CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213072Orig1s000

OTHER ACTION LETTERS

NDA 213072

COMPLETE RESPONSE

Althera Life Sciences, LLC
Attention: James Medley
Senior Advisor, Regulatory Affairs
89 Headquarters Plaza, Ste 1448
Morristown, NJ 07960

Dear Mr. Medley:

Please refer to your new drug application (NDA) dated and received July 29, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for rosuvastatin and ezetimibe tablet.

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

1. During a recent inspection of the (b) (4) manufacturing facility for this NDA, our field investigator conveyed deficiencies to the representatives of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

   Due to the impact of testing data deficiencies identified at (b) (4) during pre-approval inspection (PAI) of this facility, we do not consider the method validation information provided in the NDA application as reliable.

FACILITY INSPECTIONS

2. During a recent inspection of the (b) (4) manufacturing facility for this NDA, our field investigator conveyed deficiencies to the representatives of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

INFORMATION NEEDED TO RESOLVE DEFICIENCIES

Revalidate the analytical method used for assay, chromatographic purity, content uniformity, and dissolution using suitable reference standards/working standards.

After revalidation of the analytical method, repeat runs and re-analyze the existing stability samples. Include additional long-term stability data beyond 12 months for the 40 mg/10 mg and 10 mg/10 mg strengths, and beyond 9 months for the 5 mg/10 mg strength in your complete response. In addition, provide at least six-month long-term (25°C/60%RH) and accelerated (40°C/75%RH) stability data for new lots of drug product, one batch each strength, using the re-validated method.

In your response, dated March 16, 2020, to our information request dated February 6, 2020, you indicated that [redacted (b) (4)] " and the revised batch manufacturing records were provided. Please note the following comments and respond with supporting data and corresponding corrected documents:

a) We noticed that executed batch manufacturing records for [redacted (b) (4)] of rosuvastatin 5 mg/ezetimibe 10 mg tablets manufactured in batches REBTA002, REBTA003, and REBTA004, and the proposed commercial batch manufacturing records for this strength did not have a provision for recording the [redacted (b) (4)], contrary to your response.

b) For 20 mg/10 mg, [redacted (b) (4)] are not supported by the actual observed data on the exhibit batches. Provide data to support these limits.

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 PLR Requirements for Prescribing Information[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]

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

Please refer to correspondence dated, November 8, 2019, which addresses the proposed proprietary name, Roszet. 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/product 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/product. Include an updated estimate of use for drug/product 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

As we notified you previously, this application is subject to requirements of the Pediatric Research Equity Act (PREA) to include a pediatric assessment for all indications it seeks in adults. Your application did not provide sufficient evidence to support the safety and efficacy of the ezetimibe component of your product Roszet in pediatric homozygous familial hypercholesterolemia (HoFH), ages (b) (4) to 17 years of age. As part of your PREA requirement, you would be responsible for addressing this evidence gap in FDA's previous findings of pediatric safety and efficacy for ezetimibe with either evidence from published literature or from a completed trial in pediatric patients in the resubmission. For published literature, although data from randomized controlled trials (RCTs) is preferable, note that evidence from observational or uncontrolled studies may also be submitted. Published RCTs do not need to be limited to trials with treatment arms comparing ezetimibe monotherapy versus placebo. For example, you may include trials in which ezetimibe was administered in combination with other therapies (such as statins) and compared to active treatment arms. Additionally, ezetimibe need not be a treatment arm in published RCTs; for example, trials that include pediatric HoFH patients on background ezetimibe and that provide sub-analyses by use of baseline ezetimibe may be sufficient.

If your resubmission contains data supporting approval in adults, but the pediatric data remains insufficient to support approval, we would anticipate issuing postmarketing study requirements under PREA to support the safe and effective use of both components of Roszet (rosuvastatin and ezetimibe) for the treatment of pediatric (b) (4) HoFH.

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.

There is one pending citizen petition (Docket No. FDA-2015-P-4582) relevant to the class of drugs to which this application belongs currently undergoing review with the Agency. The issues raised by this petition are currently under review by the Agency, and FDA has not made a final decision on the issues raised in the pending citizen petition. The comments included in this communication reflect only our current thinking, and this communication should not be construed to grant, deny, or otherwise comment on the pending citizen petition.

If you have any questions, call Richard Whitehead, M.S., Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

John Sharretts, M.D.
Deputy Director (Acting)
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
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/

JOHN M SHARRETTS
05/26/2020 05:47:35 PM