRF.
	Day 100		Both automated and manual CBC differentials were performed, but automated values were reported in the CRF.
	Day 6		Eosinophil value was reported on the CRF as 0.05/nl, where the CRF required a % measurement (3.9% per the laboratory record).
	Post-Surveillance		• The absolute values instead of the percentages were recorded on the CRF for monocytes and lymphocytes. • Lymphocyte lab value= 20.2%, CRF= 1.19% • Monocyte lab value= 7.6%, CRF= 0.45%
	Post-Surveillance		• The absolute value instead of the percentage was recorded for monocytes. • Monocyte lab value= 12.1%, CRF= 0.60%
	Day 28		• Leukocyte value was reported incorrectly on the CRF. • Leukocyte lab value= 5.90 /nl, CRF= 5.96 /nl
	Month 9		• Hemoglobin value was reported incorrectly on the CRF. • Hemoglobin lab value= 13.9 g/dl, CRF= 13.8 g/dl
	Screening		• Screening laboratory report from (b) (6) showed 1% leukemic blasts, per Dr. Beelen. Value was not recorded/reported in the CRF.
	Day 16		• The absolute values instead of the percentages were recorded on the CRF for monocytes and lymphocytes.

Reviewer Comments:
The DHM1 medical review team was notified of the above reporting inconsistencies, transcription errors or deviations in recorded measurements (automated versus manual differential counts in the peripheral blood sampling results). The above discussion items noted during the FDA inspection were not considered to have a significant impact on the study efficacy results.

A Form FDA 483 (Inspectional Observations) was not issued at the end of the site inspection.

2. Prof. Dr. Matthias Stelljes/ Site: 17
Universitätsklinikum Münster
Knochenmarktransplantationszentrum
Albert-Schweitzer-Campus 1 A12
48149 Münster
Germany

Inspection dates: October 31 to November 4, 2022

A targeted inspection was conducted at clinical site 17 (Dr. Stelljes) with relevant sponsor-submitted data for Agency review.

The clinical study was closed with 49 subjects screened and 48 subjects randomized. Records reviewed for the study comprised complete blood count laboratory values at the study visits for all subjects: hemoglobin, platelets, leukocytes and differential components. Further, a random check of the bone marrow results (if performed) was also completed.

During the active site audit, CDER OSI GCP Assessment Branch hematology group was in close communication with the ORA staff. Exchange of information between the two FDA centers collaborated on efficient methods to conduct a review of the Münster site's comprehensive database in a timely manner.

Source laboratory records evaluated were verifiable. At the close out inspection meeting, discussion items included transcription discrepancies, missing lab values, and inconsistent method of cell counting for the peripheral blood samples. Dr. Stelljes acknowledged the items, provided explanations, and stated and action plan to monitor staff will be considered.

(1) Several subjects had differentials performed according to protocol during the follow up visits, but they were not included within the CRF, or there were transcription errors in the recorded lab result values.

Abridged examples:

- For patient (b) (6) Day 100, (b) (6), leukocyte lab value= 2.40 10^9/l but 2.15 10^9/l on the data line listing. No value was recorded on the CRF.
- For patient (b) (6) Month 24, (b) (6), leukocyte lab value= 4.34 10^9/l, CRF states 3.34 10^9/l.

- For patient (b) (6) Day 10, (b) (6) lab results for CBC differential were available, but not on Day 10 CRF.
- For patient (b) (6) Day 14, (b) (6) lab results were available for CBC differential, but not on day 14 CRF. Dr. Stelljes stated that "cell count was under 50"; lab result was not accurate.
- For patient (b) (6) Day-1, (b) (6) lab results were available for CBC differential, but not on day-1 CRF. Dr. Stelljes stated that "cell count was under 50"; lab result was not accurate.
- For patient (b) (6) Day 10, (b) (6) hemoglobin and hematocrit lab values were switched.
- For patient (b) (6) Day 100, (b) (6) neutrophil count=73%, recorded CRF count= 78%.

(2) Inconsistencies with respect to how neutrophils were determined and counted. Dr. Stelljes stated that "myelocytes, metamyelocytes, and promyelocytes were calculated into the neutrophil count, but not necessarily correct". The site investigator mentioned upon further review, it was "uncertain if these cells developed into neutrophils".

Reviewer's Comments:
The above inspectional discussion items were discussed with the DHM1 medical team. These discrepancies noted at close out inspection were not deemed to be significant. Peripheral blood sampling may have low diagnostic sensitivity in detecting presence of blasts. The laboratory blast assay for peripheral blood sample may not be the optimal diagnostic test due to unreliable results below the limit of quantification. DHM1 will conduct comprehensive review of all bone marrow data submitted by the sponsor to the Agency.

For diagnostic accuracy, blast phenotyping with implications for AML classification and prognosis, or assay reliability, active areas of AML subtype inquiry may involve, in part: (a) improved peripheral or bone marrow blasts sampling evaluation as part of treatment response, rather than conventional automated or manual cellular count techniques, or (b) flow cytometry assessments of blast cells at thresholds below the limit of quantification (Conventional differential count methods demonstrated a deficiency in limitations of quantification for study subjects (b) (6) and for myeloid blast counts). Advanced quantitative analytic systems could ameliorate, in part, or resolve issues regarding inconsistencies with leukocyte subpopulation (e.g., neutrophil) or confirmatory blast counts (for instance, as could be reflected in the discussion at the close out meeting with Dr. Stelljes and clinical colleagues).

Finally, as supplemental information, chimerism detection in evaluating the ratio of donor and recipient DNA in the recipient's blood or bone marrow, plus a companion diagnostic device approval is relevant in AML early therapeutic intervention studies. Such analysis is well-established for monitoring state of allogenic hematopoietic stem cell transplant periodically, via analyzing peripheral blood or bone marrow sampling of the AML recipient.

A Form FDA 483 (Inspectional Observations) was not issued at the end of the site inspection.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Jenn Sellers, M.D., Ph.D., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 29, 2022

To: Brad McKenzie, Regulatory Project Manager
Division of Hematologic Malignancies I (DHM1)

From: Valerie Guerrier, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for GRAFAPEX (treosulfan) injection, for intravenous use

NDA: 214759

This memo is in response to DHM1's labeling consult request dated August 12, 2022. OPDP defers comments on the proposed labeling at this time, and we request that DHM1 submit a new consult request during the subsequent review cycle. If you have any questions, please contact Valerie Guerrier at (240) 402-2162 or Valerie.Guerrier@fda.hhs.gov.

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/s/

VALERIE GUERRIER
11/29/2022 07:58:15 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 22, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 214759
Product Name and Strength:	Grafapex (treosulfan) for Injection, 1 g/vial and 5 g/vial
Applicant/Sponsor Name:	Medac Gesellschaft für klinische Spezialpräparate mbH (Medac)
OSE RCM #:	2020-1687-2
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on June 14, 2021 for Grafapex. We reviewed the revised container labels and carton labeling for Grafapex (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions were submitted due to technical requirements and to improve readability. In addition, the Applicant revised the trademark symbol and harmonized the spelling of "Single-dose Vial".

2 CONCLUSION

We note the container label text will appear in a horizontal position to improve readability. The revised container labels and carton labeling are acceptable from a medication error perspective and we have no additional recommendations at this time.

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HINA S MEHTA
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 20, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 214759
Product Name and Strength:	Grafapex (treosulfan) for Injection, 1 g/vial, 5 g/vial
Applicant/Sponsor Name:	Medac Gesellschaft für klinische Spezialpräparate mbH (Medac)
OSE RCM #:	2020-1687-1
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 8, 2021 for Grafapex. We reviewed the revised container labels and carton labeling for Grafapex (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] The revisions were also in response to information requests dated March 16, 2021[b] asking the Applicant to confirm how the container label will be adhered to the vial and March 30, 2020[c] asking the Applicant to include the descriptor "Sterile" on the container labels and carton labeling.

2 CONCLUSION

We note the Applicant confirmed that the linear barcode and container label text will appear in a vertical position, which means the user will have to rotate the vial by 90° to read all of the

[a] Iverson N. Label and Labeling Review for Grafapex (NDA 214759). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 19. RCM No.: 2020-1687.
[b] Kolibab K. FDA Communication: Information Request for Grafapex (NDA 214759). Silver Spring (MD): FDA, CDER, OOD, DHM1 (US); 2021 MAR 16.
[c] Yesmin S. FDA Communication: Information Request for Grafapex (NDA 214759). Silver Spring (MD): FDA, CDER, OOD, DHM1 (US); 2021 MAR 30.

information on the label. The long side of the label will be in a horizontal position. The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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HINA S MEHTA
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 04/29/21

To: Kris Kolibab, Senior Regulatory Project Manager, DHM1

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, Team Leader, OPDP

Subject: OPDP Labeling Comments for GRAFAPEX (treosulfan) for injection

NDA: 214759

In response to DHM1's consult request dated August 20, 2020, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for GRAFAPEX (treosulfan) for injection (Grafapex).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling emailed to OPDP on April 15, 2021, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 8, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at Rachael.Conklin@fda.hhs.gov.

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RACHAEL E CONKLIN
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 19, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 214759
Product Name, Dosage Form, and Strength:	treosulfan* for Injection, 1 g/vial, 5 g/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Medac Gesellschaft für klinische Spezialpräparate mbH (Medac)
FDA Received Date:	August 11, 2020 and January 28, 2021
OSE RCM #:	2020-1687
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

* The proposed proprietary name has not yet been determined. Therefore, the active ingredient, "treosulfan" is used throughout this review.

1 REASON FOR REVIEW

As part of the approval process for NDA 214759 treosulfan for Injection, 1 g/vial and 5 g/vial, this review evaluates the proposed container labels, carton labeling, and Prescribing Information (PI) for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C– N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other – Information Request	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Medac Gesellschaft für klinische Spezialpräparate mbH (Medac) submitted a 505(b)(1) application to obtain marketing approval of treosulfan for Injection. Treosulfan is proposed for Is an alkylating drug 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).

We performed a risk assessment of the proposed container labels, carton labeling, and PI for treosulfan for Injection to determine whether there are significant concerns in terms of safety related to preventable medication errors. We note the PI states (b) (4) (b) (4) We discussed the requirement (b) (4) (b) (4) with the Office of Pharmaceutical Quality. On January 13, 2021 we (jointly with OPQ) sent

an information request (IR) to the Applicant to clarify (b) (4) (b) (4). On January 28, 2021 the Applicant responded to the IR stating "The wording in the label is slightly misleading (b) (4)". In addition, the Applicant submitted revised labeling to reflect this.

We identified areas of the proposed label and labeling that could be revised to improve clarity and readability of important information. For the Division, we note that the PI lacks clarity in the reconstitution instructions, administration instructions, dosage form, how supplied and storage information. We also note numeric doses and strengths are presented in multiple units of measure and PI uses the incorrect dosage form. For the Applicant, we note the storage information lacks prominence, the format for the expiration date is not defined, prominence of the Rx only statement, and the incorrect dosage form. In addition, we note overlapping colors utilized (b) (4). These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed container labels, carton labeling, and PI, that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Medac Gesellschaft für klinische Spezialpräparate mbH (Medac) to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Highlights of Prescribing Information

1. Dosage and Administration Section
    a. We note the proposed proprietary name, (b) (4) was found unacceptable as communicated in the Proprietary Name Review Denial letter dated November 24, 2020 under IND 054552 and NDA 214759. Therefore, we recommend replacing the proprietary name, (b) (4) in the Prescribing Information with "Tradename" as a placeholder until a proprietary name is found conditionally acceptable.
    b. Delete the (b) (4) (b) (4) (b) (4) and include the statement, as this information is located in the Full Prescribing

Information. We recommend including the statement, "See Full Prescribing Information for instructions on preparation and administration. (2.2)".

c. We recommend including a third bullet, "Administer TRADENAME in combination with Fludarabine." since this product should be administered with Fludarabine.

2. Dosage Forms and Strengths

a. Numeric doses and strengths are presented in multiple units of measure. For example, the recommended dosage is presented in units of, "g/m^2" and the strength is presented in units of "mg". Developing a product strength or expressing the strength in a manner that is incongruent with the dosage and administration of the product complicates the calculating of dosage and may lead to dosing errors. We recommend expressing the strength in "g" to ensure the unit of measure for the strength (g) and dose (g/m^2) in the Prescribing Information are consistent.

b. The dosage form lacks clarity. Therefore, we recommend revising the following statement, (b) (4) (b) (4) to "For injection:1 g/vial and 5 g/vial of treosulfan as a lyophilized powder in single dose vials for reconstitution. (3)

B. Prescribing Information

1. We note the proposed proprietary name, (b) (4) was found unacceptable as communicated in the Proprietary Name Review Denial letter dated November 24, 2020 under IND 054552 and NDA 214759. Therefore, we recommend replacing the proprietary name, (b) (4) in the Prescribing Information with "Tradename" as a placeholder until a proprietary name is found conditionally acceptable.

2. Dosage and Administration Section

a. As currently presented, the reconstitution instructions lack clarity, which may lead to product preparations errors. Therefore, we recommend the following revisions in *Section 2.2 Preparation and Administration Instructions* of the PI:

i. Include as the first statement, "Reconstitute treosulfan prior to intravenous infusion."

ii. Treosulfan is a hazardous drug. We recommend replacing the word, (b) (4) with "hazardous" as this is the current terminology recommended in labeling. Thus, add a second

statement, “Treosulfan is a hazardous drug. Follow applicable special handling and disposal procedures.[1]”

iii. We recommend revising and relocating the following statements as the first bullet, “Reconstitute each vial (b) (4) (b) (4) with 0.45% or 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP or Sterile Water for Injection, USP in its original glass container using volumes described in Table 1 to obtain a concentration of 0.05 g/mL of treosulfan.”

iv. Add the following table after the first bullet

Table 1: Reconstitution Solution Volumes	
Strength	Volume
1 g/vial	20 mL
5 g/vial	100 mL

v. Revise and relocate the statements, (b) (4) (b) (4) (b) (4) to “Dissolve treosulfan by shaking the vial. (b) (4) (b) (4)

vi. Revise and relocate the statements, (b) (4) (b) (4) (b) (4) to “Inspect the reconstituted solution for discoloration and particulate matter. The reconstituted solution (b) (4) (b) (4) appears as a clear colorless solution. Solutions showing any sign of precipitation should not be used.”

vii. Revise and relocate the statements, (b) (4) (b) (4) (b) (4) as the first bullet under the Administration sub heading as, (b) (4) (b) (4)

[redacted]

viii. Delete the statements, [redacted]

[redacted]

ix. Revise the statement, [redacted] using the proper nomenclature, "Reconstitute [redacted] with 0.45% or 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP or Sterile Water for Injection, USP."

x. Numeric doses and strengths are presented in multiple units of measure. For example, the recommended dosage is presented in units of, "g/m^2" and the strength is presented in units of "mg". Developing a product strength or expressing the strength in a manner that is incongruent with the dosage and administration of the product complicates the calculating of dosage and may lead to dosing errors. We recommend expressing the strength "1000 mg" and "5000 mg" as "g" to ensure the unit of measure for the strength (g) and dose (g/m^2) in the Prescribing Information are consistent.

3. Dosage Forms and Strengths

   a. The dosage form lacks clarity. Therefore, we recommend revising the statements, [redacted] to "For injection: 1 g/vial or 5 g/vial of treosulfan as a white, sterile, lyophilized powder in single-dose vials for reconstitution."

4. How Supplied/Storage and Handling Section

   a. Section 16.1 How Supplied

      i. Revise the statement, [redacted]

[redacted] to "TRADENAME for injection is a sterile, white, lyophilized powder for reconstitution [redacted]."

ii. We recommend deleting the statement, [redacted] as this information is located in Section 2 *Dosage and Administration* of the PI.

iii. We recommend expressing the strength "1000 mg" and "5000 mg" as "g" to ensure the unit of measure for the strength (g) and dose (g/m^2) in the Prescribing Information are consistent.

b. Section 16.2 Storage and Handling

i. Relocate the statement, [redacted] to Section 2.2 of the prescribing Information in the Reconstitution instructions." as this storage and stability information refers to the reconstituted product.

ii. Treosulfan is a hazardous drug. We recommend replacing the word, [redacted] with "hazardous" as this is the current terminology recommended in labeling.

iii. Revise the storage information in prescribing information, [redacted] to be consistent with the container labels and carton labeling, "Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].

4.2 RECOMMENDATIONS FOR MEDAC GESELLSCHAFT FÜR KLINISCHE SPEZIALPRÄPARATE MBH (MEDAC)

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. We note the proposed proprietary name, [redacted] was found unacceptable as communicated in the Proprietary Name Review Denial letter dated November 24, 2020 under IND 054552 and NDA 214759. Therefore, we recommend

replacing the proprietary name, [redacted] with "Tradename" as a placeholder until a proprietary name is found conditionally acceptable.

2. The finished dosage form listed on the principal display panel is not consistent with USP General Chapter <1121> Nomenclature. We recommend revising the dosage form from, [redacted] to "For Injection" to be in accordance with USP General Chapter <1121> Nomenclature.

3. The product strength located in the blue and pink colored boxes are not expressed in terms of the total quantity of drug per vial. The product strength should be expressed as the total quantity of drug per vial, as described in USP General Chapter <7>. Failure to express the strength statement in the total amount of drug per vial may lead to confusion regarding the total content of the drug in the container. Revise the strength statement to express the total quantity of drug per vial, for example, 1 g/vial or 1 g per vial in accordance with USP General Chapter <7>. In addition, we recommend moving the strength to below the dosage form on the principal display panel. As currently presented the strength may be misinterpreted as part of the proprietary name.
4. Numeric doses and strengths are presented in multiple units of measure. For example, the recommended dosage is presented in units of, "g/m^2" and the strength is presented in units of "mg" on the principal display panel of the container labels and carton labeling. Developing a product strength or expressing the strength in a manner that is incongruent with the dosage and administration of the product complicates the calculating of dosage and may lead to dosing errors. We recommend deleting the statement [redacted] to ensure the unit of measure for the strength (g) and dose (g/m^2) in the Prescribing Information are consistent.
5. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

6. We recommend replacing the word, [redacted] with "hazardous" as this is the current terminology recommended in labeling. In addition, the [redacted] is used to bring prominence to the cautionary statement, [redacted] The use of same [redacted] minimizes the difference between them. We recommend you revise and consider using a different color, boxing, or some other means to bring prominence to the cautionary statement, "Hazardous [redacted]" in order to maintain prominence of the strength statement.
7. Please delete the word, [redacted] from the principal display panel as this statement is not necessary.
8. The Rx Only statement appears as prominent as the route of administration. We recommend decreasing the prominence of the Rx only by debolding.

B. Container Labels

1. Consider reorienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.[a]
2. We recommend replacing the statement [redacted] with "Recommended dosage: See Prescribing Information".
3. Consider adding the statement "Single-Dose Vial. Discard Unused Portion" to minimize risk of the entire contents of the vial being given as a single dose.
4. The storage statement includes an extra space between the value and degree sign. We recommend revising the presentation of the storage statement as follows, "Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]."

C. Carton Labeling

1. The side display panel is cluttered. We recommend deleting [redacted] as this information appears on the principal display panel.
2. [redacted] relocate and revise the recommended dosage statement, [redacted] to the side panel as "Recommended Dosage: See Prescribing Information."

[a] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

3. The net quantity statement does not appear on the principal display panel of the carton labeling. Failure to include the net quantity statement on the principal display panel may result in confusion regarding the contents of the carton. We recommend including a net quantity statement on the principal display panel as "One Single Dose Vial" and ensure it is located away from and less prominent than the product strength. We also recommend deleting the statement (b) (4) (b) (4) as this statement is no longer necessary.
4. The storage statement prior to reconstitution is missing from the carton labeling. We recommend including and bolding the statement, "Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for treosulfan received on August 11, 2020 from Medac Gesellschaft für klinische Spezialpräparate mbH (Medac).

Table 2. Relevant Product Information for treosulfan	
Initial Approval Date	N/A
Active Ingredient	treosulfan
Indication	Is an alkylating drug 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)
Route of Administration	Intravenous infusion
Dosage Form	for Injection
Strength	1 g/vial, 5 g/vial
Dose and Frequency	• The recommended dose for treosulfan is 10 g/m^2 body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -4, -3, -2) before hematopoietic stem cell infusion (day 0). The total treosulfan dose is 30 g/m^2. • Fludarabine 30 mg/m^2 BSA per day (b) (4) , given on five consecutive days (day -6, -5, -4, -3, -2) before hematopoietic stem cell infusion (day 0). The total fludarabine dose is 150 mg/ m^2. • Treosulfan should be administered (b) (4) on days -4, -3, -2 ((b) (4)).
How Supplied	Treosulfan is supplied as a white, sterile, lyophilized powder for injection in single dose glass vials containing 1 g or 5 g. Treosulfan is distributed as unit cartons of one vial treosulfan 1 g and one vial treosulfan 5 g.
Storage	Unopened vials of treosulfan should be stored at room temperature (25°C / 77°F).

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 7, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, treosulfan. Our search did not identify and previous label and labeling reviews.

APPENDIX F. INFORMATION REQUEST

On January 13, 2021, we sent the following information request to the Applicant:

We refer to your NDA 214759 Treosulfan submitted on August 11, 2020. We note Section 2.2 of the your proposed prescribing information states that, (b) (4) (b) (4) (b) (4). Provide data to support an assertion that (b) (4) (b) (4). Please respond to this request by close of business January 28, 2021.

On January 28, 2021 the Applicant responded, "The wording in the label is slightly misleading. (b) (4) (b) (4) The Applicant proposed labeling statements including (b) (4) (b) (4) (b) (4). See reference below for full IR response[b].

[b] \\CDSESUB1\evsprod\nda214759\0025\m1\us\111-info-amend\quality-information-amendment.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following treosulfan labels and labeling submitted by Medac Gesellschaft für klinische Spezialpräparate mbH (Medac).

- Container labels received on August 11, 2020
- Carton labeling received on August 11, 2020
- Prescribing Information (Image not shown) received on August 11, 2020, available from \\CDSESUB1\evsprod\nda214759\0001\m1\us\114-labeling\114a-draft-label\draft-label-text.pdf

G.2 Label and Labeling Images

Container labels

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

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CLINICAL INSPECTION SUMMARY

Date	February 9, 2021
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Cara Rabik, M.D., Ph.D., Medical Officer Donna Przepiorka, M.D., Ph.D., Medical Team Leader R. Angelo de Claro, M.D., Director Kris Kolibab, Ph.D., Senior Regulatory Project Manager Division of Hematology Malignancies 1 Office of Oncologic Diseases
NDA	214759
Applicant	medac Gesellschaft für klinische Spezialpräparate mbH
Drug	(b) (4)™ (treosulfan)
NME	Yes
Division Classification	Alkylating agent
Proposed Indication	Conditioning treatment prior to allogeneic hematopoietic stem cell transplantation.
Consultation Request Date	August 20, 2020 (Priority Review)
Summary Goal Date	February 15, 2021
Action Goal Date	April 9, 2021
PDUFA Date	April 11, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from a single Study Mc-FludT.14/L was submitted to the Agency in support of a New Drug Application (NDA 214759) for treosulfan. The proposed indication is 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). Two clinical site investigators (Dietrich Beelen, M.D. and Eva Wagner-Drouet, M.D.) were inspected for Study Mc-FludT.14/L in support of NDA 214759.

Based on the inspections, the conduct at the study sites was adequate and study data derived from Dr. Beelen's and Dr. Wagner's clinical investigator sites appeared reliable.

II. BACKGROUND

Treosulfan is a bifunctional alkylating agent approved in several European countries for the therapy of advanced ovarian carcinoma. In clinical studies, treosulfan/fludarabine conditioning of study subjects demonstrated sustained engraftment experience, and the majority of study patients developed a stable complete donor chimerism, in limited patient clinical studies such as acute myeloid leukemia and myelodysplastic syndromes.

The data presented in this application is to support the drug treosulfan as an alkylating agent with the followings proposed indication: 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).

A single study, Study Mc-FludT.14/L, will form the basis for the regulatory decision-making process for this application.

Study Mc-FludT.14/L

Study Mc-FludT.14/L was a randomized, parallel-group, open label, multicenter, international, group-sequential Phase III non-inferiority trial.

The primary study objective was show at least non-inferiority of treosulfan-based conditioning to reduced-intensity conditioning therapy based on intravenous. busulfan and to compare the associated safety profiles. The aim of the study was to compare event-free survival within two years after transplantation between treosulfan-based conditioning and busulfan-based conditioning. Events were defined as relapse of disease, graft failure or death (whatever occurs first).

The primary study endpoint was event free survival. Event-free survival (EFS) within one year after transplantation was measured from time of start of hematopoietic stem cell transplant (equivalent to Day 0) to time of event. Events were defined as relapse of disease, graft failure, or death (whatever occurred first).

The first subject enrolled June 13, 2013. The last patient completed on June 25, 2018. The study planned to enroll 930 study subjects. The full analyses data set comprised 551 study subjects.

Study Mc-FludT.14/L was conducted at 31 study sites, with 20 of the 31 study sites conducted in Germany.

DHM1 requested an inspection of two foreign clinical investigators site that had enrollment of large number of patients.

III. RESULTS (by site)

1. Dietrich Beelen, M.D./ Site 01
Hufelandstr. 55, Universitätsklinikum Essen, Klinik für Knochenmarktransplantation
Essen, 45122, Germany

Inspection dates: October 26 - 30, 2020

This site visit is the first FDA inspection of Dr. Dietrich Beelen. A total of 113 subjects were screened, and 113 study patients were enrolled at the site. Sixty-five study subjects received study treatment and remained in Study Mc-FludT.14/L. There were 45 subjects who died, two patients were lost to follow-up, and one patient was withdrawn due to adverse event prior to receiving treatment.

Source documents were reviewed for study eligibility, review/approval, monitoring, test article accountability, concomitant medication, adverse event/serious adverse event reporting, laboratory results, ECGs, and radiology documents such as imaging. Source documents included medical histories, in-patient and out-patient records and discharge summaries. Records review of the 82 of the 113 enrolled subjects indicated that the eligibility criteria for enrollment were met.

Mucositis site assessments and reports were comprehensively reviewed in detail in randomized patients with acute graft-versus-host disease. Study records of all subjects who died or relapsed were also evaluated to confirm their dates of death and relapse. There were no limitations during conduct of the clinical investigation.

The primary efficacy data endpoint (event free survival) were verifiable. Safety evaluation and verification of data were unremarkable. There was no under-reporting of adverse events.

2. Eva Wagner-Drouet, M.D./Site 27
Universitätsmedizin der Johannes Gutenberg-Universität Mainz
III. Medizinische Klinik und Poliklinik
Langenbeckstr. 1,
Mainz, 55131, Germany

Inspection dates: November 11 - 18, 2020

A total of 35 subjects were screened, and 30 study patients were enrolled at the site. All enrolled subjects entered into the treatment phase of the study and received study treatment, either with treosulfan-based conditioning and busulfan-based conditioning regimen. There were 17 subjects who did not complete follow-up study period: ten patients died, and seven study subjects did not complete the follow-up period because the study ended prior to the participant’s 24-month follow-up visit.

Source documents were reviewed for study eligibility, review/approval, monitoring, test

article accountability, concomitant medication, adverse event/serious adverse event reporting, laboratory results, and radiology documents such as imaging. Source documents included medical histories, progress reports, nursing flow charts, and discharge summaries. Records review of the 30 enrolled subjects indicated that the eligibility criteria for enrollment were met. There were no limitations during conduct of the clinical investigation.

The primary efficacy endpoint data (event free survival) were verifiable. Study records of all subjects who died or relapsed were also evaluated to confirm their dates of death and relapse. Mucositis adverse event data reports were also evaluated. No discrepancies were noted. There was no under-reporting of serious adverse events.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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

/s/

ANTHONY J ORENCIA
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MIN LU
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KASSA AYALEW
02/10/2021 04:40:55 PM