CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212479Orig1s000
212479Orig2s000
212479Orig3s000
212479Orig4s000

OTHER ACTION LETTERS

NDA 212479

COMPLETE RESPONSE

Therakind Limited
c/o Poppyridge LLC
22345 Bracketts Road
Shorewood, MN 55331

Attention: Dayton T. Reardan, PhD, RAC
US Agent of Therakind Limited

Dear Dr. Reardan:

Please refer to your new drug application (NDA) dated and received March 1, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Jylamvo (methotrexate) oral solution.

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.

PRODUCT QUALITY

Facility:

1. During a review of records requested under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act, and provided by (b) (4) manufacturing facility, the FDA noted objectionable conditions. These objectionable conditions will be conveyed to the representative of the facility within 10 business days of this Complete Response Letter. Satisfactory resolution of these objectionable conditions is required (e.g., preapproval inspection and/or adequate facility responses addressing these conditions) before this application may be approved.

   If it is determined that an inspection is needed to approve your application, please note that FDA continues to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

   For more information, please see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

Drug Product:

2. Include the test for Deliverable Volume per USP <698> “Deliverable Volume” in the drug product specifications.

3. The proposed 18 month expiration dating period is not supported by the stability data as two out of the six (6) commercial batches (THE/16/0273, THE/17/0330, THE/17/0331, THE/17/0332, THE/17/0356, **and** THE/18/0407) tested at 18 months, failed (THE/17/0331, THE/17/0332). Please provide your course of action to resolve this issue.

4. Provide additional stability data for batch THE/19/0554 manufactured on September 12, 2019 and for batch THE/20/0604 manufactured on February 2, 2020.

5. You state in your post approval stability protocol: (b) (4) Clarify whether you propose: (b) (4)

6. Provide appropriate in-use stability data to support the proposed 3-month period during patient use once the bottle is opened. You should use the aged stability sample (toward the end of the proposed shelf life) to represent the worst case scenario. See comment 4 above.

7. Revise the post approval stability protocol to include a testing station at 15 months.

8. Include the following statement in your post approval stability commitment: Withdraw from the market any batches found to fall outside the approved specifications for the drug product. If the applicant has evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, the applicant should discuss it with the agency as soon as possible and provide justification for the continued distribution of that batch. The change or deterioration in the distributed drug product must be reported under 21 CFR 314.81(b)(1)(ii).

PRESCRIBING INFORMATION

9. 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 Resources[1] and Pregnancy and Lactation Labeling Final

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

Rule[2] 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

10. Submit your November 18, 2021 draft carton and container labeling based on our proposed revisions dated, November 12, 2021.

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.

[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

(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.

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, call Cindy Chee, Regulatory Project Manager, at 301-796-0889.

Sincerely,

{See appended electronic signature page}

Nikolay Nikolov, MD
Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
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/

NIKOLAY P NIKOLOV
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