

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214759Orig1s000

OTHER ACTION LETTERS



NDA 214759

COMPLETE RESPONSE

medac Gesellschaft für klinische Spezialpräparate mbH
c/o Clinipace Inc.
Attention: Frank Schmidberger
US Agent, Senior Manager, Regulatory Strategic Development
1434 Spruce Street, Suite 100
Boulder, CO 80302

Dear Mr. Schmidberger:

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 for Grafapex (treosulfan) for injection, for intravenous use.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL/STATISTICAL

1. You have not provided substantial evidence of effectiveness of treosulfan as a part of a preparative regimen for allogeneic hematopoietic stem cell transplantation for adult and pediatric patients with AML or MDS for the following reasons:
 - The primary endpoint of Study MC-FLudT-14/L Trial II was event-free survival (EFS). Because all complete blood cell (CBC) and marrow results were not submitted, we were unable to independently confirm the results of the analysis of the primary endpoint of EFS for Study MC-FLudT-14/L Trial II.
 - Additionally, because of the missing CBC and marrow results, we were not able complete our assessment of whether the results of the study would support the indications for treatment of patients with AML and for treatment of patients with MDS.

To address this issue, submit the CBC and marrow results through the complete assessment period for EFS for MC-FLudT.14/L Trial II. Whether the results would be adequate to support approval of both indications will be a review issue.

2. (b) (4) OS cannot be used as the sole basis for approval for the following reasons:

- The statistical plan for Study MC-FLudT-14/L Trial II did not include control of Type 1 error for overall survival (OS).
- There was no prespecified boundary for OS interim analyses and no alpha allocation for multiple OS analyses. Therefore, p-values are nominal, and analysis of OS is considered to be exploratory.

To address this issue, submit data from an adequate and well-controlled trial of treosulfan vs busulfan with a prespecified analysis of OS for each indication with control of Type 1 error.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources¹ and Pregnancy and Lactation Labeling Final Rule² websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.³

CARTON AND CONTAINER LABELING

We reserve comment on the proposed carton and container until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, April 22, 2021 which addresses the proposed proprietary name, Grafapex. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

² <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

³ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

SAFETY UPDATE


When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

- (1) Describe in detail any significant changes or findings in the safety profile.
- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
- (3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
- (6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
- (7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

CLINICAL/STATISTICAL

1. Treatment of AML and treatment of MDS are considered different indications. In order to obtain approval for both indications, you would need to demonstrate substantial evidence of effectiveness for each individually.
2. Your subgroup analyses of EFS and OS suggest a substantial difference in treatment effect by donor type. Clarify how the results support your claim of noninferiority of treosulfan for HSCT from both related and unrelated donors (with the latter using ATG).
3. You conducted your efficacy analyses in the Full Analysis Set (FAS). For a randomized trial with EFS and/or OS endpoints, the analyses should be conducted on the intent-to-treat (ITT) population.
4. For Study MC-FludT.14/L II, the variable RACE in ADSL has no data element for any of the study subjects. Consequently, the submission did not provide adequate information to ensure that the study results are applicable to the US population. Consider conducting a study to assess outcomes by race and ethnicity for patients undergoing allogeneic HSCT using treosulfan-fludarabine as the preparative regimen. Include subgroup analyses by race and ethnicity for overall survival, nonrelapse mortality and relapse-free survival with at least 3 years of follow-up.
5.  (b) (4)

CLINICAL PHARMACOLOGY

6. Address the following in the NDA resubmission:
 - a. Provide data to determine an appropriate safe dose of treosulfan for patients with moderate renal impairment (CLcr 30-59 mL/min). This should be 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."
 - b. Provide data to support the evaluation of the effects of treosulfan on the QTc interval. This should be done in accordance with ICH E14.

- c. Provide data evaluating treosulfan and its epoxide metabolites as substrates of metabolizing enzymes *in vitro*.
- d. Provide data evaluating the pharmacokinetics (PK) of treosulfan active metabolites in adult patients.
- e. Provide data evaluating the effects of race and ethnicity on treosulfan PK.

NONCLINICAL

- 7. We recommend that prior to the resubmission of the NDA, you conduct an in vitro study demonstrating DNA alkylation and breakage with treosulfan to adequately characterize the alkylating and genotoxicity properties and determine the potential serious risk of reproductive and developmental toxicity and carcinogenicity with treosulfan. This study should be submitted to the NDA with the resubmission.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

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

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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