CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215040Orig1s000

OTHER ACTION LETTERS

NDA 215040

COMPLETE RESPONSE

Galephar Pharmaceutical Research Inc.
Attention: Britta Martinez
Director Regulatory Affairs
Carr 925 Km 6.1 Bo Junquito
HC-04 Box 4540
Humacao, PR 00791

Dear Ms. Martinez:

Please refer to your new drug application (NDA) dated and received July 7, 2022, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Legubeti (acetylcysteine) for 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.

CLINICAL

1. You have not provided data to demonstrate the tolerability of Legubeti, the lysine salt of acetylcysteine, for the full range of loading and maintenance doses for patients with all body weights proposed in labeling.

   Both lysine and acetylcysteine have an unpleasant taste, and acetylcysteine has an unpleasant odor that may affect the tolerability of oral ingestion. The data to address the effect of the lysine on the palatability of Legubeti is inadequate. The completed relative bioavailability study with Legubeti and the acetylcysteine oral solution (a reference standard as a substitute for the relied-upon listed drug) conducted with 1 gm of acetylcysteine is not adequate to address palatability because most patients will receive higher doses (up to 15 gm) based on the proposed weight-based dosage. Because timely administration of acetylcysteine is essential to mitigate toxicity from acetaminophen overdose, uncertainty remains as to whether ingestion of the full Legubeti dose can be administered, either due to inadequate palatability or inadequate tolerability. Consequently, these uncertainties place patients at increased risk of acetaminophen-induced toxicity.

   To resolve this deficiency conduct palatability and tolerability studies at clinically relevant dose(s). The proposed clinical investigation to address this deficiency

should include a patient reported outcomes (PRO) instrument that is fit-for-purpose. Before embarking on tolerability and palatability studies we recommend reaching agreement with the Division of Clinical Outcomes Assessment (DCOA) regarding your PRO to ensure it is valid.

2. You have not provided adequate information to support the safety of L-lysine administration to pediatric patients weighing down to 1 kg. This information is needed to inform the benefit-risk assessment of this product in the pediatric population. The maximum daily amount of L-lysine expected to be administered with Legubeti at the proposed dosage ranges from 502.6 mg/kg/day including the loading dose on the first day to 313 mg/kg/day after completion of the maintenance doses on the last day of treatment. The amount of L-lysine expected to be delivered with the proposed dosage of Legubeti exceeds the estimated daily intake of L-lysine in enterally fed term neonates.

   To resolve this deficiency provide additional information (e.g., published literature or a study) to justify the safety of the L-lysine exposure in pediatric patients down to 1 kg, for the proposed indication.

REGULATORY

3. The relied-upon listed drug for this 505(b)(2) application is Mucomyst. You cited the Cetylev prescribing information in order to comply with the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR). It is acceptable to refer to the Cetylev label for the purpose of PLR and PLLR formatting. However, if you are relying on FDA's finding of safety and/or effectiveness for Cetylev (or another listed drug) concerning Lactation, Pregnancy, and Females and Males of Reproductive Potential information, you must comply with the legal/regulatory requirements for such reliance (e.g., establishing a scientific bridge, patent certification). Alternatively, you may rely on non-product-specific published literature concerning Lactation, Pregnancy, and Females and Males of Reproductive Potential to comply with PLLR.

   To resolve this deficiency you may (1) cite and provide original publications corroborating the proposed labeling language that are not based on FDA's finding of a listed drug (including the labeling of a listed drug); or (2) cite reliance on Cetylev and comply with the legal/regulatory requirements for such reliance.

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 Resources[1] and Pregnancy and Lactation Labeling Final 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

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated December 29, 2022, which addresses the proposed proprietary name, Legubeti. 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.

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:

[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

- 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 subject 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:

Consistent with USP nomenclature, we recommend that the dosage form of your proposed product be “for oral solution” instead of “powder for oral solution”.

We recommend you provide a comprehensive summary of clinical pharmacology information for N-acetylcysteine and L-Lysine available in the published literature along with the original articles.

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 Chinedu Ebonine, Regulatory Project Manager, at 240-402-3448.

Sincerely,

{See appended electronic signature page}

Frank A. Anania, MD, FACP, AGAF, FAASLD
(Acting) Director
Division of Hepatology and Nutrition
Office of Immunology and Inflammation
Office of New Drugs
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/

FRANK A ANANIA
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