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APPLICATION NUMBER:

213260Orig1s000

OTHER ACTION LETTERS

U.S. FOOD & DRUG ADMINISTRATION

NDA 213260

COMPLETE RESPONSE

CMP Development LLC
Attention: Ellen Barkley
Regulatory Affairs Manager
P.O. Box 147
8026 US Highway 264A
Farmville, NC 27828

Dear Ms. Barkley:

Please refer to your new drug application (NDA) dated and received January 13, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for atorvastatin calcium oral suspension.

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. The proposed commercial (b) (4) batch records provided in module 3.2.P.3.3 currently do not contain any specific detail (b) (4)

FACILITY INSPECTIONS

2. During a review of records requested under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act, and provided b (b) (4) manufacturing facility, the FDA noted objectionable conditions.

3. During a recent inspection of the (b) (4) manufacturing facility, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection.

CLINICAL PHARMACOLOGY

4. Since the application does not contain clinical efficacy and safety data for the proposed atorvastatin calcium oral suspension (proposed product), relative bioavailability results are the fundamental bridge to the efficacy and safety data of the listed drug product. Relative bioavailability between the proposed product and the listed drug did not meet the conventional 80 – 125% criteria based on results from Study 18-VIN-0235. The 90% confidence interval for the geometric mean ratios (GMRs) between the proposed product and the listed drug for all primary PK parameters (AUC0-t, AUC0-∞ and Cmax) were outside the conventional 80 – 125% limits for all moieties measured (atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin) under fasting conditions. The exposures of atorvastatin, 2-hydroxy atorvastatin, and 4-hydroxy atorvastatin were [redacted] (b) (4) respectively following administration of the proposed product as compared to those following administration of the listed drug. In addition, results from Study 18-VIN-0236 indicate that the proposed product had a greater magnitude of food effect (30% reduction in AUC and 63% reduction in Cmax) compared to the reported values of 9% reduction in AUC and 25% reduction in Cmax for the listed drug when administered with food.

   The deficiency cannot be addressed with labeling, because there is no condition of use that would ensure safety and effectiveness of the product. When the proposed product is administered under fed conditions, the magnitude of the decrease in atorvastatin and its metabolites exposure is much greater for the proposed product compared to the listed drug, which could lead to loss of efficacy. On the other hand, if the product is administered under fasting conditions, the large increase in atorvastatin and its metabolites exposure compared to the listed drug is a safety issue. Additionally, there is a wide fluctuation in atorvastatin and metabolite levels following administration of the proposed product compared to the listed drug under both fasting and fed conditions. Thus, the clinical pharmacology and other relevant findings of the listed drug cannot be relied upon for the proposed atorvastatin product and the data do not support its approval.

INFORMATION NEEDED TO RESOLVE DEFICIENCIES

1. Revise the submitted [redacted] (b) (4) batch records to include [redacted] (b) (4) Update module 3.2.P.3.3 accordingly.

2. The objectionable conditions noted above at [redacted] (b) (4) manufacturing facility, 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-andresponse/coronavirus-disease-2019-covid-19/covid-19-related-guidancedocuments-industry-fda-staff-and-other-stakeholders

3. Satisfactory resolution of the observations noted at (b) (4) manufacturing facility is required before this NDA may be approved. Please list communications submitted to, or held with, the Agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.

4. Reformulate the proposed product and conduct additional relative bioavailability studies to demonstrate the bioequivalence to the listed drug or conduct a clinical study to support the effective and safe use of the proposed atorvastatin oral suspension product.

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

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

updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

PROPRIETARY NAME

The review of your proposed proprietary name has been terminated due to the deficiencies with the application as described in this letter. 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 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.

[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

(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 product. Include an updated estimate of use for 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:

We acknowledge the environmental analysis submitted under the eCTD module section 1.12.14. Per the 21 CFR 314.50 (d) (l) (iii), an environmental assessment exemption request should be completed as per the CFR § 25.30 or 25.31 or § 25.40. Therefore, resubmit your environmental assessment exception request accordingly.

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 Martin White, M.S., Regulatory Project Manager, at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

John Sharretts, M.D.
Deputy Director
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
10/16/2020 05:07:32 PM