NDA 214759

NDA APPROVAL

medac Gesellschaft für klinische Spezialpräparate mbH
c/o ProPharma
Attention: Daniel S. Solorio
US Agent; Senior Vice President, Regulatory Program Management
1129 20th Street NW, Suite 600
Washington, DC 20036

Dear Daniel Solorio:

Please refer to your new drug application (NDA) dated August 11, 2020, received August 11, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for GRAFAPEX (treosulfan) for injection, for intravenous use.

We acknowledge receipt of your amendment dated April 30, 2024, which constituted a complete response to our July 30, 2021, action letter.

We acknowledge receipt of your major amendment dated July 30, 2024, which extended the goal date by three months.

This NDA provides for the use of GRAFAPEX (treosulfan) for injection, for intravenous use for:

- Use in combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation in adult and pediatric patients 1 year of age and older with acute myeloid leukemia (AML).
- Use in combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation in adult and pediatric patients 1 year of age and older with myelodysplastic syndrome (MDS).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on January 13, 2025, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 214759**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for GRAFAPEX (treosulfan) for injection, for intravenous use shall be 24 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].

ADVISORY COMMITTEE

Your application for GRAFAPEX was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of increased drug toxicity in patients with moderate renal impairment; to identify an unexpected serious risk of QTc prolongation with treosulfan and its active metabolite; and to identify an unexpected serious risk of increased drug toxicity due to treosulfan active metabolites.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4099-1 Conduct a clinical pharmacokinetic trial to evaluate a serious potential risk of increased drug toxicity and determine an appropriate, safe dose of treosulfan in patients with moderate renal impairment (estimated glomerular filtration rate or creatinine clearance 30-59 mL/min). This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

The timetable you submitted on December 19, 2024, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	11/2022 (completed)
Trial Completion:	07/2025
Final Report Submission:	02/2026

4099-2 Conduct a clinical trial to characterize the serious potential risk of QTc prolongation (i.e., exclude large mean increases of >20 msec in the QTc interval) with treosulfan and its active metabolite. Design and conduct the study in accordance with the ICH E14 Guidances for Industry titled, E14 Clinical Evaluation of QT/QTc and E14 Clinical Evaluation of QT/QTc

Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions and Answers (R3) Guidance for Industry.

The timetable you submitted on December 19, 2024, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 04/2022 (completed)
Trial Completion: 12/2025
Final Report Submission: 05/2026

4099-3 Conduct a clinical pharmacokinetic trial to characterize the serious potential risk of increased drug toxicity and further characterize the safety of treosulfan by evaluating the pharmacokinetics of the active monoepoxide intermediate [(2S,3S)-1,2-epoxybutane-3,4-diol-4-methanesulfonate] in adult patients after administration of treosulfan.

The timetable you submitted on December 19, 2024, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 11/2022 (completed)
Trial Completion: 07/2025
Final Report Submission: 02/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 054552 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4099-4 Conduct a clinical trial to assess the pharmacokinetics of treosulfan among U.S. racial and ethnic groups. This study should characterize the exposure (including pharmacokinetics data) of treosulfan.

The timetable you submitted on December 19, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2022 (completed)
Trial Completion: 07/2025
Final Report Submission: 02/2026

4099-5 Conduct a registry-based observational study to assess outcomes by race and ethnicity for patients undergoing allogeneic hematopoietic stem cell transplantation using treosulfan-fludarabine as the preparative regimen. Include subgroup analyses by race and ethnicity for overall survival, nonrelapse mortality and relapse-free survival.

The timetable you submitted on December 19, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 07/2025
Final Protocol Submission: 10/2025
Study Completion: 01/2029
Final Report Submission: 07/2029

Submit the datasets with at least 3 years of follow up in the final report submission.

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 054552 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[7].

If you have any questions, email Brad McKenzie, Senior Regulatory Health Project Manager, at bradley.mckenzie@fda.hhs.gov or call (301) 796-2583.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

[7] https://www.uspnf.com/

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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